Module 2.7.1

Summary of Biopharmaceutic Studies and Associated Analytical Methods

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
Ae	amount of drug excreted in the urine
ARV	Antiretroviral
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time 0 to the last measurable timepoint
BA	Bioavailability
BE	Bioequivalence
BCS	Biopharmaceutical Classification System
BLLQ	Below lower limit of quantitation
BST	Bioanalytical Sciences and Toxicokinetics
C24	Drug concentration at 24 hours post-dose
CI	Confidence interval
CL/F	Apparent oral clearance
Cmax	Maximum observed concentration
CV	Coefficient of variance
DCS	Developability Classification System
DMPK	Drug Metabolism and Pharmacokinetics
DTG	Dolutegravir, Tivicay
DTG/3TC FDC	DTG/3TC 50 mg/300 mg FDC
DTG/3TC Tablets	DTG and 3TC Tablets, 50 mg/300 mg
EDTA	Ethylenediaminetetraacetic acid
EU	European Union
FaSSIF	Fasted state simulated intestinal fluid
FDC	Fixed-dose combination
GLS	Geometric least-squares
GSK	GlaxoSmithKline
h or hr	Hour(s)
HIV	Human immunodeficiency virus
HPLC-MS/MS	High-performance liquid chromatography with tandem mass spectrometric detection
HPLC-UV	High-performance liquid chromatography ultraviolet method
INSTI	Integrase strand transfer inhibitor
IV	Intravenous
λz	Apparent elimination rate constant
LLQ	Lower limit of quantitation
M	Molar
mL	Milliliter(s)

ng	Nanogram(s)
nm	Nanometer(s)
PK	Pharmacokinetic
QC	Quality control
RBA	Relative bioavailability
RNA	Ribonucleic acid
rpm	Revolutions per minute
RTP	Research Triangle Park
SDS	Sodium dodecyl sulfate
SE	Single entity
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
tlag	Lag time before observation of drug concentrations in sampled matrix
tlast	Time of last quantifiable concentration
tmax	Time of occurrence of Cmax
µg	Microgram(s)
UK	United Kingdom
US	United States
USP	United States Pharmacopeia

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Epivir
Epzicom/Kivexa
Tivicay
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1. BACKGROUND AND OVERVIEW

Dolutegravir (DTG; Tivicay, GSK1349572) is an HIV INSTI approved for use in combination in ARV treatment-naïve and treatment-experienced HIV-infected adults and adolescents at a dose of 50 mg once daily as a single agent (Tivicay) and 50 mg BID when certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance is present. Lamivudine (3TC; GR109714) is a cytidine nucleoside analog HIV-1 reverse transcriptase inhibitor indicated in combination with other ARV agents for the treatment of HIV-1 infection at a dose of 300 mg once daily.

DTG and 3TC are currently under clinical development as a FDC tablet. Both DTG and 3TC are commercially available products in many markets worldwide. Tivicay (DTG) is approved as a 50 mg tablet in 124 countries, including the US, EU, and Canada. Available since 1995 as a single agent (Epivir) [Epivir Package Insert, 2018], 3TC is also available as part of two backbone FDC products (ZDV/3TC, COMBIVIR and ABC/3TC, Epzicom/Kivexa). Both DTG and 3TC are also available as part of a FDC product (ABC/DTG/3TC, Triumeq). DTG is also available as part of a two-drug combination FDC product (DTG/RPV, Juluca).

The new formulation being developed is a FDC of DTG/3TC 50 mg/300 mg as a 2-drug regimen with a proposed indication for the treatment of HIV-1 infection in HIV-infected adult and adolescents (≥40 kg) patients without known or suspected resistance to either component who are either treatment naïve or virologically-suppressed (HIV-1 RNA <50 c/mL) on a stable ARV regimen and switching their current regimen.

The proposed recommended oral dose for adults and adolescents above 12 years of age weighing at least 40 kg is 1 tablet administered once a day without regard to meals. The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are approved doses for adolescents ≥12 years of age weighing ≥40 kg (DTG) or for pediatric patients weighing ≥25 kg (3TC). Prior studies have shown that DTG and 3TC PK exposures in adolescents are sufficiently similar to those in adults and allows extrapolation of GEMINI efficacy data to adolescents.

This document summarizes the relevant biopharmaceutical characteristics of the FDC consisting of DTG/3TC 50 mg/300 mg referred to as DTG/3TC FDC and the SEs DTG and 3TC.

1.1. Organization of Data

Information on the DTG/3TC FDC includes data from the following studies:

- The pivotal BE Study (204994) completed for the DTG/3TC FDC (Section 2.1);
- The RBA Study (204993) completed for the experimental DTG/3TC FDC formulations (Section 2.3); and
- The impact of food on the systemic exposure of DTG and 3TC for DTG/3TC FDC formulations (pivotal BE Study 204994 Section 2.4).

Previously submitted studies from DTG or 3TC SE development programs support this application and are categorized as "supportive":

Supportive SE Studies: these studies are not essential for the FDC Benefit Risk Assessment, but are considered helpful to the reviewer and supportive of the proposed indication because it demonstrates the BE of experimental FDC tablet(s) of DTG and 3TC relative to co-administration of the SE products, the RBA of 2 experimental [redacted] FDC formulations, and the effect of food on the BA of the proposed commercial DTG/3TC FDC tablet formulation and on the PK of DTG and 3TC. A summary of supportive studies is presented in Appendix Table 1, but reports will be made available upon request for the convenience of the reviewer.

1.2. Main Biopharmaceutical Findings

The conclusions from the DTG/3TC FDC biopharmaceutic evaluations are as follows:

- In fasted state, the [redacted] DTG/3TC FDC tablet was bioequivalent for DTG AUC and Cmax and for 3TC AUC; however, the [redacted] had an approximately 32% higher 3TC Cmax than that seen following 3TC dosed as SE.
- The higher 3TC Cmax, which reflects differences in the rate of absorption but not extent of absorption, does not significantly affect patient safety and antiviral efficacy based on historical clinical efficacy and safety data at higher 3TC doses/exposures.
- The data from the pivotal BE Study 204994, combined with data from the 3TC historical studies, provides an acceptable PK bridge to the SEs used in GEMINI-1 and GEMINI-2 Phase III trials and supports the proposed submission for the [redacted] FDC tablet.
    - The DTG/3TC FDC may be taken with or without food. This is consistent with the prescribing information for the DTG and 3TC single entities and is supported by the food effect results for the [redacted] FDC tablet.
- The bioanalytical methods used to measure concentrations of DTG and 3TC in biological samples were selective, accurate, and reproducible.

1.3. Dolutegravir/Lamivudine Fixed-dose Combination

1.3.1. Formulation Development

During the development of the formulation of DTG and 3TC Tablets, 50 mg/300 mg (hereafter referred to as DTG/3TC Tablets), fixed dose combination tablets of DTG (50 mg) and 3TC (300 mg), a [redacted] and [redacted] tablet approach, were investigated.

[redacted] DTG/3TC Tablet formulations were dosed in the initial RBA Study 204993. Complete statements of the components and quantitative composition of the [redacted] DTG/3TC Tablets dosed in Study 204993 are presented in m3.2.P.2.2., Section 1.2.1.

Based on the RBA study results, a [redacted] formulation was developed in parallel. Both a [redacted] and [redacted] formulation were dosed in the pivotal bioequivalence Study

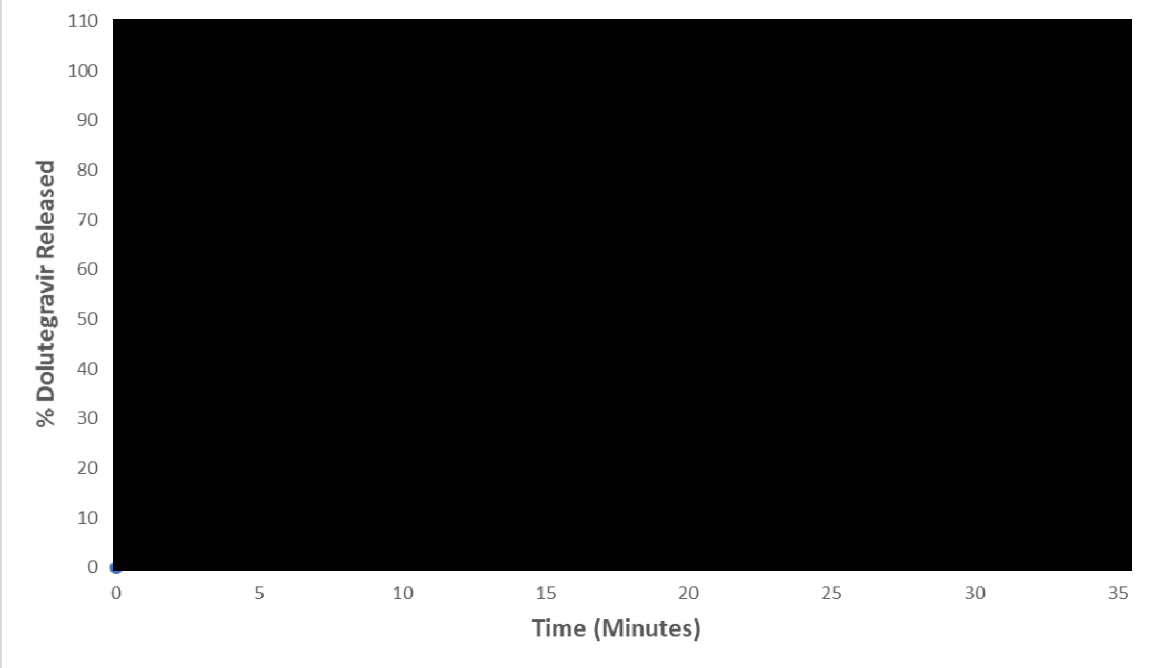
204994. Based on the pharmacokinetic results from study 204994, the [redacted] formulation was selected as the commercial formulation. The proposed commercial formulation for DTG/3TC Tablets, is a fixed dose, [redacted], combination tablet of DTG (50 mg) and 3TC (300 mg), using conventional excipients. [redacted] A summary of the [redacted] formulation selection and complete statements of the components and quantitative compositions of the DTG/3TC Tablets dosed in Study 204994 are presented in m3.2.P.2.2., Section 1.2.1.

1.3.2. In Vitro Dissolution Data

In vitro dissolution testing was performed on all batches of tablets used in the RBA Study 204993 and Bioequivalence Study 204994. A summary of the batches used are in Appendix Table 2 and the dissolution results are presented in Appendix Table 3. A summary of the dissolution method used for the DTG/3TC Tablets dosed in the bioequivalence study are presented in m3.2.P.5.2., Analytical Procedures.

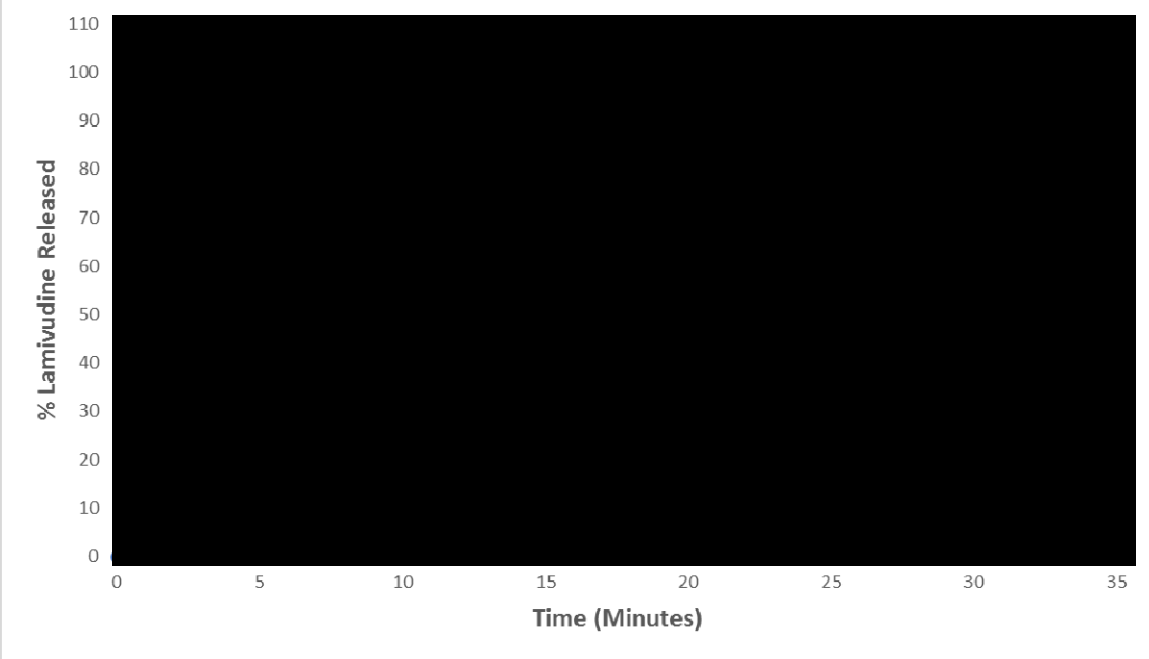
Dissolution profiles for the proposed commercial [redacted] formulation of the DTG/3TC Tablets (Formula code AK) used in the BE Study 204994 are shown in Figure 1 for DTG and Figure 2 for 3TC. Tabulated results are presented in Table 1.

Figure 1 Dissolution Profile of DTG in DTG/3TC FDC Batch 7ZM1988 (n=12) Used in Bioequivalence Study 204994



2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Figure 2 Dissolution Profile of 3TC in DTG/3TC FDC Batch 7ZM1988 (n=12) Used in Bioequivalence Study 204994



2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Table 1 Dissolution Results for DTG/3TC FDC Batch 7ZM1988 Used in Bioequivalence Study 204994

Tablet	% Dissolved	
	Dolutegravir	Lamivudine
1	[redacted]	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
Mean		
Min		
Max		
%RSD		

1.4. Analytical Methods

1.4.1. Dolutegravir/Lamivudine Fixed-dose Combination

1.4.1.1. Validation

A summary of the validation data that supported application of the bioanalytical methods for each PK study during the development of the DTG/3TC FDC is summarized in Appendix Table 4. All of the methods were validated to perform to the same, predefined acceptance criteria for precision and accuracy.

Dolutegravir

The bioanalytical method for the measurement of DTG concentrations in plasma in the presence of 3TC, performed by [redacted], was based on extraction by protein precipitation using acetonitrile containing an isotopically labeled internal standard ([$^{2}H_{7}$ ^{15}N]-DTG) followed by HPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring. The DTG method in the presence of 3TC was followed to provide analysis of DTG concentrations in plasma samples from studies 204993 and 204994.

Lamivudine

The bioanalytical method for the measurement of 3TC concentrations in plasma in the presence of DTG, performed by [redacted], was based on extraction by protein precipitation using acetonitrile containing an isotopically labeled internal standard ([^{13}C $^{15}N_{2}$-3TC) followed by UHPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring. The 3TC method in the presence of DTG was followed to provide analysis of 3TC concentrations in plasma samples from studies 204993 and 204994.

Serum concentrations of 3TC were performed by Glaxo Research Laboratories, based on solid phase extraction followed by HPLC-UV analysis. The 3TC method was followed to provide analysis of 3TC in serum samples from Study NUCA1006 and NUCA1001.

Serum concentrations of 3TC were performed by [redacted], based on solid phase extraction followed by HPLC-UV analysis. The 3TC method was followed to provide analysis of 3TC in serum samples from Study NUCB1004.

Urine concentrations of 3TC were performed by Glaxo Research Laboratories, based on direct injection with column switching method followed by HPLC-UV analysis. The 3TC method was followed to provide analysis of 3TC in urine samples from Study NUCA1001.

1.4.1.2. Summary of within study quality control sample analysis for dolutegravir/lamivudine fixed-dose combination studies

QC samples were analyzed with each batch of study samples. Performance results of the bioanalytical methods used for each study were generated from bioanalytical runs

meeting the same run acceptance criteria based upon the predefined requirements for QC performance that no more than one-third of the QC results and 50% from each QC concentration were to deviate from the nominal concentration by more than 15%.

The overall precision (%CV) and accuracy (%Bias) of the DTG assays for Study 204993 and Study 204994 are shown in Appendix Table 5. The between-run precision for DTG in Study 204993 and Study 204994 including statistical outliers ranged from 3.40% to 17.6% and 4.51% to 22.7% with a bias that ranged from -2.97% to 9.25% and -5.21% to 4.11% for each study, respectively.

The between-run precision for DTG in Study 204993 and Study 204994 excluding statistical outliers ranged from 3.40% to 12.9% and 4.51% to 5.96% with a bias that ranged from -2.97% to 9.25% and -4.99% to 3.69% for each study, respectively.

The overall precision and accuracy of the 3TC assays for Study 204993 and 204994 are shown in Appendix Table 6. The between-run precision for 3TC in Study 204993 and Study 204994 including statistical outliers ranged from 3.70% to 23.3% and 5.43% to 87.4% (all individual runs met acceptance criteria) with a bias that ranged from -2.36% to 3.57% and -0.726% to 15.0% for each study, respectively.

1.4.2. Dolutegravir Analytical Methods for Single Entity Studies

This section summarizes the validation and assay performance data for the development of DTG as a SE product.

1.4.2.1. Validation

The bioanalytical method for the measurement of DTG concentrations in plasma was based on extraction by protein precipitation using acetonitrile containing an isotopically labeled internal standard ($[^{2}H_{7}\ ^{15}N]$-DTG) followed by HPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring. The method was first validated over a range of 5 to 5000 ng/mL and then was validated at a range of 20 to 20,000 ng/mL to accommodate the higher concentrations of DTG being seen at the clinical dose of 50 mg [GlaxoSmithKline Document Number RD2010/00175/00]. These validations were conducted by the BST Section of Platform Technology and Science DMPK (PTS DMPK), GSK, RTP, North Carolina. The assay was transferred to [redacted], [redacted], and [redacted] and independently validated over the concentration range of 20 to 20,000 ng/mL by [redacted], [redacted], and [redacted] to provide continuing support.

A summary of the validation data that supported application of the bioanalytical method used for Study ING113674 is presented in Appendix Table 4.

1.4.2.2. Summary of Within Study Quality Control Sample Analysis for Dolutegravir Studies

QC samples were analyzed with each batch of study samples. Performance results of the bioanalytical methods used for each study were generated from bioanalytical runs meeting the same run acceptance criteria based upon the predefined requirements for QC

performance that no more than one-third of the QC results and 50% from each QC concentration were to deviate from the nominal concentration by more than 15%. The overall precision (%CV) and accuracy (%Bias) of the DTG assays for ING113674 are shown in Appendix Table 5. The between-run precision for DTG ranged from 3.5% to 4.4% with a bias that ranged from 0.2% to 3.9%.

1.4.3. Lamivudine Analytical Methods for Single Entity Studies

This section summarizes the validation and assay performance data for the development of 3TC as a SE product.

1.4.3.1. Validation

The bioanalytical method for the measurement of 3TC concentrations in serum, performed by Glaxo Research Laboratories, was based on extraction using solid phase extraction and GR90352 (Carbovir) as internal standard followed by HPLC-UV analysis. The 3TC method was followed to provide analysis of 3TC in serum samples from Study NUCA1006 and NUCA1001. The method was validated over the range of 3 to 5000 ng/mL.

The bioanalytical method for the measurement of 3TC concentrations in serum, performed by [redacted], was based on extraction using solid phase extraction followed by HPLC-UV analysis. The 3TC method was followed to provide analysis of 3TC in serum samples from Study NUCB1004. The method was validated over the range of 10 to 1000 ng/mL.

The bioanalytical method for the measurement of 3TC concentrations in urine, performed by Glaxo Research Laboratories, was based on direction injection with column switching method followed by HPLC-UV analysis. The 3TC method was followed to provide analysis of 3TC in urine samples from Study NUCA1001. The method was validated over the range of 0.5 to 500 μg/mL.

A summary of the validation data that supported application of these bioanalytical methods is provided in Appendix Table 4.

1.4.3.2. Summary of Within Study Quality Control Sample Analysis for Lamivudine Studies

Quality control samples for 3TC were analyzed with each batch of study samples. Performance results of the bioanalytical methods were generated from bioanalytical runs meeting the same run acceptance criteria based upon the predefined requirements that for each QC concentration (low, medium and high) QC results must be within 20%, 15%, and 10%, respectively, of the nominal concentrations. The overall precision (combined within run and between run) and accuracy of the assays for each study are shown in Appendix Table 6.

The precision for 3TC in serum ranged from 3.8% to 10.3% with a bias that ranged from -2.3% to 2.0%. The precision for 3TC in urine ranged from 3.2% to 9.1% with a bias that ranged from -6.9% to -0.7%.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

A tabular summary of the study design, objectives, and treatment arms in each of the biopharmaceutical studies conducted with DTG/3TC FDC, DTG, and 3TC formulations are provided in Appendix Table 7, and a tabular summary of the PK data is provided in Appendix Table 8.

2.1. Pivotal Bioequivalence

2.1.1. Dolutegravir/Lamivudine Fixed-dose Combination

2.1.1.1. Study 204994: Pivotal Bioequivalence Study

Study title: An Open-label, Randomized, Single dose, Crossover, Pivotal Bioequivalence Study of Fixed-dose Combination Tablet(s) of Dolutegravir and Lamivudine versus Dolutegravir and Lamivudine Single Entities and Food Effect Assessment in Healthy Volunteers

Location of Report: m5.3.1.2, Study 204994

Formulations Used:

- DTG/3TC FDC
  - Product code AH ([redacted] tablet formulation)
  - Product code AK ([redacted] tablet formulation)
- DTG (clinical image of Tivicay Tablets, 50 mg, which were also used in the Phase III GEMINI clinical studies 204861 and 205543), 3TC (Epivir tablet)

Methods:

This was a single-center, open-label, randomized, 2-part study. The purpose of the study was to evaluate the BE of experimental FDC tablet(s) of DTG and 3TC relative to co-administration of the SE products in healthy adult subjects. This study also assessed the effect of food on these FDC formulation(s).

Part 1 of the study was an open-label, randomized, 2-period, single-dose, crossover study in 76 healthy adult subjects. The first 16 subjects who completed the first 2 treatment periods and consented to continue, returned for a third treatment period. There was a washout of at least 7 days between each dose of study drug. During the first 2 treatment periods, subjects received either oral FDC [redacted] tablet formulation (DTG 50 mg and 3TC 300 mg) or co-administration of the separate tablet formulations of DTG 50 mg (clinical trial material image) and 3TC 300 mg (Epivir) in the fasted state after at least 10 hours of fasting. During the third treatment period, subjects received a single oral dose of the FDC tablet formulation administered with a high-fat meal. An interim analysis was performed following completion of Part 1 of the study, wherein preliminary PK data from Part 1 were analyzed.

Part 2 of the study incorporated the [redacted] FDC formulation. The study design and reference treatment for Part 2 were similar to those of Part 1.

Study Treatments:

Treatment A	DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet (Reference)
Treatment B	DTG 50 mg/3TC 300 mg FDC [redacted] (Product code AH)
Treatment C	DTG 50 mg/3TC 300 mg FDC [redacted] (Product code AK)

The food effect results of the study are summarized in Section 2.4.1.

Results:

For the [redacted] FDC:

- DTG did not meet the GLS mean ratio BE criteria (90% CI between 0.8 to 1.25). The plasma AUC(0-∞), AUC(0-t), and Cmax following administration of the [redacted] FDC were approximately 27% to 28% higher than those following the co-administration of DTG and Epivir tablets (Table 2, Figure 3, Figure 4).
- 3TC met the BE criteria for all PK parameters (Table 2, Figure 3, Figure 4).

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Table 2 Assessment of Bioequivalence: Statistical Comparison Plasma DTG and 3TC PK Parameters Derived Based on Actual Sampling Times (Part 1, [redacted] FDC)

PK Parameter	Test vs. Reference	Adjusted Geometric Means				Ratio	90% CI of the Ratio
		n	Test	n	Reference		
DTG PK Parameters							
AUC(0-∞) (h*μg/mL)	B vs A	73	54.858	73	43.162	1.2710	(1.1894,1.3582)
AUC(0-t) (h*μg/mL)[a]	B vs A	73	52.856	73	41.436	1.2756	(1.1919,1.3651)
AUC(0-72) (h*μg/mL)[b]	B vs A	73	52.883	73	41.574	1.2720	(1.1898, 1.3599)
Cmax (μg/mL)	B vs A	73	3.082	73	2.407	1.2805	(1.1890,1.3790)
C24 (μg/mL)	B vs A	73	0.806	73	0.638	1.2632	(1.1811,1.3511)
tmax (h)[c]		73	2.00 (0.500, 5.01)	73	2.01 (0.500, 8.01)		
$t_{1/2}$ (h)		73	14.7 (15.3)	73	14.7 (15.6)		
3TC PK Parameters							
AUC(0-∞) (h*μg/mL)	B vs A	73	12.757	73	12.337	1.0341	(1.0097,1.0591)
AUC(0-t) (h*μg/mL)[a]	B vs A	73	12.612	73	12.160	1.0372	(1.0116,1.0634)
AUC(0-72) (h*μg/mL)[b]	B vs A	73	12.612	73	12.165	1.0368	(1.0113, 1.0692)
Cmax (μg/mL)	B vs A	73	3.187	73	2.666	1.1956	(1.1437,1.2498)
C24 (μg/mL)	B vs A	73	0.032	73	0.033	0.9598	(0.9268,0.9941)
tmax (h)[c]		73	1.00 (0.500, 3.500)	73	1.00 (0.500, 4.00)		
$t_{1/2}$ (h)		73	17.7 (22.9)	73	17.6 (27.9)		

Data Source: 204994 In-text Table 17, In-text Table 11, In-text Table 12, Table 2.07, Table 2.08, Table 2.09, Table 2.10

n = number of subjects per treatment with non-missing value.

a. t = t_{last}. Median t_{last} ~72 h for all treatments.

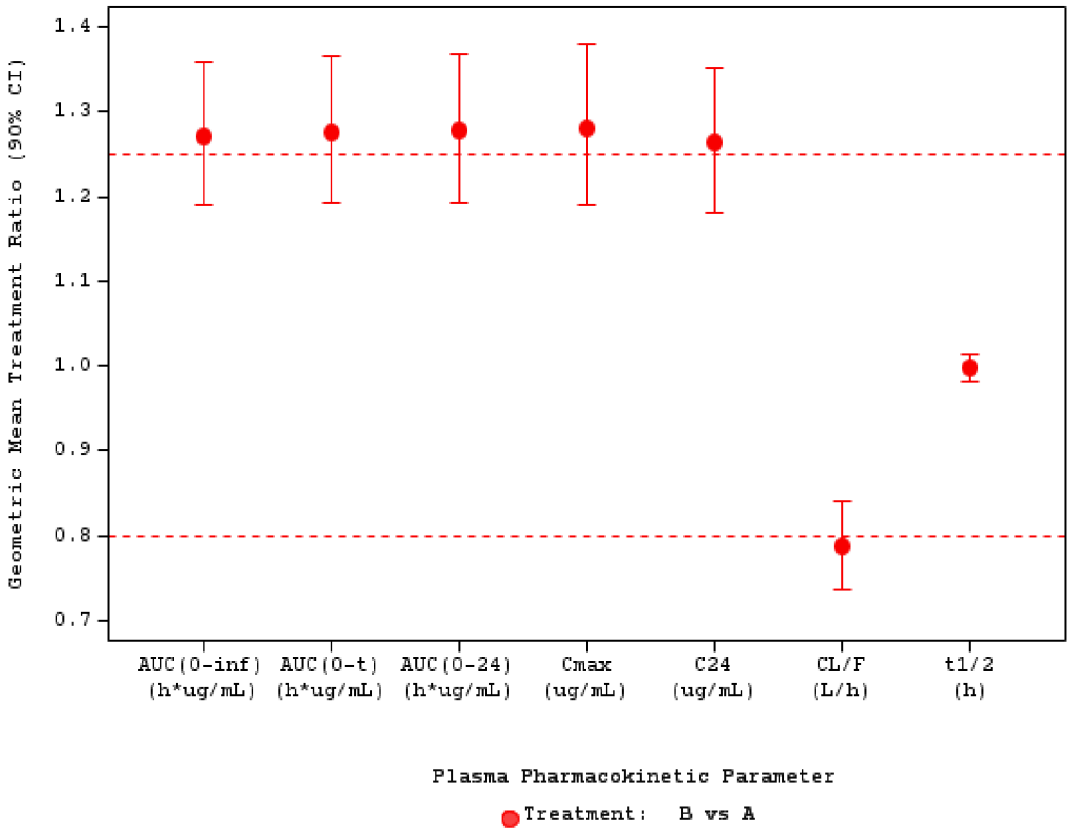
b. Ad-hoc analysis

c. Expressed as median and range

Treatment A = DTG 50 mg (clinical image) + Epivir 300 mg (fasted)

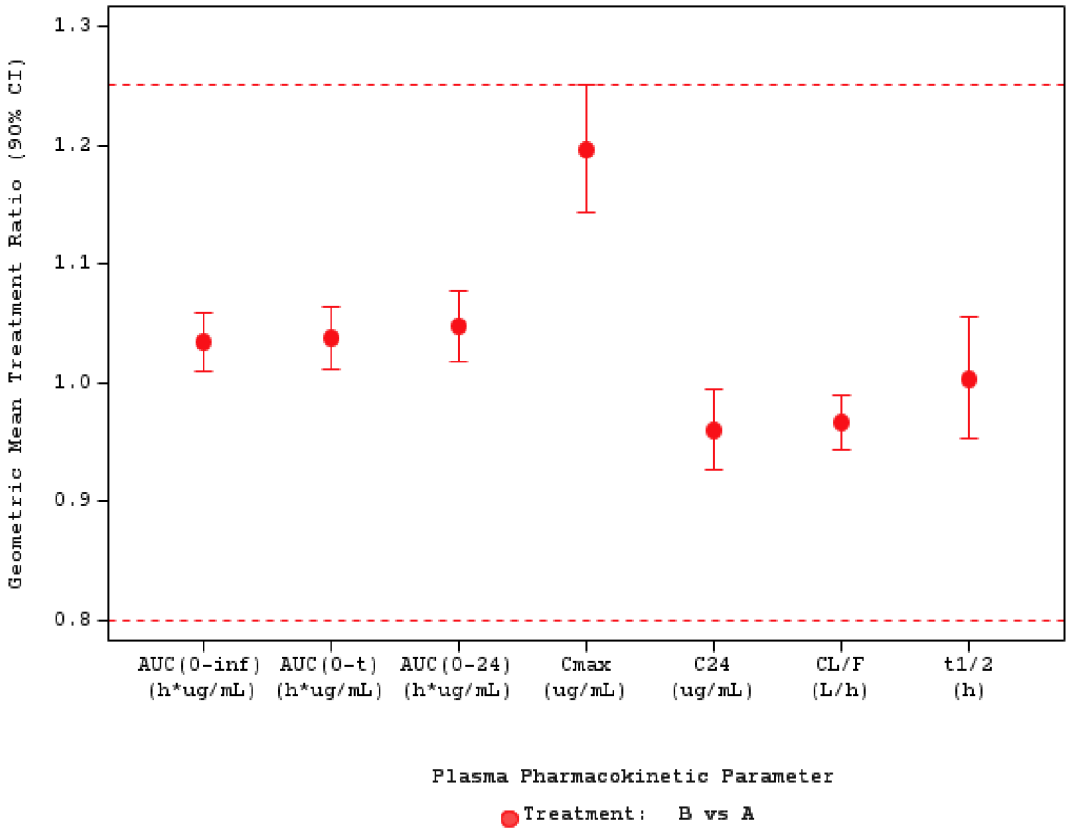
Treatment B = DTG 50 mg and 3TC 300 mg [redacted] FDC (fasted)

Figure 3 Geometric Mean Ratios and 90% CIs for DTG plasma PK Parameters for Bioequivalence Assessment (Part 1, [redacted] FDC)[a]



Data Source: 204994 In-text Figure 3
a. The ad-hoc sensitivity analysis for DTG AUC(0-72) (See Table 2) was not included in this figure
Treatment A = DTG 50 mg (clinical image) + Epivir 300 mg (fasted)
Treatment B = DTG 50 mg and 3TC 300 mg [redacted] FDC (fasted)

Figure 4 Geometric Mean Ratios and 90% CIs for 3TC plasma PK Parameters for Bioequivalence Assessment (Part 1, [redacted] FDC)[a]



Data Source: 204994 In-text Figure 4
a. The ad-hoc sensitivity analysis for 3TC AUC(0-72) (See Table 2) was not included in this figure
Treatment A = DTG 50 mg (clinical image) + Epivir 300 mg (fasted)
Treatment B = DTG 50 mg and 3TC 300 mg [redacted] FDC (fasted)

For the [redacted] FDC:

- DTG met the GLS mean ratio BE criteria (90% CI between 0.8 to 1.25) for AUC(0-∞) and Cmax. The GLS mean ratio upper limit of the 90% CI for AUC(0-t) was slightly above the 1.25 limit for BE (Table 3, Figure 5, Figure 6). However, an ad-hoc sensitivity analysis conducted to exclude 2 subjects who had a BLLQ concentration at the last sample collection time, showed that DTG AUC(0-t) met the GLS mean ratio BE criteria. Furthermore, an additional ad-hoc bioequivalence analysis showed that AUC(0-72) met the BE criteria.
- 3TC met the BE criteria for AUC(0-∞) and AUC(0-t). However, 3TC Cmax was 31.8% higher for the [redacted] FDC compared with the reference formulation (Table 3, Figure 5, Figure 6).

Table 3 Assessment of Bioequivalence: Statistical Comparison of Plasma DTG and 3TC PK Parameters Derived Based on Actual Sampling Times (Part 2, [redacted] FDC)

PK Parameter	Test vs. Reference	Adjusted Geometric Means				Ratio	90% CI of the Ratio
		n	Test	n	Reference		
DTG PK Parameters							
AUC(0-∞) (h*μg/mL)	C vs A	74	54.559	74	47.239	1.1550	(1.0699,1.2468)
AUC(0-t) (h*μg/mL)[a]	C vs A	74	52.337	74	45.204	1.1578	(1.0718,1.2507)
	C vs A[b]	72	52.353	72	46.109	1.1354	(1.0527, 1.2246)
AUC(0-72) (h*μg/mL)[c]	C vs A	74	52.361	74	45.277	1.1565	(1.0710, 1.2487)
Cmax (μg/mL)	C vs A	74	2.913	74	2.553	1.1410	(1.0533,1.2361)
C24 (μg/mL)	C vs A	74	0.807	74	0.706	1.1425	(1.0597,1.2317)
tmax (h)[d]		74	2.50 (0.500, 6.00)	74	2.50 (0.500, 5.01)		
$t_{1/2}$ (h)		74	15.0 (18.2)	74	15.1(17.8)		
3TC PK Parameters							
AUC(0-∞) (h*μg/mL)	C vs A[e]	73	13.587	73	12.772	1.0638	(1.0416,1.0865)
	C vs. A[f]	74	13.562	73	12.753	1.0635	(1.0413,1.0861)
AUC(0-t) (h*μg/mL)[a]	C vs A	74	13.355	74	12.479	1.0702	(1.0464,1.0946)
	C vs A[g]	72	13.409	72	12.526	1.0705	(1.0460, 1.0956)
AUC(0-72) (h*μg/mL)[c]	C vs A	74	13.358	74	12.482	1.0702	(1.0464, 1.0946)
Cmax (μg/mL)	C vs A	74	3.219	74	2.443	1.3176	(1.2616,1.3760)
C24 (μg/mL)	C vs A	74	0.035	74	0.037	0.9548	(0.9299,0.9804)
tmax (h)[d]		74	1.00 (0.500, 3.50)	74	1.00 (0.500, 4.00)		
$t_{1/2}$ (h)		74	18.8 (27.7)	74	19.2 (29.5)		

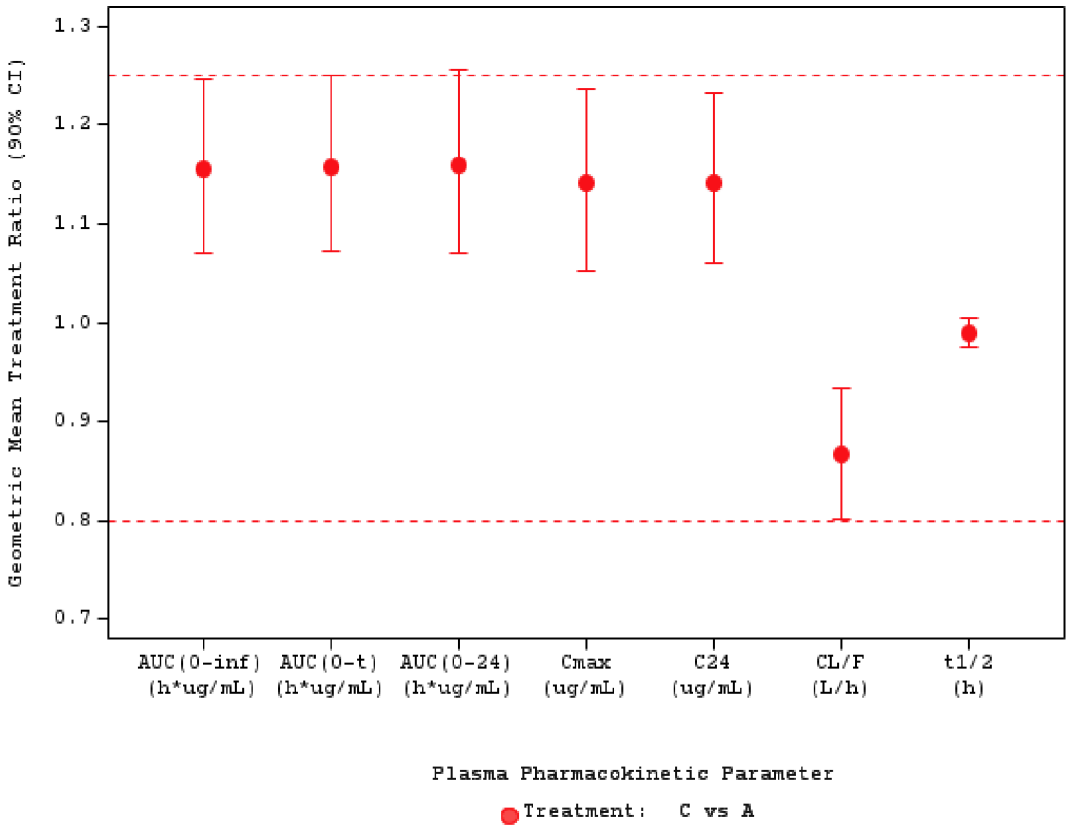
Data Source: 204994 In-text Table 19, In-text Table 14, In-text Table 15, Table 2.107, Table 2.108, Table 2.109, Table 2.110

n = number of subjects per treatment with non-missing value.

a. t = t_{last}. Median t_{last} ~72 h for all treatments.
b. Subjects [redacted] (Treatment A, Period 2) and [redacted] (Treatment A, Period 1) had a non-measurable concentration at 72h time point and tlast = 48h. An ad-hoc sensitivity analysis was conducted by excluding the subjects from analysis.
c. Ad-hoc analysis
d. Expressed as median and range
e. Subject [redacted] (Treatment A, Period 2) did not conform to the prescribed criteria for acceptance (i.e., lambda_z time duration <2x the calculated $t_{1/2}$ and >20% AUC(0-∞) extrapolated), therefore it was excluded from analysis.
f. Sensitivity analysis was conducted by including Subject [redacted] Treatment C, Period 1 data.
g. Subjects [redacted] (Treatment A, Period 1) and [redacted] (Treatment C, Period 2) had a non-measurable concentration at 72h time point and tlast = 48h. An ad-hoc sensitivity analysis was conducted by excluding the subjects from analysis.

Treatment A = DTG 50 mg (clinical image) + Epivir 300 mg (fasted)
Treatment C = DTG 50 mg and 3TC 300 mg [redacted] FDC (fasted)

Figure 5 Geometric Mean Ratios and 90% CIs for DTG plasma PK Parameters for Bioequivalence Assessment (Part 2, [redacted] FDC)[a, b]



Data Source: 204994 In-text Figure 5

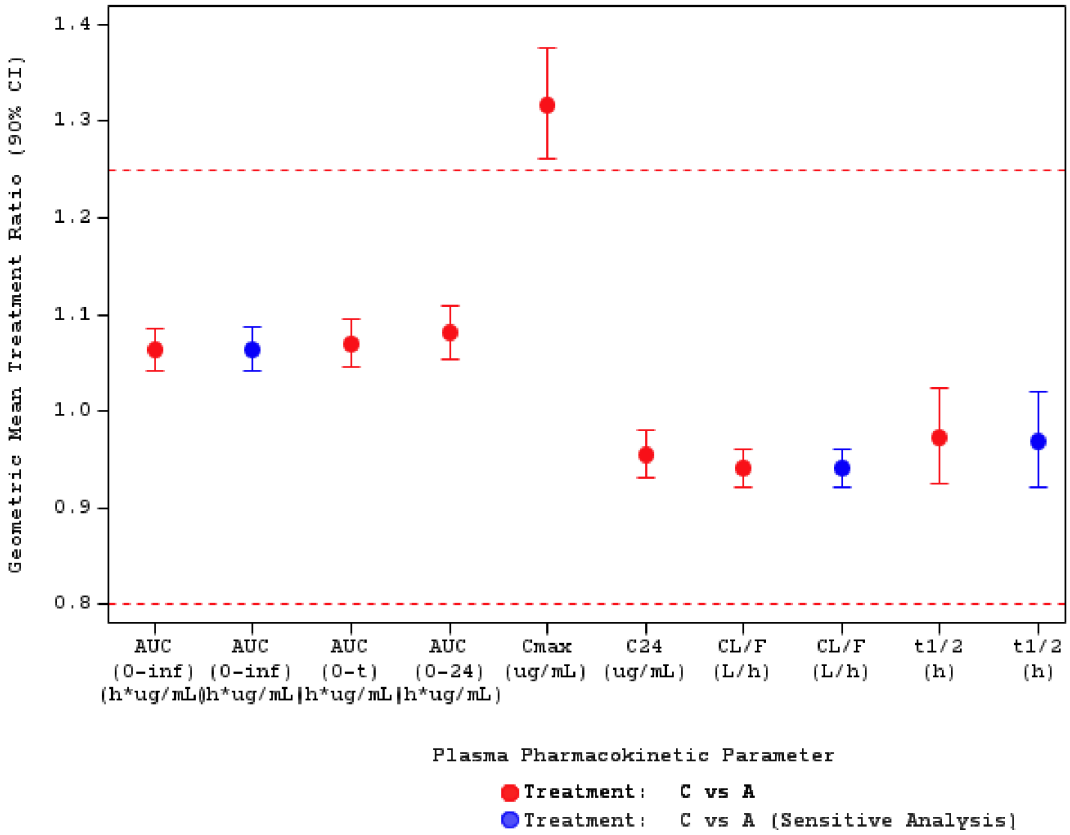
a. The ad-hoc sensitivity analysis for DTG AUC(0-t) (See Table 3) was not included in this figure

b. The ad-hoc sensitivity analysis for DTG AUC(0-72) (See Table 3) was not included in this figure

Treatment A = DTG 50 mg (clinical image) + Epivir 300 mg (fasted)

Treatment C = DTG 50 mg and 3TC 300 mg [redacted] FDC (fasted)

Figure 6 Geometric Mean Ratios and 90% CIs for 3TC plasma PK Parameters for Bioequivalence Assessment (Part 2, [redacted] FDC)[a, b]



Data Source: 204994 In-text Figure 6

a. Subject [redacted] (Treatment A, Period 2) did not conform to the prescribed criteria for acceptance (i.e. lambda_z time duration <2x the calculated t1/2 and >20% AUC(0-∞) extrapolated), therefore it was excluded from analysis (red). A sensitivity analysis was conducted by including Subject [redacted] Treatment C, Period 1 data (blue).

b. The ad-hoc sensitivity analysis for 3TC AUC(0-t) (See Table 3) was not included in this figure

Treatment A = DTG 50 mg (clinical image) + Epivir 300 mg (fasted)

Treatment C = DTG 50 mg and 3TC 300 mg [redacted] FDC (fasted)

Conclusions:

In fasted state, the [redacted] FDC tablet formulation of DTG 50 mg and 3TC 300 mg was bioequivalent for 3TC, however DTG showed higher AUC(0-∞), AUC(0-t), and Cmax compared with the co-administered DTG and Epivir tablets. This tablet was not selected for further development.

In fasted state, the [redacted] FDC formulation of DTG 50 mg and 3TC 300 mg was bioequivalent for DTG AUC(0-∞), AUC(0-t) (based on ad-hoc sensitivity analysis), AUC(0-72) (ad-hoc analysis) and Cmax, and for 3TC AUC(0-∞) and AUC(0-t). However, 3TC Cmax was 31.8% higher than that of Epivir. Based on the previously reported safety profile of higher dose 3TC, the higher Cmax is not considered clinically relevant (See module 2.7.4, Section 5.6.2). Therefore, the PK of the [redacted] FDC provide

an acceptable bridge to the co-administration of Tivicay and Epivir tablets in Phase III trials. The [redacted] FDC was selected for further clinical development.

2.2. Absolute Bioavailability

2.2.1. Dolutegravir/Lamivudine Fixed-dose Combination

No absolute (IV/oral) BA studies have been carried out with the DTG/3TC FDC formulation.

2.2.2. Dolutegravir Single Entity

No absolute (IV/oral) BA studies have been carried out with the DTG SE.

2.2.3. Lamivudine Single Entity

The conclusions of the SE clinical pharmacology studies are summarized in Appendix Table 1.

The absolute bioavailability of 3TC was reported in 2 studies. Study NUCB1001 was an open-label, cross-over study in which 5 dosing groups (0.25, 1, 2, 4, 8 mg/kg) each received (as single doses) oral and IV 3TC in HIV infected patients. Following oral dosing, absolute bioavailability was on average approximately 80 to 85%. Study NUCA1003 was an open-label, single-dose, 4-way crossover study in HIV infected patients in which oral 3TC formulations of a solution (1 mg/mL, 10% EtOH), capsule, and tablet administered at a 100-mg single dose showed absolute bioavailability of 87%, 88%, and 86%, respectively.

2.3. Relative Bioavailability

2.3.1. Dolutegravir/Lamivudine Fixed-dose Combination

2.3.1.1. Study 204993: Relative Bioavailability of Fixed-dose Combinations of Dolutegravir and Lamivudine

Study title: A Phase I, Relative Oral Bioavailability Study of Different Fixed Dose Combinations of Dolutegravir and Lamivudine in Healthy Subjects

Location of Report: m5.3.1.2, Study 204993

Formulations Used:

- DTG/3TC FDC:
  - Formulations: Product Code AA and AB
- DTG (clinical trial material image tablet, Tivicay), 3TC (Epivir)

Methods: This study was conducted as a randomized, open label, three-way crossover design in 30 subjects to evaluate the relative bioavailability of 2 experimental FDC formulations. There were 6 treatment sequences, each consisting of 3 periods with the

following single-dose treatments (A, B, and C, as shown below) taken in a different order as ABC, BCA, CAB, ACB, BAC, and CBA. Each subject was to receive the reference Treatment A, DTG 50 mg and 3TC 300 mg, administered as SE tablets, and 2 experimental [redacted] DTG/3TC FDC tablets (Treatment B and C); under a fasted state over 3 treatment periods in 6 sequences in a randomized fashion. The reference and test formulations were administered to subjects after at least a 10-hour fast. There was a washout period of 7 days between dosing periods.

Study Treatments:

Treatment A DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet (Reference)
Treatment B GSK3515864 (Dolutegravir/Lamivudine) Tablets, 50 mg/300 mg (Product Code AA)
Treatment C GSK3515864 (Dolutegravir/Lamivudine) Tablets, 50 mg/300 mg (Product Code AB)

Results: DTG systemic exposures from Treatment B appeared higher, whereas those from Treatment C were similar to the reference treatment of DTG 50 mg (clinical image) and Epivir 300 mg administered as separate tablets (Table 4).

Table 4 Summary of Plasma DTG PK Parameters[a] (PK Population)

DTG PK Parameter	Treatment		
	A (n=30)	B (n=29)	C (n=29)
AUC(0-∞) (μg.h/mL)	51.6 (45.5)	57.6 (31)	52.2 (25.6)
AUC(0-t) (μg.h/mL)	49.5 (45.5)	55.4 (30.4)	50 (25)
Cmax (μg/mL)	2.64 (41.6)	3.01 (31.3)	2.69 (26.7)
CL/F (L/h)	0.97 (45.5)	0.87 (31)	0.96 (25.6)
C24 (μg/mL)	0.80 (45.1)	0.88 (30)	0.81 (25.9)
t½ (h)	15.1 (13.7)	14.9 (13.2)	15.1 (17.3)
tmax (h)	2 (0.5, 7)	1.51 (0.5, 5.01)	2.01 (0.5, 5.0)
tlag (h)	0.0 (0.0, 0.5)	0.0 (0.0, 0.25)	0.0 (0.0, 0.25)

Data Source: 204993 In-text Table 10
a. Values denote geometric mean (CVb%) except for tmax and tlag which are presented as median (range).
Treatment A: DTG 50 mg tablet (clinical image) plus Epivir 300 mg tablet
Treatment B: GSK3515864 (Dolutegravir/Lamivudine) Tablet, 50 mg/ 300 mg Product Code AA
Treatment C: GSK3515864 (Dolutegravir/Lamivudine) Tablet, 50 mg/ 300 mg Product Code AB

3TC AUC appeared similar across all treatments. However, 3TC Cmax from Treatments B (FDC Product code AA) and C (FDC Product code AB) appeared higher than the Cmax from the reference tablet formulations of DTG 50 mg (clinical image) and Epivir 300 mg (Treatment A) (Table 5).

Table 5 Summary of Plasma 3TC PK Parameters[a] (PK Population)

3TC PK Parameter	Treatment		
	A (n=30)	B (n=29)	C (n=29)
AUC(0-∞) (μg.h/mL)[b]	14.9 (25.4)	15.6 (26.2)	15.2 (25)
AUC(0-t) (μg.h/mL)	14.5 (25.1)	14.7 (28.4)	15 (24.2)
Cmax (μg/mL)	2.68 (23.8)	3.14 (28.2)	3.29 (23.4)
CL/F (L/h)[b]	20.1 (25.4)	19.2 (26.2)	19.8 (25)
C24 (μg/mL)	0.04 (40.3)	0.04 (39.9)	0.04 (38.6)
t½ (h)[b]	18.8 (18.3)	18.5 (17.2)	19.3 (24.2)
tmax (h)	1.51 (0.5, 4.0)	1.0 (0.5, 2.0)	1.0 (0.5, 3.0)
tlag (h)	0.0 (0.0, 0.0)	0.0 (0.0, 0.25)	0.0 (0.0, 0.25)

Data Source: 204993 In-text Table 11

a. Values denote geometric mean (CVb%) except for tmax and tlag which are presented as median (range).

b. AUC(0-∞), CL/F and t½: n=28 for Treatment A, n=26 for Treatment B, n=27 for Treatment C. 5 subjects ([redacted], Treatments A, B; [redacted] Treatments A, C; [redacted], Treatment C; and both [redacted], [redacted] Treatment B) were excluded because the duration for the calculation of λz (apparent terminal slope) was <2x the calculated λz and/or the R squared adjusted was < 0.85.

Treatment A: DTG 50 mg tablet (clinical image) plus Epivir 300 mg tablet
Treatment B: GSK3515864 (Dolutegravir/Lamivudine) Tablet, 50mg/ 300mg Product Code AA
Treatment C: GSK3515864 (Dolutegravir/Lamivudine) Tablet, 50mg/ 300mg Product Code AB

The results from the statistical comparisons for DTG showed that the plasma AUC(0-∞) and Cmax of DTG following Treatment B (FDC Product Code AA) administration were approximately 12.2% and 14.5% higher than those following the co-administration of the reference tablet formulations of DTG 50 mg and Epivir 300 mg (Treatment A), respectively (Table 6). In addition, the upper bounds for the 90% CIs were outside the standard BE interval. Plasma AUC(0-∞) and Cmax of DTG following Treatment C (FDC Product Code AB) administration were similar to those following the co-administration of the separate tablets of DTG and Epivir, and the upper and lower bounds for the 90% CIs were within the standard BE interval.

For 3TC, the results from the statistical analyses indicate that the AUC(0-∞) from administration of both FDC tablet formulations were similar to those from reference tablet formulations of DTG 50 mg and Epivir 300 mg, and the upper and lower bounds of the 90% CI were within the standard BE interval (Table 6). However, the Cmax from FDC formulations AA and AB were, 17.8% and 23.1%, respectively, higher than those from the reference tablets, and the upper bounds of the 90% CIs were outside the standard BE interval.

Table 6 Statistical Comparison of Selected Plasma Dolutegravir and Lamivudine PK Parameters (PK Population)

	Ratio of GLS Means (90% CI) (Test vs. Reference)	
	B (n=29) vs A (n=30)	C (n=29) vs A (n=30)
DTG PK Parameters		
AUC(0-∞) (μg.h/mL)	1.122 [1.005, 1.252]	1.015 [0.909, 1.132]
Cmax (μg/mL)	1.145 [1.025, 1.278]	1.020 [0.913, 1.140]
C24 (μg/mL)	1.116 [1.001, 1.245]	1.016 [0.911, 1.133]
3TC PK Parameters		
AUC(0-∞) (μg.h/mL)[a]	1.033 [0.991, 1.078]	1.030 [0.988, 1.074]
Cmax (μg/mL)	1.178 [1.080, 1.284]	1.231 [1.129, 1.342]
C24 (μg/mL)	0.943 [0.894, 0.996]	0.931 [0.882, 0.983]

Data Source: 204993 In-text Table 12

a. For 3TC, AUC(0-∞), CL/F and t½: n=28 for treatment A, n=26 for Treatment B, n=27 for Treatment C. 5 subjects ([redacted], Treatments A, B; [redacted] Treatments A, C; [redacted], Treatment C; and both [redacted], [redacted] Treatment B) were excluded because the duration for the calculation of λ_z (apparent terminal slope) was <2x the calculated λ_z and/or the R squared adjusted was < 0.85.

Treatment A: DTG 50 mg tablet (clinical image) plus Epivir 300 mg tablet (Reference)
Treatment B: GSK3515864 (Dolutegravir/Lamivudine) Tablet, 50mg/ 300mg Product Code AA
Treatment C: GSK3515864 (Dolutegravir/Lamivudine) Tablet, 50mg/ 300mg Product Code AB
GLS = Geometric least-squares

Conclusions:

- Following administration of FDC formulation AA, DTG plasma exposures, AUC(0-∞) and Cmax, were approximately 12.2% and 14.5% higher than those following the co-administration of DTG 50 mg and Epivir 300 mg, respectively
- Following administration of FDC formulation AB, DTG plasma exposures, AUC(0-∞) and Cmax, were similar to those following the co-administration of DTG 50 mg and Epivir 300 mg, respectively.
- Following FDC formulation AA administration, 3TC AUC(0-∞) was similar to AUC(0-∞) following co-administration of DTG 50 mg and Epivir 300 mg, however 3TC Cmax was 17.8% higher.
- Following FDC formulation AB administration, 3TC AUC(0-∞) was similar to AUC(0-∞) following the co-administration of DTG 50 mg and Epivir 300 mg, however 3TC Cmax was 23.1% higher.

2.4. Effect of Food on Bioavailability

The effect of food on the BA of the proposed commercial DTG/3TC FDC tablet formulation was evaluated in Study 204994.

2.4.1. Dolutegravir/Lamivudine Fixed-dose Combination

2.4.1.1. Study 204994: Pivotal Bioequivalence Study

Study title: An Open-label, Randomized, Single dose, Crossover, Pivotal Bioequivalence Study of Fixed-dose Combination Tablet(s) of Dolutegravir and Lamivudine versus Dolutegravir and Lamivudine Single Entities and Food Effect Assessment in Healthy Volunteers

Location of Report: m5.3.1.2, Study 204994

Formulations Used:

- DTG/3TC FDC
  - Product code AH ([redacted] tablet formulation with a composition identical to that of Product Code AA tablet used in study 204993 with exception of the using a different target level of film coat).
  - Product code AK ([redacted] tablet formulation)
- DTG (clinical trial material image tablet, Tivicay), 3TC (Epivir tablet)

Methods:

This was a single-center, open-label, randomized, 2-part study. The purpose of the study was to evaluate the BE of experimental FDC tablet(s) of DTG and 3TC relative to co-administration of the SE products in healthy adult subjects. This study also assessed the effect of food on these FDC formulation(s). The study design and methods are described in Section 2.1.1.

Study Treatments:

Treatment A	DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet
Treatment B	DTG 50 mg/3TC 300 mg FDC monolayer formulation (Product code AH)
Treatment C	DTG 50 mg/3TC 300 mg FDC [redacted] formulation (Product code AK)

The BE results of the study are summarized in Section 2.1.1.

Results:

The food effect analysis for selected DTG and 3TC parameters showed that administration of the [redacted] FDC with a high-fat meal results in a modest increase (~15%) in DTG AUC(0-∞) and AUC(0-t) and in a modest decrease in 3TC Cmax of ~ 30% (Table 7).

Table 7 Assessment of Food Effect: Statistical Comparison of Plasma DTG and 3TC PK Parameters Derived Based on Actual Sampling Times (Part 1, [redacted] FDC)

PK Parameter	Test vs. Reference	Adjusted Geometric Means				Ratio	90% CI of the Ratio
		n	Test	n	Reference		
DTG PK Parameters							
AUC(0-∞) (h*μg/mL)	B fed vs B	16	71.978	16	62.344	1.1545	(1.0208,1.3058)
AUC(0-t) (h*μg/mL)[a]	B fed vs B	16	69.256	16	60.321	1.1481	(1.0154,1.2982)
Cmax (μg/mL)	B fed vs B	16	3.790	16	3.507	1.0808	(0.9527,1.2261)
C24 (μg/mL)	B fed vs B	16	1.192	16	0.922	1.2929	(1.1281,1.4819)
tmax (h)[b]		16	5.00 (2.00, 12.0)	16	1.50 (0.503, 5.00)		
$t_{1/2}$ (h)		16	14.5 (13.3)	16	14.5 (8.89)		
3TC PK Parameters							
AUC(0-∞) (h*μg/mL)	B fed vs B	16	12.867	16	13.436	0.9577	(0.9126,1.0049)
AUC(0-t) (h*μg/mL)[a]	B fed vs B	16	12.649	16	13.282	0.9524	(0.9086,0.9983)
Cmax (μg/mL)	B fed vs B	16	2.513	16	3.541	0.7097	(0.6474,0.7779)
C24 (μg/mL)	B fed vs B	16	0.037	16	0.030	1.2015	(1.1074,1.3036)
tmax (h)[b]		16	3.50 (1.01, 5.00)	16	1.00 (0.500, 2.00)		
$t_{1/2}$ (h)		16	19.1(30.7)	16	18.4 (21.9)		

Data Source: 204994 In-text Table 18. In-text Table 13, Table 2.11, Table 2.12
n = number of subjects per treatment with non-missing value.
a. t = t_{last}. Median t_{last} ~72 h for all treatments.
b. Expressed as median and range
Treatment B = DTG 50 mg and 3TC 300 mg [redacted] FDC (fasted)
Treatment B fed = DTG 50 mg and 3TC 300 mg [redacted] FDC (high-fat meal)

The food effect analysis for selected DTG and 3TC parameters showed that administration of the [redacted] FDC with a high-fat meal results in a modest increase (~32%) in DTG AUC(0-∞) and AUC(0-t) and in a modest decrease in 3TC Cmax of ~ 30% (Table 8).

Table 8 Assessment of Food Effect: Statistical Comparison of Plasma DTG and 3TC PK Parameters Derived Based on Actual Sampling Times (Part 2, [redacted] FDC)

PK Parameter	Test vs. Reference	Adjusted Geometric Means				Ratio	90% CI of the Ratio
		n	Test	n	Reference		
DTG PK Parameters							
AUC(0-∞) (h*μg/mL)	C fed vs C	16	76.428	16	57.656	1.3256	(1.1837,1.4845)
AUC(0-t) (h*μg/mL)[a]	C fed vs C	16	72.755	16	55.218	1.3176	(1.1750,1.4775)
Cmax (μg/mL)	C fed vs C	16	3.752	16	3.101	1.2096	(1.0521,1.3908)
C24 (μg/mL)	C fed vs C	16	1.227	16	0.835	1.4690	(1.3009,1.6588)
tmax (h)[b]		16	5.00 (1.01, 8.00)	16	1.50 (0.751, 3.00)		
$t_{1/2}$ (h)		16	15.5 (16.0)	16	15.3 (17.3)		
3TC PK Parameters							
AUC(0-∞) (h*μg/mL)	C fed vs C	16	13.344	16	14.642	0.9114	(0.8658,0.9593)
AUC(0-t) (h*μg/mL)[a]	C fed vs C	16	13.092	16	14.471	0.9048	(0.8592,0.9528)
Cmax (μg/mL)	C fed vs C	16	2.445	16	3.582	0.6826	(0.5861,0.7950)
C24 (μg/mL)	C fed vs C	16	0.042	16	0.035	1.1935	(1.1142,1.2785)
tmax (h)[b]		16	2.75 (1.00, 6.00)	16	1.00 (0.503, 2.51)		
$t_{1/2}$ (h)		16	19.8 (20.4)	16	18.1 (24.4)		

Data Source: 204994 In-text Table 20, In-text Table 16, Table 2.111, Table 2.112
n = number of subjects per treatment with non-missing value.
a. $t = t_{last}$. Median t_{last} ~ 72 h for all treatments.
b. Expressed as median and range
Treatment C= DTG 50 mg and 3TC 300 mg [redacted] FDC (fasted)
Treatment C fed = DTG 50 mg and 3TC 300 mg [redacted] FDC (high-fat meal)

Conclusions:

Administration of the [redacted] or [redacted] FDC tablets with a high-fat meal resulted in higher plasma DTG AUC(0-∞) and AUC(0-t) and lower plasma 3TC Cmax. The magnitude of the food effect on DTG and 3TC was no greater than that observed in prior food effect studies of the individual components and is not considered clinically significant.

2.4.2. Dolutegravir Single Entity

The conclusions of the SE clinical pharmacology studies are summarized in Appendix Table 1.

Study ING113674 was designed to assess the RBA of three different tablet formulations of DTG 50 mg and the effect of food (low-, moderate-, high-fat meals) on the BA of the DTG formulation selected for Phase III studies and commercialization. This study is supportive to the DTG/3TC FDC submission as it shows the effect of different types of meals on the PK of DTG; the conclusions are summarized in Appendix Table 1. In summary, food increased systemic exposure of DTG by 33% to 66%.

2.4.3. Lamivudine Single Entity

The conclusions of the SE clinical pharmacology studies are summarized in Appendix Table 1.

Study NUCA1001 was a randomized, open-label, single-dose, two-way crossover study in HIV-infected patients to determine the effect of food on the PK of 3TC. This study is supportive to the DTG/3TC FDC submission as it shows the effect of a standard high-fat meal on the PK of 3TC; the conclusions are summarized in Appendix Table 1. This study demonstrated that 3TC AUC was unchanged, while Cmax was 47% lower when 3TC was administered with a standard high-fat meal.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. In Vitro Dissolution and In Vivo Bioavailability

The physicochemical and biological properties of DTG sodium and 3TC are discussed in m3.2.P.2.2., Section 3.

DTG sodium is considered a poorly soluble compound, demonstrating low solubility over the physiological pH range (pH 1 to 7.4). DTG sodium was determined to have high passive membrane permeability (333 nm/s at pH 7.4). The absorptive membrane permeabilities were also high in the presence of FaSSIF at pH 7.4 and pH 5.5 (P7.4[abs] value of 253 nm/s and a P5.5[abs] value of 265 nm/s, respectively). Based on solubility and permeability determinations, DTG sodium is classified as a BCS Class 2. The absolute bioavailability of DTG sodium has not been determined.

3TC is highly soluble and is classified as BCS Class 3 (m3.2.P.2.2, Section 3.2.3). Previous PK studies demonstrated that 3TC is a well-absorbed drug with an absolute bioavailability of 86% in adults [Yuen, 1995].

In study 204994, bioequivalence was established for DTG AUC and Cmax and 3TC AUC. However, the Cmax for 3TC from the DTG/3TC FDC was approximately 32% higher and was accompanied by an earlier tmax, with no difference in the 3TC elimination t1/2 between the two formulations. Collectively, these findings reflect differences in the rate, but not extent of 3TC absorption. The following factors have been considered as potential explanations for the faster 3TC rate of absorption from the DTG/3TC FDC, but, the cause remains unexplained:

- **Formulation & 3TC Solubility –** [redacted] in the DTG/3TC FDC are [redacted].
  It is unlikely the DTG/3TC FDC formulation contributed to a faster rate of absorption due to improved solubility of 3TC relative to the reference given:
  - 3TC is highly soluble over the physiologic pH range and the dose of 300 mg can be solubilized in <5 mL.

- Bioenhancement was not observed as the AUC for 3TC was similar in both the reference arm and the test formulation indicating the extent of absorption was the same.

- **Formulation and 3TC Dissolution** - It is unlikely the differences in the rate of absorption are due to differences in 3TC dissolution given:

  - DTG/3TC Tablets demonstrate rapid and complete 3TC dissolution within 10 minutes using the intended [redacted] dissolution method (Figure 2). The dissolution of 3TC from the DTG/3TC FDC was also evaluated using BCS Biowaiver media at pH 1.2, 4.5, and 6.8, thereby spanning the gastro-intestinal pH range, and USP Apparatus [redacted] at [redacted] rpm in [redacted] mL. At each pH, greater than 85% of 3TC dissolved in 15 minutes (m3.2.P.5.3, Section 1.4.2) for both the DTG/3TC FDC and EPIVIR reference tablets. Therefore, according to the BCS, the 3TC component of DTG/3TC Tablets can be classified as very rapidly dissolving.

  - A RBA study demonstrated that the 100 mg capsule, 100 mg tablet, and a 1 mg/mL alcohol-free oral solution were equivalent for AUC and Cmax [Yuen, 1995] indicating that disintegration and dissolution are likely not rate limiting factors for the absorption of 3TC.

- **Permeability**: An evaluation of permeability was conducted in Caco-2 cells to determine if DTG could significantly alter the permeability of 3TC (m2.6.5**)**. The permeability of lamivudine in Caco-2 cells was similar in both the presence and absence of dolutegravir and does not provide an explanation for the elevated Cmax.

- **Elimination:** In Study 204994, the 3TC elimination half-life was similar between the FDC and reference (Table 3) indicating that the higher3TC C_{max} was not related to differences in the 3TC elimination rate between the two formulations. The lack of an elimination-based interaction is also supported by the following:

  - No clinically significant interaction was expected given the different routes of elimination. The primary route of elimination of 3TC is renal excretion, whereas the primary route of elimination of DTG is metabolism in the liver by UGT1A1 and CYP3A (minor) enzymes. (m2.7.2, Section 3.1.6.2).

  - DTG and 3TC have minimal effect on drug metabolizing enzymes or transporters and no clinically relevant drug interaction has been observed between DTG and 3TC. This is supported by the cross-study comparison demonstrating that the PK of 3TC when given as ABC/3TC FDC tablet co-administered with DTG (Study ING114580) were similar to those obtained when given as ABC/3TC FDC alone (Study CAL10001).

  - A drug interaction that impacted elimination of either DTG or 3TC would be expected to occur whether administered as the DTG/3TC FDC or as co-administered single entities (m2.7.2, Section 3.1.6.2).

In conclusion, while a number of factors to explain the higher Cmax have been evaluated, the exact cause has not been determined. The higher 3TC Cmax, which reflects differences in the rate of absorption but not extent of absorption, does not significantly affect patient safety and antiviral efficacy based on historical clinical PK, efficacy and

safety data at higher 3TC doses/exposures (m2.7.2 Section 3.3.1; m2.7.4 Section 5.6.2) and therefore serves as an acceptable bridge to the Phase 3 trials which co-administered the single entity formulations without regard to meal intake.

3.2. Dosing Relative to Food

Co-administration of DTG/3TC FDC with a high-fat meal increased DTG AUC for the [redacted] and [redacted] tablets by ~15% and ~32%, respectively, compared with the fasted state. In addition, a high-fat meal resulted in a ~21% increase in DTG Cmax for the [redacted] FDC. The magnitude of the increases in DTG exposure is no greater than that observed with DTG single entity (Study ING113674) and is not considered clinically significant.

The 3TC Cmax for both the [redacted] and [redacted] FDCs was ~30% lower in the presence of a high-fat meal compared with the fasted state, while the AUC remained unchanged. The magnitude of 3TC Cmax decrease in the presence of a high-fat meal is no greater than that observed in previous investigations of food effect on 3TC (Study NUCA1001) and are not considered clinically significant.

The food effect assessment on the FDC formulations and the cross-study comparison with DTG and 3TC single entity food effect studies support the recommendation that the DTG/3TC FDC may be taken with or without food. This is consistent with the prescribing information for the DTG and 3TC single entities.

For additional information on the biopharmaceutics and food effects studies of the individual DTG product, please refer to the clinical pharmacology information in the current Package Insert [Tivicay Package Insert, 2017] for Tivicay (DTG) tablets.

For results from the biopharmaceutics and food effects studies of the individual 3TC product, please refer to the clinical pharmacology information in the current Package Insert [Epivir Package Insert, 2018].

3.3. Clinical Significance of Higher 3TC Cmax

The 3TC Cmax for the proposed commercial DTG/3TC [redacted] FDC was ~32% higher compared with Epivir when administered concurrently with DTG, which reflects differences in the rate of absorption but not the extent of absorption. This higher Cmax is not clinically significant (does not significantly affect patient safety and efficacy) for the following considerations:

- The actual magnitude (geometric mean) of 3.22 μg/mL for DTG/3TC FDC 3TC Cmax was similar to the magnitude of 3.09 μg/mL, 3.28 μg/mL and 3.15 μg/mL, observed in other single dose Epivir 300 mg studies: NUCA1006, NUCB1004 (Appendix Table 8) and NUCA1005 (module 2.7.2, Appendix Table 5), respectively.
- Similar 3TC Cmax values (3.67 μg/mL and 3.42 μg/mL) were observed in several fasted bioequivalence studies for generic 3TC formulations (EMA, 2009; MHRA, 2016, respectively).

- Data from the 3TC dose ranging studies (NUCA2001 and NUCB2001) demonstrated no dose-related increase in the overall incidence of AEs or the overall incidence of study-drug related AEs at doses up to 840 mg daily dose (module 2.7.4, Section 5.6.2). In these studies, the Cmax following 560 mg daily dose or 840 mg daily dose administration overlapped with the predicted steady-state Cmax for the proposed commercial DTG/3TC [redacted] FDC (module 2.7.2, Section 3.3.1.1).
- Several previously submitted registrational pivotal Phase II/III studies (NUCA3001, NUCA3002, and NUCB3002) showed no significant safety and efficacy differences between the 3TC 300 mg/day and the 3TC 600 mg/day doses (see module 2.7.4, Section 5.6.2). In these studies, the steady-state Cmax range observed for the 300 mg BID doses (600 mg total daily doses) overlaps with the predicted steady-state 3TC Cmax for the [redacted] FDC in the fed state and overlaps with the steady-state Cmax range observed for the proposed commercial DTG/3TC [redacted] FDC.

Therefore, the bioequivalence and food effect results provide an acceptable PK bridge between the proposed commercial DTG/3TC [redacted] FDC and single entities used in GEMINI-1 and GEMINI-2 Phase III studies.

4. MAIN BIOPHARMACEUTICAL FINDINGS

The conclusions from the fasted DTG/3TC FDC biopharmaceutic evaluations are as follows:

- In the fasted state, the [redacted] DTG/3TC FDC tablet was bioequivalent for DTG AUC and Cmax and for 3TC AUC; however, the [redacted] had an approximately 32% higher 3TC Cmax than Epivir.
- The higher 3TC Cmax, which reflects differences in the rate of absorption but not extent of absorption, does not significantly affect patient safety and antiviral efficacy based on historical clinical efficacy and safety data at higher 3TC doses/exposures (module 2.7.4 Section 5.6.2).
- The data from the pivotal BE Study 204994, combined with data from the 3TC historical studies, provides an acceptable PK bridge to the SEs used in GEMINI-1 and GEMINI-2 Phase III trials and supports the proposed submission for the [redacted] FDC tablet.
- The DTG/3TC FDC may be taken with or without food. This is consistent with the prescribing information for the DTG and 3TC single entities and is supported by the food effect results for the [redacted] FDC tablet.
- The bioanalytical methods used to measure concentrations of DTG and 3TC in biological samples were selective, accurate, and reproducible.

5. REFERENCES

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6. APPENDIX

Appendix Table 1 Summary of Completed Biopharmaceutic Studies that were Previously Submitted as Part of the Tivicay or Epivir Registration and are "Supportive" Studies to the DTG/3TC FDC Submission

Study	Study Title	Main Conclusions
Bioequivalence and Bioavailability		
ING113674 (DTG) GlaxoSmithKline Document Number: 2010N105142_00 Status: Complete	RBA study of three different tablet formulations of GSK1349572 50 mg and the dose proportionality of and effect of food on the selected formulation in healthy male and female volunteers	Results of the analysis showed that the 2 test tablet formulations (AW and AX) met the criteria for BE with the reference (Phase IIb) tablet formulation. Plasma DTG AUC(0-∞) increased by 33%, 41%, and 66% when AW tablets were administered with low-fat, moderate-fat, and high-fat food, respectively. Plasma DTG Cmax increased by 46%, 52%, and 67% when the AW tablets were administered with low-fat, moderate-fat, and high-fat food, respectively. Tmax increased with increasing fat content and median values were 2.0, 3.0, 4.0, and 5.0 hours for fasting, low-fat, moderate-fat, and high-fat meals, respectively. The increased exposure with food is not considered clinically significant based on the accumulated safety data in Phase IIb and III studies which permitted DTG dosing without restriction to food or food content.
NUCA1001 (3TC) GlaxoSmithKline Document Number: UCP/92/015 Status: Complete	Pharmacokinetics of GRI09714X (3TC) in asymptomatic, HIV-infected patients when administered orally with and without food	The Cmax and tmax were decreased and delayed when 3TC was administered with food, while the area under the concentration-time curve (AUC(0-∞) and the amount of unchanged drug excreted in the urine (Ae) were not significantly affected.

2.7.1 Summary of Biopharmaceutic Studies
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Study	Study Title	Main Conclusions
Bioequivalence and Bioavailability		
NUCB1001 (3TC) GSK Document Number: UCP/91/010 Status: Complete	A Phase I pilot study of the pharmacokinetics. bioavailability and safety of intravenous and oral GRI097I4X in HIV positive (CDC classification II/III) patients	After oral dosing, BA was 82%. The majority of the dose was excreted unchanged in the urine (approximately 70%), regardless of the BA and the route of administration. CLr exceeded GFR, suggesting that 3TC CLr involves tubular secretion.
NUCA1003 (3TC) GSK Document Number: UCP/93/011 Status: Complete	Bioequivalence and bioavailability of GRI09714X (3TC) in asymptomatic HIV-positive patients when administered as three oral formulations compared to intravenous infusion.	The oral formulations of a solution, capsule. and tablet showed absolute BA of 87%,88%, and 86% respectively. The capsule and tablet were BE compared with the solutions for extent of absorption with the 90% CIs well within the 80 to 125 criteria for bioequivalence (Log transformed analysis of ratios for AUC∞ and Cmax). Untransformed analysis of AUC∞ and Cmax provided essential similar results. The comparison of tmax values demonstrated no difference between the capsule and the solution. The comparison of tmax ' for the tablet to the solution demonstrated that the central tendency (median difference) was equivalent but the variability produced a CI outside the 80 to 120 criterion for equivalence. This variability is clinically irrelevant as maximum tmax values observed for all oral formulations in this study were still acceptable at 1.5 hours. The PK parameter estimates obtained from the IV formulation, solution, capsule, and tablet are similar to those obtained in NUCB1001 and NUCA1001 with the exception of λz and terminal half-life. Inspection of serum concentrations at 12, 16, and 24 h in the current study were similar to those obtained in NUCB1001 and NUCA1001 when adjusted for dose. The observed difference in these parameters is due to the inclusion of blood sample at 20 hours resulting in a slightly longer terminal half-life of approximately 8.5 hours. Single and multiple dose

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study	Study Title	Main Conclusions
Bioequivalence and Bioavailability		
		data from NUCA2001 suggest that single dose PK (based on a sample schedule of 0 to 12 hours) predicts serum concentrations after fourteen days multiple dosing in doses ranging from 0.5 mg/kg/day to 20 mg/kg/day. This suggest that the clinically effective half-life is in the range of 3 to 5 hours and that the difference in AUC extrapolated using the previously described half-lives of 3 to 5 hours and the current estimation of half-life of 8.5 is clinically insignificant.
NUCA1006 (3TC) GlaxoSmithKline Document Number: UCP/94/008 Status: Complete	Bioequivalence of Lamivudine [GR109714X, 3TC] 75 mg, 100 mg, and 300 mg Tablets in Asymptomatic HIV-infected Male Patients	The criteria for establishing bioequivalence of Treatments A (four 3TC 75 mg tablets, test), B (three 3TC 100 mg tablets, reference), and C (one 3TC 300 mg tablet, test) was that the 90% CIs for the treatment ratios for both AUC∞ and Cmax were within the range of 0.80 to 1.25. The GLS mean ratios and 90% CIs for the A to B comparison were 1.04 (0.96 - 1.13) for AUC∞ and 1.03 (0.90 - 1.19) for Cmax. The GLS mean ratios and 90% CIs for the C to B comparison were 1.01 (0.93 - 1.10) for AUC∞ and 1.08 (0.94 1.24) for Cmax. Thus, the 3TC 75 mg and 300 mg tablets were bioequivalent to the 3TC 100 mg tablets.
NUCB1004 GlaxoSmithKline Document Number: GCP/93/086 Status: Complete	A Study to Investigate the Comparative Bioavailability of Two Oral Formulations of GR109714X (Lamivudine)	The serum concentrations and the derived PK parameters of GR109714X were very similar after administration of two route 4, 150 mg tablets as compared with one route 2, 300 mg tablet. The point-estimates and 90% CIs of the treatment ratios for AUC∞ and Cmax were well within the set equivalence range of 80 to 125%. Therefore, it is concluded that the two formulations are equivalent when the same dose is administered.

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 2 Summary of Drug Substance and Drug Product

Study Ref. No.	Formula Code	Drug Product Batch No.	Dosage Form	Input Drug Substance Batch		Study Report Location
				Dolutegravir Sodium	Lamivudine	
204993	AA	152394382	[redacted] Tablet, 50 mg/300 mg	154017	K300312	m5.3.1.2
	AB	152394383	[redacted] Tablet, 50 mg/300 mg	154017	K300312	
	BC	R634009	Dolutegravir Tablet, 50 mg (clinical image) [1]	108004A	N/A	
	Commercial	R742408	Epivir Tablet, 300 mg	N/A	K298972 K298961 K298942	
204994	AH	6ZP6802	[redacted] Tablet, 50 mg/300 mg	162015	20056277	m5.3.1.2
	AK	7ZP2105	[redacted] Tablet, 50 mg/300 mg	DTG-16Y094	20064233	
	BC	R683552	Dolutegravir Tablet, 50 mg (clinical image) [a]	108005C	N/A	
	Commercial	6ZP7456	Epivir Tablet, 300 mg	N/A	K300216	

a. The clinical image of TIVICAY Tablets, 50 mg was established as equivalent to TIVICAY Tablets, 50 mg in the TIVICAY marketing application.

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 3 Summary of In vitro Dissolution Data for Bioavailability and Bioequivalence Study Batches for DTG/3TC Studies

Study Ref. No.	Product Code	Dosage Form	Conditions: USP Apparatus [redacted] (Media, Volume, Paddle Speed)	No. of Dosage Units	Component	Collection times (min) Mean % Dissolved (range)	Study Report Location
204993	AA	DTG/3TC Tablets 50 mg/300 mg ([redacted])	pH 6.8 + [redacted] ml rpm	6	DTG	[redacted]	m5.3.1.2
					3TC		
	AB	DTG/3TC Tablets 50 mg/300 mg ([redacted])	pH 6.8 + [redacted] ml rpm	6	DTG		
					3TC		
	BC	DTG Tablet, 50 mg	pH6.8 + [redacted] ml rpm	12	DTG		
	Commercial	Epivir Tablet, 300 mg	0.1M HCl ml rpm	6	3TC		
204994	AH	DTG/3TC Tablets 50 mg/300 mg ([redacted])	pH 6.8 + [redacted] ml rpm	24	DTG		m5.3.1.2
					3TC		
	AK	DTG/3TC Tablets 50 mg/300 mg ([redacted])	pH 6.8 + [redacted] ml rpm	6	DTG		
					3TC		
	BC	DTG Tablets, 50 mg	pH6.8 + [redacted] ml rpm	6	DTG		
	Commercial	Epivir Tablets, 300 mg	0.1M HCl ml rpm	6	3TC		

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 4 Bioanalytical Methods Summary

Validation Report	Clinical Studies Supported	Method Description and Performance	
Dolutegravir **Human Plasma (EDTA)** GlaxoSmithKline, Five Moore Drive Research Triangle Park, NC 27709 **Title:** The Validation of a Method for the Determination of GSK1349572 (range 20 to 20000 ng/mL) in Human Plasma using HPLC-MS/MS GlaxoSmithKline Document Number: RD2010/00175 **Supplemental Reports (Incorporation of long term stability and interference checks)** GlaxoSmithKline Document Number: 2011N112542	ING113674	Dolutegravir is extracted from 25 μL human plasma by protein precipitation using acetonitrile containing [$^{2}H_{7}{}^{15}N$]-dolutegravir as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	20.0 ng/mL
		Validated Range	20.0 to 20000 ng/mL
		Within-run Precision (%CV)	≤4.5%
		Between-run Precision (%CV)	≤2.7%
		Accuracy (%Bias)	-0.3% ≤ bias ≤ 9.6%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature at least 265 days at approximately -20°C
Dolutegravir **Human Plasma (EDTA)** [redacted] **Title:** Quantitation of	204993 204994	Dolutegravir is extracted from 25 μL human plasma by protein precipitation using acetonitrile containing [$^{2}H_{7}{}^{15}N$]-dolutegravir as an internal standard. Extracts are analyzed by UPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	20.0 ng/mL
		Validated Range	20.0 to 20000 ng/mL

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
GSK1349572 in Human Plasma via UPLC with MS/MS Detection GlaxoSmithKline Document Number: 2012N147635_00 **Supplemental Report (Incorporation of long term stability and interference checks)** GlaxoSmithKline Document Number: 2014N188856_00		Within-run Precision (%CV)	≤13.6%
		Between-run Precision (%CV)	≤8.01
		Accuracy (%Bias)	-7.07% ≤ bias ≤ 7.48%
		Stability in Human Plasma	5 freeze-thaw cycles to room temperature (protected from light) from approximately -20°C and -70°C at least 24.75 hours at ambient temperature, protected from light at least 558 days at approximately -20°C and -70°C
		Processed Extract Stability	At least 96.5 hours at 5ºC
Lamivudine (GR109714X; 3TC) Human Urine GlaxoSmithKline Clinical Pharmacology **Title:** Determination of GR109714X in Human Urine: Direct Injection with Column Switching Method and Validation Document Number: UCP/92/024	NUCA1001	Lamivudine method uses direction injection of 10 µL urine with column switching followed by HPLC-UV detection.	
		LLQ	0.5 µg/mL
		Validated Range	0.5 to 500 µg/mL
		Within-run Precision (%CV)	≤11.9%
		Between-run Precision (%CV)	≤4.6%
		Accuracy (%Bias)	-15.3 ≤bias ≤2.5%
		Stability in Human Urine	3 hours at 60°C 24 days at -30°C 24 days at 4°C at least 4 hours at room temperature
Lamivudine (GR109714X; 3TC) Human Serum	NUCB1004	Lamivudine was extracted from 0.5mL human serum by robotic sample preparation and solid phase extraction procedure. Extracts were analyzed by HPLUV	

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
[redacted] The Netherlands **Title:** Determination of GR109714 in Human Serum by Robotic Sample preparation and High-Performance Liquid Chromatography and UV-Detection Document Number: 2013N164861_00		LLQ	10 ng/mL
		Validated Range	10 to 1000 ng/mL
		Within-run Precision (%CV)	** Not possible to calculate as only singlicate QCs were run on each day of analysis, therefore an SD/CV cannot be calculated within a run*
		Between-run Precision (%CV)	≤10.5%
		Accuracy (%Bias)	-0.8% ≤bias ≤ 4.5%.
		Stability in Human Serum	3 freeze-thaw cycles At least 25 hours at room temperature At least 3 hours at 60°C
Lamivudine (GR109714X; 3TC) Human Serum GlaxoSmithKline Clinical Pharmacology **Title:** Determination of GR109714X in Human Serum Robotic Method Document Number: UCP/92/008	NUCA1006 NUCA1001	Lamivudine was extracted from 1000 μL human serum by a solid-phase extraction procedure. GR90352 (Carbovir) was used as an internal standard. Extracts were analyzed by HPLC- UV.	
		LLQ	3.0 ng/mL
		Validated Range	3.0 to 5000 ng/mL
		Within-run Precision (%CV)	≤.9.8%
		Between-run Precision (%CV)	≤6.0

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
		Accuracy (%Bias)	-6.40 ≤ bias ≤ 7.83%
		Stability in Human Serum	2 freeze-thaw cycles at least 4 days at 4°C at least 5 days at 58°C at least 4 days at ambient temperature
Lamivudine GR109714X; 3TC) Human Plasma (EDTA) [redacted] **Title:** Quantitation of Abacavir and Lamivudine in Human Plasma via UHPLC with MS/MS Detection GlaxoSmithKline Document Number: 2012N150069_02 Long term stability GlaxoSmithKline Document Number: CD2003/00036/01	204993 204994	Lamivudine is extracted from 50 μL human plasma by protein precipitation using acetonitrile containing [$^{13}C^{15}N_2$]-lamivudine as an internal standard. Extracts are analyzed by UPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	2.5 ng/mL
		Validated Range	2.5 to 2500 ng/mL
		Within-run Precision (%CV)	≤18.9%
		Between-run Precision (%CV)	≤11.4%
		Accuracy (%Bias)	-14.8 ≤ bias ≤5.54%
		Stability in Human Plasma	3 freeze-thaw cycles from -70°C at least 292 days at -70°C at least 29 hours at ambient temperature
		Processed Extract Stability	90.5 hour at 5ºC

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 5 Between-run Accuracy and Precision of Quality Control (QC) Samples for Dolutegravir with Statistical Outliers Included, Values in Parentheses are those Calculated with Statistical Outliers Excluded

Study (GlaxoSmithKline Document Number)		Nominal Concentration (ng/mL)				
204993 (2016N288237_00)		**60**	**160**	**640**	**2400**	**15200**
	Overall Mean (ng/mL)	63.1 (61.2)	175	664	2450	14700
	S.D. (within-run means)	11.1 (2.41)	22.6	26.1	83.4	612
	Precision (%CV)	17.6 (3.93)	12.9	3.93	3.40	4.15
	Average Bias (%)	5.16 (2.07)	9.25	3.80	2.28	-2.97
	n=	34 (33)	34	34	34	34
204994 (2017N329307_00)	Overall Mean (ng/mL)	62.2	167 (164)	649 (650)	2430	14400
	S.D. (within-run means)	3.69	37.8 (7.99)	35.1 (29.9)	109	1010 (860)
	Precision (%CV)	5.94	22.7 (4.86)	5.42 (4.60)	4.51	6.98 (5.96)
	Average Bias (%)	3.69	4.11 (2.64)	1.33 (1.52)	1.12	-5.21 (-4.99)
	n=	246	246 (245)	246 (245)	246	246
ING113674 (RD2010/00558/00)		**60**	**1600**	**16000**		
	Overall Mean (ng/mL)	61.3	1662.6	16024.6		
	S.D. (within-run means)	2.1	67.7	707.1		
	Precision (%CV)	3.5	4.1	4.4		
	Average Bias (%)	2.1	3.9	0.2		
	n=	44	44	44		

Appendix Table 6 Between-run Accuracy and Precision of Quality Control (QC) Samples for Lamivudine with Statistical Outliers Included, Values in Parentheses are those Calculated with Statistical Outliers Excluded

Study (GlaxoSmithKline Document Number)		Nominal Concentration (ng/mL)				
204993 (2016N288223_00)		**7.5**	**20.0**	**80.0**	**300**	**1900**
	Overall Mean (ng/mL)	7.59	20.3	82.9 (80.1)	306	1860
	S.D. (within-run means)	0.441	0.904	19.3 (3.67)	14.3	68.6
	Precision (%CV)	5.80	4.44	23.3 (4.59)	4.68	3.70
	Average Bias (%)	1.26	1.70	3.57 (0.0712)	2.14	-2.36
	n=	46	46	46	46	46
204994 (2017N329308_01)	Overall Mean (ng/mL)	8.62 (8.30)	20.8 (20.6)	81.3	304	1890 (1860)
	S.D. (within-run means)	7.54 (5.36)	4.81 (2.33)	4.41	23.1	573 (422)
	Precision (%CV)	87.4 [a] (64.6) [a]	23.1 [a] (11.3)	5.43	7.59	30.4 [a] (22.7) [a]
	Average Bias (%)	15.0 (10.7)	4.11 (2.83)	1.61	1.38	-0.726 (-1.97)
	n=	270	270	270	270	270
NUCB1004		**30**		**300**		**800**
	Overall Mean (ng/mL)	29.3		298		814
	S.D. (within-run means)	2.8		11		3.5
	Precision (%CV)	9.6		3.8		4.3
	Average Bias (%)	-2.3		-0.7		1.8
	n=	26		27		27
NUCA1006		**6.0**		**300**		**3500**
	Overall Mean (ng/mL)	6.12		299.90		3432.48
	S.D. (within-run means)	0.628		15.526		201.173
	Precision (%CV)	10.3		5.2		5.9
	Average Bias (%)	2.0		0.0		-1.9
	n=	39		40		40
NUCA1001 (serum)		**6.0**		**300**		**3500**
	Overall Mean (ng/mL)	6.01		301.81		3457.40

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study (GlaxoSmithKline Document Number)		Nominal Concentration (ng/mL)		
	S.D. (within-run means)	0.533	10.913	108.635
	Precision (%CV)	8.9	3.6	3.1
	Average Bias (%)	0.2	0.6	-1.2
	n=	14	14	13
NUCA1001 (urine)		**1.5**	**175.00**	**375.00**
	Overall Mean (ng/mL)	1.49	166.34	349.15
	S.D. (within-run means)	0.136	5.295	11.461
	Precision (%CV)	9.1	3.2	3.3
	Average Bias (%)	-0.7	-4.9	-6.9
	n=	4	4	4

a. Precision >15%. All individual runs met acceptance criteria

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 7 Tabular Listing of all Biopharmaceutic Studies

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
Dolutegravir/Lamivudine FDC								
204993	PK Relative BA Food effect	To evaluate the relative BA of a single dose of DTG 50 mg and 3TC 300 mg when administered together in each of two FDC tablet formulations compared to the co-administration of a single dose of the single-entity DTG and 3TC products.	R, OL, XO	Healthy subjects	30: 20/10: 47.3 yrs (2[redacted]-6[redacted] yrs)	**Treatment A:** DTG 50 mg tablet (clinical image) plus Epivir 300 mg tablet **Treatment B:** GSK3515864 (DTG/3TC) Tablet, 50 mg/300 mg Item Code DP275912 Product Code AA **Treatment C:** GSK3515864 (DTG/3TC) Tablet, 50 mg/300 mg Item Code DP275912 Product Code AB	Complete; Full	m5.3.1.2
204994	PK Bioequivalence	To evaluate the bioequivalence of FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state.	R, OL, XO	Healthy subjects	154: 103/51: 30.5 yrs (1[redacted]-5[redacted] yrs)	**Treatment A:** DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet **Treatment B:** DTG/3TC Tablets, 50 mg/300 mg FDC [redacted] formulation Product Code AH **Treatment C:** DTG/3TC Tablets, 50 mg/300 mg FDC	Complete; Full	m5.3.1.2

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
						[redacted] formulation Product Code AK		
Dolutegravir								
ING113674	PK Relative BA Food effect	To evaluate the relative BA of three different tablet formulations of DTG 50 mg and effect of food on the selected formulation	R, OL, XO	Healthy subjects	24: 10/14: 38.6 yrs (2[redacted]-6[redacted] yrs)	**Part A (fasted)** DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AP DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AW DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AX **Part B (fed)** DTG/ 50 mg/ tablet/ oral/ single dose DTG/ 50 mg/ tablet/ oral/ single dose, low fat DTG/ 50 mg/ tablet/ oral/ single dose, high fat DTG/ 50 mg/ tablet/ oral/ single dose, mod fat	Complete; Full	m5.3.1.2
Lamivudine								
NUCA1001	PK Food effect	To determine the effect of food on the PK of GRI09714X following a single oral dose of GRI09714X	R, OL, XO	HIV infected patients	13: 13/0: 34 yrs (2[redacted] – 4[redacted] yrs)	50 mg 3TC (2 x 25 mg capsules) single oral dose under fasting or fed conditions	Complete; Full	m5.3.1.2

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
NUCB1001	Absolute BA	PK, BA and safety of IV and oral doses of GR109714X (3TC)	OL, XO (3-day washout). Five dosing groups (0.25, 1, 2, 4, 8 mg/kg) each receiving (as single doses) oral and IV 3TC	HIV-positive patients	20: 20/0: 36 (2[redacted]-5[redacted])	3TC; 0.25, 1, 2, 4, 8 mg/kg/ single dose/oral and IV	Completed Full CPSR	m5.3.1.2
NUCA1006	BE	Bioequivalence and bioavailability of 3TC	OL, R, XO	HIV-positive patients	25: 25/0: 33 yrs (2[redacted]-4[redacted] yrs)	3TC/300 mg/4x75 mg tablet/oral/single dose 3TC/300 mg/3x100 mg/ oral/single dose 3TC/300 mg/1x300 mg tablet/oral/single dose	Complete; Full	m5.3.1.2
NUCB1004	Comparative Bioavailability	To determine the comparative bioavailability of GR109714X when administered as 2x150mg (Route 4) tablets or as a single 300 mg (Route 2) tablet.	OL, R, XO	Healthy subjects	24 (24/0) 22.6 yrs (1[redacted]-2[redacted] yrs) Healthy Subjects	GR109714X, Route 4, 150 mg tablet, (x2) GR109714X, Route 2, 300 mg tablet	Complete; Full	m5.3.1.2

Degree of Blinding
OL = Open-label
ABC = Abacavir

Degree of Control
PK = Pharmacokinetic
3TC = Lamivudine

Treatment Assignment
R = Random
DTG = Dolutegravir

Treatment Sequence
XO = Crossover
FDC = Fixed-dose combination

M - Male
F – Female

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report

BA = Bioavailability

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Legend to Table 8 Summary Results of All Biopharmaceutic Studies

Protocol No.	The Study identifier.
Study Design:	Degree of blinding: O=open, SB=single blind, DB=double blind Degree of control: UC=uncontrolled, PLC=placebo, AC=active control Treatment assignment: R=random, NR=nonrandom Treatment sequence: XO=crossover, PRL=parallel, DR=Dose rising
Number of subjects (M/F):	Number of subjects/patients who received study medication; (number of males M/ females F)
Age Mean Range:	Provides the mean and range of ages in years
Treatment Details (Drug/Dose/Form/ Route/Frequency):	Study treatments are identified Dose (mg) of each treatment as specified in the protocol (od=once daily, bd=twice daily) Number of individual days receiving study medication
Cmax	Maximum observed plasma concentration.
tmax	Time to reach the maximum observed plasma concentration.
AUC(0-t)	Area under the plasma concentration versus time curve from time zero to the last time point that concentrations were quantifiable.
AUC(0-∞)	Area under the plasma concentration versus time curve from time zero to infinity.
t½	Apparent terminal elimination half-life
Others	Add As appropriate

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 8 Summary Results of all Biopharmaceutic Studies

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
Dolutegravir/Lamivudine FDC								
					Dolutegravir PK Parameters			
204993	To evaluate the relative BA of a single dose of DTG 50 mg and 3TC 300 mg when administered together in each of two FDC tablet formulations compared to the co-administration of a single dose of the single-entity DTG and 3TC products.	R, OL, XO	30 (20/10) 47.3 yrs (2[redacted]-6[redacted] yrs) Healthy subjects	**Treatment A:** DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet	2.64 (41.6)	2.0 (0.5, 7.0)	51.6 (45.5)	15.1 (13.7)
				Treatment B: DTG/3TC FDC Tablets, 50 mg/300 mg Item Code DP275912 Product Code AA	3.01 (31.3)	1.51 (0.5, 5.0)	57.6 (31)	14.9 (13.2)
				Treatment C: DTG/3TC Tablets, 50 mg/300 mg Item Code DP275913 Product Code AB	2.69 (26.7)	2.01 (0.5, 5.0)	52.2 (25.6)	15.1 (17.3)

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
					Lamivudine PK Parameters[a]			
				Treatment A: DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet	2.68 (23.8)	1.51 (0.5, 4.0)	14.9 (25.4)	18.8 (18.3)
				Treatment B: DTG/3TC FDC Tablets, 50 mg/300 mg Item Code DP275912 Product Code AA	3.14 (28.2)	1.0 (0.5, 2.0)	15.6 (26.2)	18.5 (17.2)
				Treatment C: DTG/3TC Tablets, 50 mg/300 mg Item Code DP275913 Product Code AB	3.29 (23.4)	1.0 (0.5, 3.0)	15.2 (25)	19.3 (24.2)

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
					Dolutegravir PK Parameters – Part 1			
					Bioequivalence			
204994	To evaluate the bioequivalence of FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state.	R, OL, XO	154 (103/51) 30.5 yrs (1[redacted]-5[redacted] yrs) Healthy subjects	**Treatment A:** DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet (Fasted)	2.41 (39.0)	2.01 (0.500, 8.01)	43.1 (39.3)	14.7 (15.6)
				Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH) (Fasted)	3.08 (31.9)	2.00 (0.500, 5.01)	54.9 (31.6)	14.7 (15.3)
					Food effect			
				Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH) (Fasted)	3.51 (30.3)	1.50 (0.503, 5.00)	62.3 (32.3)	14.5 (8.89)
				Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH) (High-fat meal)	3.79 (21.0)	5.00 (2.00, 12.0)	72.0 (20.0)	14.5 (13.3)

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
					Lamivudine PK Parameters – Part 1			
					Bioequivalence			
				Treatment A: DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet (Fasted)	2.67 (29.0)	1.00 (0.500, 4.00)	12.3 (19.9)	17.6 (27.9)
				Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH) (Fasted)	3.19 (28.1)	1.00 (0.500, 3.50)	12.8 (19.8)	17.7 (22.9)
					Food effect			
				Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH) (Fasted)	3.54 (27.1)	1.00 (0.500, 2.00)	13.4 (21.0)	18.4 (21.9)
				Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH) (High-fat meal)	2.51 (18.7)	3.50 (1.01, 5.00)	12.9 (18.5)	19.1 (30.7)

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
					Dolutegravir PK Parameters – Part 2			
					Bioequivalence			
				Treatment A: DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet (Fasted)	2.55 (36.4)	2.50 (0.500, 5.01)	47.2 (40.3)	15.1 (17.8)
				Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) (Fasted)	2.91 (30.6)	2.50 (0.500, 6.00)	54.6 (32.1)	15.0 (18.2)
					Food effect			
				Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) (Fasted)	3.10 (35.6)	1.50 (0.751, 3.00)	57.7 (36.0)	15.3 (17.3)
				Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) (High-fat meal)	3.75 (21.3)	5.00 (1.01, 8.00)	76.4 (22.4)	15.5 (16.0)

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
					Lamivudine PK Parameters – Part 2			
					Bioequivalence			
				Treatment A: DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet (Fasted)	2.44 (28.3)	1.00 (0.500, 4.00)	12.8 (18.6)[b]	19.2 (29.5)[b]
				Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) (Fasted)	3.22 (29.3)	1.00 (0.500, 3.50)	13.6 (18.0)[b] 13.6 (17.9)[c]	18.6 (26.9)[b] 18.8 (27.7)[c]
				Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) (Fasted)	3.58 (35.2)	1.00 (0.503, 2.51)	14.6 (18.5)	18.1 (24.4)
				Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) (High-fat meal)	2.45 (33.9)	2.75 (1.00, 6.00)	13.3 (20.3)	19.8 (20.4)

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
Dolutegravir								
ING113674	To evaluate relative BA study of three different tablet formulations of DTG 50 mg and effect of food on the selected formulation	R, OL, XO	24: (10/14) 38.6 yrs (2[redacted]-6[redacted] yrs) Healthy subjects	Part A DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AP	2.67 (35)	3.00 (1.0, 5.0)	53.2 (34)	14.2 (19)
				DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AW	2.64 (30)	2.56 (1.0, 6.0)	50.6 (27)	14.1 (21)
				DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AX	2.77 (32)	2.04 (1.0, 4.0)	53.7 (34)	14.4 (19)
				Part B (formulation AW) DTG/ 50 mg/ tablet/ oral/ single dose, fasted	2.65 (28)	2.06 (1.0, 5.0)	50.3 (27)	14.1 (22)
				DTG/ 50 mg/ tablet/ oral/ single dose, low fat	3.88 (21)	3.0 (2.0, 5.1)	66.7 (35)	13.4 (19)
				DTG/ 50 mg/ tablet/ oral/ single dose, high fat	4.44 (24)	5.0 (1.0, 8.0)	83.6 (35)	13.4 (21)
				DTG/ 50 mg/ tablet/ oral/ single dose, moderate fat	4.03 (19)	4.0 (2.0, 6.0)	71.0 (31)	13.5 (19)

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
Lamivudine								
NUCB1001	PK, BA and safety of IV and oral doses of GR109714X (3TC)	OL, XO (3-day washout). Five dosing groups (0.25, 1, 2, 4, 8 mg/kg) each receiving (as single doses) oral and IV 3TC	20: (20/0): 36 yrs (2[redacted]-5[redacted] yrs) HIV-positive patients	Single doses				
				0.25 mg/kg IV	0.38 (0.27-0.54)	NA	0.75 (0.66-0.86)	2.60 (1.65-4.08)
				1 mg/kg IV	1.61 (1.40-1.85)	NA	3.27 (2.42-4.43)	2.31 (1.64-3.25)
				2 mg.kg IV	3.30 (3.02-3.60)	NA	6.65 (5.21-8.48)	2.47 (2.18-2.80)
				4 mg/kg IV	5.60 (4.71-6.65)	NA	12.79 (9.52-17.19)	3.11 (1.11-8.75)
				8 mg/kg IV	10.48 (8.36-13.15)	NA	22.58 (17.54-29.07)	2.59 (2.25-2.99)
				0.25 mg/kg PO	0.227 (0.85)	NR	0.70 (0.09)	1.904 (NR)
				1 mg/kg PO	1.26 (0.35)	NR	3.18 (0.67)	1.615 (NR)
				2 mg.kg PO	1.73 (0.61)	NR	4.57(0.20)	1.188 (NR)
				4 mg/kg PO	2.65 (0.39)	NR	9.23(1.47)	1.916 (NR)
				8 mg/kg PO	5.82 (0.76)	NR	17.95 (2.05)	1.910 (NR)

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (95% CI)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
NUCA1001	To determine the effect of food on the PK of GRI09714X following a single oral dose of GRI09714X	R, OL, XO	13: (13/0): 34 yrs (2[redacted]-4[redacted] yrs) HIV patients	50 mg 3TC (2 x 25 mg capsules) single oral dose under fasting or fed conditions	**Fasting**			
					4.74[d] (4.00, 5.62)	0.88 ± 0.25[d, e]	16.27[d] (15.06, 17.58)	3.3[d] (3.1, 3.5)
					Fed			
					2.68[d] (2.26, 3.17)	3.15 ± 1.27[d, e]	15.29[d] (14.16, 16.52)	2.9[d] (2.8, 3.1)
NUCA1003	Determine the BE, RBA, and absolute BA of 3TC100mg, when administered as a capsule, as a tablet, or as an oral solution	OL, R, XO	14 (14/0:) 32 yrs (2[redacted]-4[redacted] yrs)	3TC/100mg/solution/IV/single dose	1.77 (1.56, 2.01)	NR	4.48 (4.04, 4.98)	8.30 (6.66, 10.59)
				3TC/100mg/solution/oral/single dose	1.03 (0.87, 1.22)	0.75 (0.75, 1.00)	3.84 (3.51, 4.21)	8.32 (7.38, 9.38)
				3TC/100mg/capsule/oral/single dose	1.07 (0.87, 1.32)	0.75 (0.50, 1.50)	3.87 (3.43, 4.35)	8.43 (7.78, 9.13)
				3TC/100mg/tablet/oral/single dose	1.00 (0.86, 1.17)	0.75 (0.50, 1.50)	3.78 (3.50, 4.08)	8.30 (7.46, 9.23)
NUCA1006	To determine the bioavailability of 3TC 75 mg and 300 mg tablets relative to 3TC 100 mg tablets in asymptomatic, HIV-positive male patients.	OL, R, XO	25 (25/0) 33 yrs (2[redacted]-4[redacted] yrs) HIV patients	3TC Tablet, 4x75 mg single dose, oral	2.96 (2.63, 3.33)	1.00 (0.50, 2.0)	12.18 (11.34,13.07)	5.40 (5.02-5.81)
				3TC Tablet, 3x100 mg single dose, oral	2.86 (2.55, 3.22)	1.00 (0.50, 3.0)	11.73 (10.93,12.60)	5.15 (4.79-5.54)
				3TC Tablet, 1x300 mg single dose, oral	3.09 (2.75, 3.47)	0.88 (0.50, 2.0)	11.89 (11.08,12.77)	5.30 (4.92-5.70)
NUCB1004	To determine the comparative bioavailability of GR109714X when administered as 2x150mg (Route 4) tablets or as a single 300 mg (Route 2) tablet.	OL, R, XO	24 (24/0) 22.6 yrs (1[redacted]-2[redacted] yrs) Healthy Subjects	GR109714X, Route 4, 150 mg tablet, (x2)	3.40 (3.10, 3.73)	0.75 (0.50, 2.00)	10.48 (9.78, 11.22)	5.82 (5.49, 6.18)
				GR109714X, Route 2, 300 mg tablet	3.28 (2.95, 3.65)	0.75 (0.50, 1.50)	10.56 (9.85, 11.31)	5.79 (5.45, 6.16)

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Cmax = maximum concentration; tmax = first occurrence of Cmax; AUC(0-∞) = area under the plasma concentration-time curve from time 0 and extrapolated to infinity; t½ = apparent plasma half-life; R&D=research and development

a. AUC(0-∞), CL/F and t½: n=28 for Treatment A, n=26 for Treatment B, n=27 for Treatment C. 5 subjects ([redacted], Treatments A, B; [redacted] Treatments A, C; [redacted], Treatment C; and both [redacted], [redacted] Treatment B) were excluded because the duration for the calculation of λz (apparent terminal slope) was <2x the calculated λz and/or the R squared adjusted was < 0.85.
b. PK parameter estimation for Subject [redacted] (Treatment A, Period 2) did not conform to the prescribed criteria for acceptance (i.e., lambda_z time duration <2x the calculated t1/2 and >20% AUC(0-∞) extrapolated), therefore it was excluded from analysis of AUC(0-∞), CL/F, and t1/2; n=73.
c. Sensitivity analysis was conducted by including Subject [redacted] Treatment C, Period 1 data.
d. n = 12
e. Arithmetic mean ± standard deviation

OL = Open-label; R = Randomized; XO = Crossover

Module 2.7.2

Summary of Clinical Pharmacology

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ABBREVIATIONS

3TC	Lamivudine, Epivir
3TC-MP	Lamivudine-monophosphate
3TC-DP	Lamivudine-diphosphate
3TC-TP	Lamivudine-triphosphate
3TC-Total Phosphate	Lamivudine-total phosphate
AAG	α1-acid glycoprotein
ABC	Abacavir
ABC/3TC	Abacavir/lamivudine, Epzicom/Kivexa
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALAG	Absorption lag time
ALT	Alanine aminotransferase
APV	Amprenavir
ARC	AIDS-related complex
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATV	Atazanavir
AUC	Area under the concentration-time curve
AUC(0-24)	Area under the concentration-time curve from zero (pre-dose) to 24 hours post dosing
AUC∞	AUC extrapolated to infinity
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex	Percentage of AUC(0-∞) obtained by extrapolation
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AZT	Azidothymidine
BA	Bioavailability
BCV	Boceprevir
BE	Bioequivalence
BID	Twice daily
C24,ss	Concentration at 24 hours at steady-state
C0	Pre-dose concentrations
C0avg	Average pre-dose concentration
C0,ss	Concentration just prior to the next administered dose at steady state; steady-state trough concentration
c/mL	Copies/mL
CBZ	Carbamazepine
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control
CI	Confidence interval

CLr	Renal clearance
CL	Systemic clearance of parent drug
CL/F, Clt/L, or Clo	Apparent clearance following oral dosing or oral clearance
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CrCl	Creatinine clearance
CSF	Cerebrospinal fluid
CSR	Clinical study report
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
Ct	Last observed quantifiable concentration
CV	Coefficient of variance
CVb	Between-subject variability
CVF	Cervicovaginal fluid
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 isozyme 3A4
DCV	Daclatasvir
ddC	Dideoxycytidine, zalcitabine
ddI	Didanosine
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DRV	Darunavir
DTG	Dolutegravir, Tivicay
DTG/3TC FDC	DTG/3TC 50 mg/300 mg FDC
EBR	Elbasvir
EC_{90}	Concentration at which 90% of the maximal effect is achieved
ECG	Electrocardiogram
EE	Ethinyl estradiol
EFV	Efavirenz
ERPF	Effective renal plasma flow
ETV	Etravirine
EU	European Union
F	Absolute bioavailability
FDC	Fixed-dose combination
FPV	Fosamprenavir
FTC	Emtricitabine
FTIH	First-time-in-human
GFR	Glomerular filtration rate
GLS	Geometric least-Squares
GZR	Grazoprevir
h or hr	Hour(s)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus, type 1

IC_{50}	Concentration at which 50% inhibition was observed
INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
IR	Immediate release
IV	Intravenous
Ka	First-order rate of absorption
kg	Kilogram
L	Liter
LPV/RTV	Lopinavir/ritonavir
µg	Microgram
µmol	Micromoles
µM	Micromolar
MATE	Multidrug and toxin extrusion transporter
MDZ	Midazolam
mg	Milligram
min	Minute
mL	Milliliter
MRP2	Multidrug resistance-associated protein 2
NA	Not applicable
NGMN	Norelgestromin/norgestimate
OBT	Optimized background therapy
OCT2	Organic cation transporter 2
OMP	Omeprazole
PAH	Para-aminohippurate
PA IC_{90}	Protein-adjusted concentration required for 90% viral inhibition
PD	Pharmacodynamic
PDVF	Protocol defined virologic failure
PGx	Pharmacogenetic
PI	Protease inhibitor
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	Per os
PoC	Proof of concept
QTc	QT interval corrected for heart rate
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAL	Raltegravir
RBT	Rifabutin
RBV	Ribavirin
RIF	Rifampin
RNA	Ribonucleic acid
RPV	Rilpivirine, EDURANT
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SD	Standard deviation
SE	Single entity

SOL	Sofosbuvir
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
τ	Dosing interval
TDF	Tenofovir disoproxil fumarate
TID	Three times daily
tlag	Lag time before observation of drug concentrations in sampled matrix
TLOVR	Time to loss of virologic response
tmax	Time of occurrence of Cmax
TMP/SMX	Trimethoprim + sulfamethoxazole
TP	Triphosphate
TPV	Tipranavir
TVR	Telaprevir
UGT	Uridine diphosphate glucuronosyltransferase
UGT1A1	Uridine diphosphate glucuronosyltransferase isozyme 1A1
US	United States
USPI	US Prescribing Information
V	Volume of distribution
VEL	Velpatasvir
VF	Virologic failure
V/F	Apparent volume of distribution after extravascular (e.g., oral) administration
Vz/F	Apparent volume of distribution after extravascular (e.g., oral) administration at terminal phase
ZDV	Zidovudine
ZDV/3TC	Zidovudine/lamivudine, COMBIVIR

Trademark Information

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1. BACKGROUND AND OVERVIEW OF CLINICAL PHARMACOLOGY

Dolutegravir (DTG; Tivicay, GSK1349572) is an HIV INSTI approved for use in combination in ARV treatment-naïve and treatment-experienced HIV-infected adults and adolescents at a dose of 50 mg once daily as a single agent (Tivicay) and 50 mg BID when certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance is present. Lamivudine (3TC; GR109714) is a cytidine nucleoside analog HIV-1 reverse transcriptase inhibitor indicated in combination with other ARV agents for the treatment of HIV-1 infection at a dose of 300 mg once daily.

DTG and 3TC are currently under clinical development as a FDC tablet. Both DTG and 3TC are commercially available products in many markets worldwide. Tivicay (DTG) is approved as a 50 mg tablet in 124 countries, including the US, EU, and Canada. Available since 1995 as a single agent (Epivir) [Epivir Product Information, 2018], 3TC is also available as part of two backbone FDC products (ZDV/3TC, Combivir and ABC/3TC, Epzicom/Kivexa). Both DTG and 3TC are also available as part of a triple FDC product (ABC/DTG/3TC, Triumeq). DTG is also available as part of a two-drug combination FDC product (DTG/RPV, Juluca).

The new formulation being developed is a FDC of DTG/3TC 50 mg/300 mg as a 2-drug regimen with a proposed indication for the treatment of HIV-1 infection in HIV-infected adult and adolescents (≥40 kg) patients without known or suspected resistance to either component who are either treatment naïve or virologically-suppressed (HIV-1 RNA <50 c/mL) on a stable ARV regimen and switching their current regimen.

The proposed recommended oral dose for adults and adolescents above 12 years of age weighing at least 40 kg is 1 tablet administered once a day without regard to meals. The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are approved doses for adolescents ≥12 years of age weighing ≥40 kg (DTG) or for pediatric patients weighing ≥25 kg (3TC). Prior studies have shown that DTG and 3TC PK exposures in adolescents are sufficiently similar to those in adults and allows extrapolation of GEMINI efficacy data to adolescents.

This document summarizes the relevant human PK, PD, and PK/PD relationships of the FDC consisting of DTG/3TC 50 mg/300 mg referred to as DTG/3TC FDC and the SEs DTG and 3TC.

1.1. Organization of Data

All data pertaining to the DTG/3TC FDC development is presented with this application. Previously submitted studies from DTG or 3TC SE development programs support this application and are categorized as “key” studies or “supportive”:

Key SE Studies: these studies provide data that may be included in labeling, and were conducted during the individual agent development programs. Summaries of key clinical pharmacology studies are presented in Appendix Table 1 and CSRs for these studies have been previously submitted.

Supportive SE Studies: these studies are not essential for the FDC Benefit Risk assessment, but are considered helpful to the reviewer and supportive of the proposed indication. A summary of supportive studies is presented in Appendix Table 2, but reports will be made available upon request for the convenience of the reviewer.

Clinical pharmacology data for the DTG/3TC FDC and each individual component are presented in separate sections as listed below.

"DTG/ 3TC FDC" Sections: A pivotal bioequivalence and food effect study with the DTG/3TC FDC is described in m2.7.1. No other clinical pharmacology study has been conducted with the DTG/3TC FDC formulation proposed for marketing. Statements regarding the DTG/3TC FDC are based on the clinical pharmacology of the individual components.

"DTG Component Studies" Sections: The data in these sections are from the Tivicay SE development program.

"3TC Component Studies" Sections: These sections present data that support the clinical pharmacology sections of Epivir global labeling documents for dosing of the 3TC component.

1.2. Dolutegravir/Lamivudine Fixed-dose Combination

The main characteristics of clinical pharmacology related to the DTG/3TC FDC product are summarized below based upon a pivotal bioequivalence and food effect study with the DTG/3TC FDC and on information obtained from the SE development programs for the individual DTG and 3TC components.

Bioequivalence

- The [redacted] DTG/3TC FDC tablet was bioequivalent for DTG AUC and Cmax and for 3TC AUC; however, the [redacted] had an approximately 32% higher 3TC Cmax than that seen following 3TC dosed as SE (m2.7.1).
- The higher 3TC Cmax, which reflects differences in the rate of absorption but not extent of absorption, does not significantly affect patient safety and antiviral efficacy based on historical clinical safety and efficacy data at higher 3TC doses/exposures.
- The data from the pivotal BE Study 204994, combined with data from the 3TC historical studies (see m2.7.4 Section 5.6.2), provides an acceptable PK bridge to the SEs used in GEMINI-1 and GEMINI-2 Phase III trials and supports the proposed submission for the [redacted] FDC tablet.

Food Effect

- The DTG/3TC FDC may be taken with or without food (m2.7.1). This is consistent with the prescribing information for the DTG and 3TC single entities.

Drug-drug interactions

- There are no significant drug interactions between DTG and 3TC – the 2 active components of the FDC tablet.
- The absence of DDI between both drugs and the results of the BE study of the FDC tablet allows extrapolation of DDI with the single agents to the FDC regimen.
- DTG and 3TC each have a generally favorable drug interaction profile with few clinically relevant interactions that require a dose adjustment, dose separation, or contraindication.
- Co-administration of DTG/3TC and the following drugs is contraindicated: dofetilide and pilsicainide.
- A dose adjustment of metformin should be considered when starting and stopping co-administration of DTG/3TC FDC with metformin to maintain glycemic control.
- 3TC is not recommended for use in combination with FTC.
- CBZ, ETV, RIF, EFV, and TPV/RTV have been shown in studies to decrease DTG exposures. Therefore, to manage this interaction, a second dose of DTG tablet should be administered daily approximately 12 hours after the DTG/3TC FDC in patients requiring co-administration of DTG/3TC FDC with these drugs.
- Co-administration of DTG and drugs that contain divalent metal cations may result in decreased DTG plasma concentrations. Therefore, avoidance or dose-separation strategies are needed to manage the following absorption-based drug interactions for DTG/3TC FDC:
    - For Mg/Al-containing antacids and sucralfate, DTG/3TC should be administered 2 hours before or 6 hours after taking the antacid.
    - For other Fe- and Ca-containing products (e.g., vitamin supplements), 2 alternatives are available:
        - DTG/3TC FDC should be administered 2 hours before or 6 hours after taking the product or,
        - Take DTG/3TC FDC and Fe/Ca together with a meal to overcome the Fe/Ca effect on DTG absorption

Special populations

- DTG/3TC FDC can be used once daily in adolescents (12 to <18 years of age weighing at least 40 kg) with or without food.
- DTG/3TC FDC may be administered without dose adjustment in patients with mild or moderate hepatic impairment (Child-Pugh Grades A & B). The effect of severe hepatic impairment (Child-Pugh Grade C) on DTG has not been studied. Therefore, DTG/3TC FDC is not recommended for use in patients with severe hepatic impairment.

- DTG/3TC FDC may be administered without dose adjustment in patients with CrCl ≥50 mL/min. DTG/3TC FDC is not recommended for use in patients with CrCl less than 50 mL/min.
- HBV/HCV co-infection had no clinically relevant effect on DTG PK (HCV, limited data on HBV). HBV co-infection has no clinically relevant effect on 3TC PK.
- There was no clinically relevant effect of gender, weight, age, race/ethnicity, UGT1A1, and smoking on DTG or 3TC PK in adults, and therefore no need for individualized dose adjustments based on these factors.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1. Dolutegravir/Lamivudine Fixed-dose Combination

A pivotal BE and food effect (Study 204994) study of the DTG/3TC FDC proposed for marketing and a relative BA (Study 204993) study with experimental DTG/3TC FDC formulations are described in m2.7.1.

2.2. Dolutegravir

A summary of the study design, treatments, and main conclusions of the SE clinical pharmacology studies are summarized in Appendix Table 1. A summary of single- and repeat-dose DTG PK parameters in clinical pharmacology studies discussed in this module are presented in Appendix Table 5 and Appendix Table 6, respectively. A summary of PK parameters for co-administered medications are provided in Appendix Table 9.

2.2.1. Pharmacokinetics and Mass Balance in Healthy Subjects

The PK profile of repeat doses of DTG 10, 25, and 50 mg suspensions in healthy subjects was investigated in Study ING111322. Appendix Table 1 provides a summary of the study design and the main results. Following repeat dosing, steady state was achieved after approximately 5 days of dosing, and DTG showed time-invariant PK; accumulation ratios after 50 mg once daily dosing were 1.42, 1.36, and 1.38 for AUC(0-∞), Cmax, and Cτ, respectively.

Study ING111853 was conducted to investigate the recovery, excretion, and PK of DTG administered as a single, oral suspension 20-mg dose containing ^{14}C-DTG in healthy adult subjects (Appendix Table 1). DTG was eliminated primarily through hepatic metabolism with minimal renal excretion (<1% of dose administered orally); UGT1A1 was the primary route of metabolism with CYP3A4 as a notable secondary metabolic pathway.

2.2.2. Pharmacokinetics and Pharmacokinetic-Pharmacodynamic Relationships in Target Patient Population

Study ING116070 (DTG 50 mg once daily + background therapy) is a key study to the DTG/3TC FDC submission and is summarized in Appendix Table 1. Study ING111521 (10-day single agent study, DTG 2-50 mg once daily), Study ING112276 (DTG 10 mg, 25 mg, or 50 mg, once daily + background therapy), and Study ING111762 (DTG 50 mg once daily + background therapy) are supportive studies to the DTG/3TC FDC submission and are summarized in Appendix Table 2.

Patients in the Phase 3 trials of DTG + 3TC (Study 204861 and Study 205543, m2.7.3) received the approved DTG dose of 50 mg once daily. The DTG/3TC FDC tablet was developed with DTG 50 mg. The DTG 50 mg once daily dose was selected for Phase 3 based on the results of Study ING111521 (10-day single agent study, DTG 2 to 50 mg once daily) and Study ING112276 (DTG 10 mg, 25 mg, or 50 mg, once daily + background therapy), and confirmed in Study ING113086 (Phase 3, 96-week, non-inferiority, DTG 50 mg once daily + 2 NRTIs). These studies are supportive of the DTG/3TC FDC submission and are summarized in Appendix Table 2.

2.2.3. Pharmacokinetics in Special Populations

The PK of DTG was investigated in healthy Japanese subjects (ING115381), and in subjects with moderate hepatic impairment (ING113097) and severe renal impairment (ING113125). In the literature, the steady-state PK of DTG following once-daily administration of Triumeq was investigated in 40 HIV-infected patients with a median (range) age of 66 (60-79) years [Elliot, 2018]. The PK of DTG was also investigated in ARV treatment-experienced, INI-naïve HIV-1 infected adolescents ≥12 to <18 years of age (ING112578). A summary of the study design and main conclusions are provided in Appendix Table 1. In summary, no dose adjustment of DTG is needed in Japanese subjects, in subjects with mild to moderate hepatic impairment, or in subjects with mild to severe renal impairment (not on renal replacement therapy). In addition, data from study ING112578 showed that plasma DTG exposure values for once daily dosing in adolescents ≥12 to <18 years of age weighing ≥40 kg were similar to those observed in adult patients on approved 50 mg QD. Lastly, compared to a younger control group, the Cmax of DTG was 25% higher in subjects ≥60 years old, while no difference was observed for DTG AUC(0-24), C24, or t1/2 [Elliot, 2018].

2.2.3.1. Pregnancy

There is limited DTG PK data in pregnant women available from clinical studies.

In the IMPAACT 1026 study, DTG PK in 21 pregnant women who received DTG 50 mg once daily showed that DTG exposure was 25 to 30% lower in the 2nd and 3rd trimesters compared to paired postpartum data [Mulligan, 2016]. However, the DTG AUC(0-24) was similar to historical non-pregnant adult controls. The median trough concentration was lower in pregnancy compared to postpartum data, but still well above the DTG PA IC_{90}. DTG readily crossed placenta with median infant cord blood concentrations higher than maternal concentrations.

In the PANNA study, DTG PK from 8 pregnant women who received DTG 50 mg once daily showed that DTG exposure and trough concentration in the third trimester appeared to be similar compared to postpartum and with reference literature values [Bollen, 2017].

A case report showed that DTG was excreted into breastmilk with a milk-to-plasma ratio of approximately 0.02. This resulted in infant plasma levels during exclusive breastfeeding comparable with proposed target concentrations in treatment-naïve patients [Kobbe, 2016].

2.2.4. Pharmacokinetic Interactions

Summaries of study design, treatments, and the main conclusions from 21 previously completed DDI studies from the DTG single agent development program that are key to the DTG/3TC FDC submission are provided in Appendix Table 1. In summary, no clinically significant drug interactions were observed between DTG and MDZ, oral contraceptives containing NGMN and EE, methadone, multivitamins, OMP, prednisone, RBT, TDF, RPV, DRV/RTV, LPV/RTV, ETV/LPV/RTV, ETV/DRV/RTV, DCV, BCV, and TVR. There are few clinically relevant interactions that require dose adjustment, dose separation, or contraindication. DTG inhibited the renal transporter OCT2, a mechanism that is consistent with a benign increase in serum creatinine. Based on this observation, DTG may reduce the excretion of dofetilide, thereby increasing plasma concentrations to toxic levels; therefore, co-administration of DTG and dofetilide or pilsicainide is contraindicated. In addition, a clinical DDI study showed that DTG increased metformin exposures which may lead to a dose adjustment for metformin.

2.2.5. Clinical Pharmacodynamics

2.2.5.1. Study ING111856 (Thorough QT) and Study ING114819 (Effect of Dolutegravir on Renal Function)

Study ING111856 investigated the effect of DTG on cardiac repolarisation compared with placebo in healthy adult subjects, and Study ING114819 was designed to confirm the mechanism behind the increase in serum creatinine observed during DTG therapy by investigating whether DTG had any effect on GFR or ERPF. Summaries of study designs, treatments, and conclusions from both studies from the SE development program for DTG are provided in Appendix Table 1. Study ING111856 showed that DTG had no effect on cardiac repolarization at a supratherapeutic dose of 250 mg administered in suspension. In Study ING114819, DTG was shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without significantly affecting GFR or ERPF. DTG inhibits the renal transporter OCT2, a mechanism that is consistent with a benign increase in serum creatinine.

2.3. Lamivudine

A summary of the study design, treatments, and main conclusions of the SE clinical pharmacology studies are summarized in Appendix Table 1. A summary of single- and repeat-dose 3TC PK parameters in clinical pharmacology studies discussed in this module and a summary of PK parameters for co-administered medications are presented in Appendix Table 7.

The clinical development of 3TC was initially targeted for the treatment of HIV infection (initial dose 150 mg BID, subsequent approval for 300 mg once daily). Preclinical (virology) studies also indicated 3TC would have utility in treating HBV viral infection at a lower daily dose (100 mg once daily). The development path thus required studies performed to support either or both of these indications. Key 3TC studies supporting once daily dosing in HIV adult/adolescent patients are presented in this module (Appendix Table 1); however, any study conducted to support either indication is available upon request.

2.3.1. Pharmacokinetics in Healthy Subjects

Study EPV10001 was designed to compare the plasma 3TC and intracellular 3TC-TP PK following a once daily 3TC regimen (300 mg once daily) versus a BID 3TC regimen (150 mg BID) given the same daily dose (300 mg of 3TC per day) in healthy subjects. The results of the study demonstrated that the same daily dose of 3TC administered either once daily (3TC 300 mg once daily) or BID (3TC 150 mg twice a day) provides equivalent plasma 3TC exposure and intracellular 3TC-TP exposures, as measured by the respective AUC(0-24),ss. Intracellular 3TC-TP trough concentrations (C0,ss and C24,ss) were 18 to 24% lower for the 3TC 300 mg once daily regimen than the 3TC 150 mg BID regimen (Appendix Table 1).

2.3.2. Pharmacokinetics in the Target Patient Population

The PK of 3TC has been studied in HIV-1-infected patients, and a summary of the results is presented in Appendix Table 1 (NUCA2001 and NUCB2001) and Appendix Table 2 (NUCB4001). In summary, in HIV-1-infected patients, following oral dosing, the absolute BA of 3TC was on average approximately 80 to 85% (NUCB1001, see m2.7.1). Similar mean absolute bioavailability values for 3TC (86 to 88%) have been reported after single 100 mg doses of tablet, capsule, and oral solution formulations (NUCA1003, see m2.7.1). 3TC is primarily eliminated as unchanged drug in urine; CLr exceeded GFR, suggesting that 3TC CLr involves tubular secretion (NUCB1001, see m2.7.1). 3TC generally displayed linear, dose-proportional PK following oral dosing of 0.5 to 20 mg/kg (NUCB2001).

2.3.3. Pharmacokinetics in Special Populations

The PK of 3TC was investigated in healthy Japanese subjects (LA-01, LA-02), healthy elderly Japanese subjects (LB-05), healthy Chinese subjects (NUCB1009), subjects with mild/moderate and severe renal impairment (NUCB1003), and subjects with moderate or severe hepatic impairment (NUCB1002). The PK of 3TC was also investigated in HIV-infected adult patients with moderate and end stage renal impairment (NUCA1004), HIV-positive children (NUCA2002, COL105677, EPV40002, COL104929), and children and adolescents with chronic HBV infection (NUCB2020). Summaries of the main conclusions of these studies are provided in Appendix Table 1. In summary, no dose adjustment of 3TC is needed in subjects with moderate or severe hepatic impairment. Because 3TC is primarily renally cleared, impairment of renal function significantly impacts 3TC exposure, requiring dose modification in subjects with CrCl <50 mL/min and severe renal impairment or HIV-infected adult patients with moderate and end stage renal impairment where CrCl falls below 50 mL/min. 3TC exposure and excretion of

3TC in urine in healthy Japanese or Chinese subjects were consistent with those obtained following similar doses in healthy Caucasian subjects when comparing with historical data. Children and adolescents (>25 kg) can be administered the adult dose of 300 mg once daily.

2.3.3.1. Pregnancy

The PK of 3TC during pregnancy, labor, and post-partum as well as placental and breastmilk transfer, amniotic fluid, cord blood, and fetal exposure has been investigated in several studies.

3TC PK were studied in pregnant women during 2 clinical trials conducted in South Africa. The trials assessed PK in 16 women at Week 36 of gestation while receiving 3TC 150 mg BID with ZDV, 10 women at Week 38 of gestation receiving 3TC 150 mg BID with ZDV, and 10 women at Week 38 of gestation receiving 3TC 150 mg BID without other ARVs. 3TC concentrations were generally similar in maternal, neonatal, and umbilical cord serum samples. In a subset of subjects, amniotic fluid specimens were collected following natural rupture of membranes and confirmed that 3TC crosses the placenta in humans. Based on limited data at delivery, median (range) amniotic fluid concentrations of 3TC were 3.9 (1.2 to 12.8)-fold greater compared with paired maternal serum concentrations (n = 8) [Epivir Product Information, 2018].

High concentrations of 3TC were also reported in amniotic fluid, where concentrations at the time of delivery averaged approximately 5-fold more than the maternal plasma concentration [Mandelbrot, 2001]

A population PK analysis of 3TC in 228 pregnant and non-pregnant women suggested that 3TC clearance is 22% higher during pregnancy. However, faster 3TC clearance did not result in suboptimal exposure; thus, dose adjustments are not required during pregnancy [Benaboud, 2012]. Placental transfer estimated by the fetal:maternal AUC ratio in this study was 0.86.

3TC crosses placenta by simple diffusion, and the ratio of 3TC concentration in maternal plasma at the time of delivery and cord blood was around 1 [Bloom, 1997, Mandelbrot, 2001].

3TC is excreted into human milk. Samples of breast milk obtained from 20 mothers receiving 3TC either as monotherapy or combination therapy had measurable concentrations of 3TC [Epivir Product Information, 2018].

2.3.4. Pharmacokinetic Interactions

3TC is cleared renally and has minimal [hepatic] metabolism. It is not an inhibitor of or inducer of CYPs. This profile, coupled with the clinical data available from a small number of DDI studies carried out, indicates 3TC is very unlikely to have a significant interaction as either victim or perpetrator. A small number (5) of DDI studies were carried out to support 3TC clinical development and labelling; the study design and main conclusions of these studies are summarized in Appendix Table 1. In summary, no clinically significant drug interactions were observed between 3TC, ABC, ZDV, and ddI

(CNAA1002, NUCA1005, NUCA2005). There was no significant DDI and no dose modification is required when 3TC is co-administered with ABC, ZDV, or ddI. No contraindication or dose adjustment of 3TC is required when co-administered with TMP or SMX at normal doses (NUCA1007). In a DDI study (204857) designed to estimate the effect of SBT-containing solutions on 3TC plasma PK parameters, co-administration of 3TC solution with SBT solution under fasting conditions decreased plasma exposures (AUC and Cmax). Therefore, when possible, it is recommended to avoid chronic co-administration of SBT-containing medicines with 3TC and to consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

2.3.5. Clinical Pharmacodynamics

2.3.5.1. Pharmacodynamics: Properties Related to Therapeutic Effect

3TC is the negative (cis) enantiomer of 2',3'-dideoxy-3'-thyacitidine, a dideoxy pyrimidine which requires intracellular triphosphorylation to the active form, 3TC-TP. In vitro, the intracellular half-life of 3TC-TP in this system ranged from 10.5 to 15.5 hours.

Studies EPV10001 and NUCB4001 evaluated plasma 3TC and intracellular 3TC-TP PK between 300 mg once daily and 150 mg BID dosing (EPV10001) and between 150 mg BID and 300 mg BID dosing (NUCB4001). In EPV10001, a higher plasma 3TC Cmax for 300 mg QD vs. 150 mg BID was observed, while the steady-state intracellular 3TC-TP Cmax did not increase. In NUCB4001, serum 3TC AUC and Cmax increased with dose, whereas the intracellular Cmax and AUC(0-12) of the 3TC mono-, di- and triphosphate moieties remained similar between the high and low dose.

Together, these studies indicate that saturation of the intracellular 3TC phosphorylation and a plateauing of intracellular 3TC-TP occur at exposures between a 300 mg to 600 mg daily dose. This is supported by the combined analysis of 4 pivotal registrational studies which showed a comparable safety profile in treatment groups that received a 3TC 600 mg daily dose (300 mg BID) to groups that received a 3TC 300 mg daily dose (150 mg BID) (See m2.7.4 Section 5.6.2). Therefore, any increase in plasma Cmax associated with the [redacted] FDC is unlikely to translate to an increased safety risk due to plateauing of intracellular 3TC-TP.

Plasma AUC is a surrogate measure of intracellular 3TC-TP concentration and is considered to be the best plasma PK predictor of NRTI efficacy [Wang, 2004, Weller 2000, Fletcher, 2000]. The 3TC AUC for the [redacted] FDC was bioequivalent to the 3TC 300 mg SE used in the GEMINI-1 and GEMINI-2 studies, indicating that the extent of absorption is the same for the [redacted] FDC and the SE 3TC 300 mg tablet and that no impact on clinical efficacy is expected.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Dolutegravir

3.1.1. Absorption

Following oral administration of tablet formulations in the absence of food, DTG absorption is rapid with no tlag and a median tmax of 2 to 3 hours post dose. Consistent with the SE, following oral administration of the DTG/3TC FDC, DTG absorption was rapid with a median tmax of 2.5 hours post dose. DTG concentration declines mono-exponentially with an average t1/2 of approximately 14 hours.

DTG absorption is increased with co-administration of food for both the single entity and the DTG/3TC FDC (m2.7.1, Section 2.4.2), and median tmax increased to 5.0 hours post dose. In addition, DTG absorption decreased when co-administered with polyvalent metal cation-containing products (Appendix Table 1). Following oral administration of tablet formulations, in general, DTG exhibits nonlinear PK with less than dose-proportional increases in plasma exposure from 2 to 100 mg (Study ING111521 and Study ING114005), likely due to different dispersion rates of various tablet strengths and solubility-limited absorption at higher doses; however, increase in DTG exposure appears dose proportional from 25 mg to 50 mg (as observed in Study ING112276).

The mean AUC(0-∞) value of the tablet was ~30% less than that of the suspension resulting in an estimated fraction absorbed from the tablet of 49 to 56%. Following single oral administration as a tablet formulation, food was noted to modestly increase systemic exposure to DTG (66%) resulting in an estimated fraction absorbed of 81 to 93%.

The absolute BA of DTG has not been directly measured due to low solubility and its non-specific binding, which present significant challenges to an IV formulation for DTG even at very low doses. However, based on accumulated data from in vitro permeability, metabolism, and biliary excretion in animals, and a human mass-balance study (ING111853, Appendix Table 1), the absolute BA of DTG is estimated to be approximately 67 to 80% from the suspension formulation and 49 to 56% from the tablet formulation.

3.1.2. Distribution

Apparent volume of distribution was estimated at 17.4 L following oral tablet dosing based on a population PK analysis in treatment-naïve subjects. The estimated Vd/F is greater than the total plasma volume (~3 L for a 70-kg person), but similar to the volume of total water in the extracellular space (~15 L for a 70-kg person). Total blood and plasma drug-related radioactivity concentration ratios, as measured in the human mass balance Study ING111853 (Appendix Table 1), were averaged at 0.441 to 0.535, indicating minimal association of DTG with blood cellular components.

In vitro, the protein binding of DTG in human serum and plasma is high (approximately 99.3%). DTG appears to primarily bind to albumin based on the hepatic impairment Study ING113097 (Appendix Table 1) where the DTG unbound fraction showed better correlation with albumin than AAG.

DTG is present in CSF at levels similar to the unbound concentration in plasma (ING116070). DTG is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue, and vaginal tissue were 6 to 10% of that in corresponding plasma at steady state (ING115465), and AUC in semen and rectal tissue were 7% and 17%, respectively, of that in corresponding plasma at steady state (ING116195). In the literature, median DTG concentrations in CSF were 18 ng/mL at Week 2 and 13 ng/mL at Week 16 in 13 HIV-1 infected male subjects receiving DTG (50 mg) + ABC/3TC (600/300 mg) once daily [Letendre, 2014, a publication from Study ING116070]. Ratios of DTG CSF to total plasma concentration were similar to the unbound fraction of DTG in plasma. Median changes from baseline in CSF (n = 11) and plasma (n = 12) HIV-1 RNA were -3.42 and -3.04 $\log_{10}$ c/mL, respectively. Nine of 11 subjects (82%) had plasma and CSF HIV-1 RNA levels <50 c/mL and 10 of 11 (91%) had CSF HIV-1 RNA levels <2 c/mL at Week 16 [Letendre, 2014, publication from Study ING116070].

3.1.3. Metabolism

Following oral administration of 20 mg ^{14}C-DTG in humans, unchanged DTG is primarily eliminated through metabolism, and renal elimination of unchanged DTG represents less than 1% of the total dose administered. The quantified metabolites in humans include an ether glucuronide of DTG (M3), an N-dealkylation metabolite (M1), a product from oxidation at the benzylic carbon (M7), and a product of oxidative defluorination with cysteine addition (M13). M3 is the major metabolite observed in urine and represents 18.9% of the total dose administered. The total radioactivity of the metabolites formed through oxidation (M1, M7, and M13) that are recovered in urine and feces accounts for approximately 9.7% (mean) of the total dose administered. The enzymes responsible for the formation of M3 are UGT1A1 (major), and UGT1A3 and UGT1A9 (minor). The enzyme responsible for forming M7 is CYP3A4, while the enzyme responsible for forming M13 is unknown. M1 is formed by hydrolysis of M7. Therefore, UGT1A1 is the primary route of metabolism, with CYP3A4 as a secondary metabolic pathway in humans. DTG is the predominant circulating compound in plasma, representing 97% of plasma total radiocarbon, while M3 represents <2.4% (Study ING111853). These human metabolites were observed in animals.

The primary metabolite, ether glucuronide of DTG (M3), in plasma shows formation rate-limited elimination following oral administration of DTG (Study ING113125). Apparent half-life of the ether glucuronide in plasma is similar to the parent compound, DTG, and renal excretion is a primary route of elimination of this metabolite (Study ING113125). In subjects with severe renal impairment (Study ING113125), exposure (AUC) of this metabolite is approximately 3-fold higher than that observed in healthy matching subjects, likely due to impaired renal elimination of the metabolite in subjects with renal impairment. However, the apparent half-life of the metabolite is unchanged.

Co-administration of EFV decreases DTG systemic exposure (AUC) by 57% (Study ING114005). The plasma and urine metabolite profiling data suggests that EFV induces both UGT1A1 and CYP3A pathways. In the presence of EFV, DTG is still the major component in plasma, while M3 is present at a mean value of <2% of DTG, similar to that observed from the treatment of DTG alone. DTG and 11 metabolites were identified in pooled human urine. The urine from subjects receiving DTG in combination with EFV displays an increase in the ratio of M3 relative to parent DTG, and a concomitant decrease in the ratio of M1 to DTG, when compared with the metabolic profile of DTG alone. No other significant urinary metabolite differences between the 2 treatments are noted.

As CYP3A4 is a secondary route of elimination of DTG, the first-pass metabolism of DTG following oral dosing is expected to be very low.

The primary metabolite, M3, is an ether glucuronide of DTG, and is not expected to have antiviral activity. As M3 is presented at very low concentrations in plasma, it is not expected to exhibit pharmacological activity leading to toxicity.

3.1.4. Excretion

Renal elimination of unchanged drug is low (<1% of the dose). Following oral administration of a ^{14}C-DTG in a suspension formulation, 31% of the total oral dose is excreted in the urine, represented by M3 (18.9% of total dose), M1 (3.6% of total dose), M7 (3.0% of total dose), and other minor metabolites. Sixty-four percent of the total oral dose is recovered in the feces, represented mainly by DTG (53% of total dose). It is unknown if all or part of the parent compound in feces is due to unabsorbed drug or biliary excretion of the glucuronide conjugate, which can be converted back to the parent compound in the gut lumen. In bile duct-cannulated animals, 7% of the administered dose was recovered as DTG in rat bile, and 12% in monkey bile; the percentage of administered drug recovered as DTG in feces was similar for humans (64%) and monkeys (59%), and higher in rats (88%). Other notable components in feces include M13 (1.8% of total dose) and M1 (1.3% of total dose) (Study ING111853).

DTG has a terminal half-life of ~14 hours and a low CL/F of 0.56 L/hr (Study ING111853), which represents <2% of liver plasma flow; therefore, the hepatic extraction ratio is low (lower than 2%). As CYP3A4 is a secondary route of elimination of DTG, the first-pass metabolism of DTG following oral dosing is expected to be very low.

3.1.5. Intrinsic Factors

Effects of intrinsic factors on DTG PK were evaluated in either Phase I studies or through population PK modeling:

- **Body size, age, gender, and smoking:** These are statistically significant covariates of DTG CL/F, Vd/F, and/or F, but the effects are not considered clinically significant; no DTG dose adjustment according to these covariates is needed. PK data of DTG in subjects of >65 years old are very limited;

- **Adolescents:** plasma DTG exposure values for 50 mg QD dosing in adolescents ≥12 to <18 years of age weighing ≥40 kg were similar to those observed in adult patients on approved 50 mg QD;
- **Race:** Race (Caucasian, African American, and Japanese ancestry) or ethnicity (Hispanic/Latino or Not-Hispanic/Latino) has no effect on DTG PK parameters; no DTG dose adjustment according to race or ethnicity is needed;
- **Hepatic impairment:** DTG PK are similar between healthy subjects and subjects with moderate hepatic impairment (Child-Pugh Grade B) (ING113097, Appendix Table 1); no DTG dose adjustment is needed in subjects with mild to moderate hepatic impairment (Child-Pugh Grade A or B); the effect of severe hepatic impairment on the PK of DTG has not been studied;
- **Renal impairment:** There is no clinically relevant difference in DTG PK in subjects with mild/moderate renal impairment (Population PK in treatment-experienced subjects, Appendix Table 1) or severe renal impairment (CrCL <30 mL/min) (Study ING113125, Appendix Table 1); no DTG dosage adjustment is needed for subjects with mild, moderate, and severe (CrCL<30 mL /min, not on dialysis) renal impairment; currently there is no data on DTG PK in subjects on hemodialysis although no effect of hemodialysis on DTG PK is expected due to high protein binding of DTG in plasma;
- ***UGT1A1*** **polymorphism:** Subjects with genotypes conferring poor metabolizer status of UGT1A1 *(*28/*28*; **28/*37*; **37/*37*) had a 32% lower clearance, 46% higher AUC, and 32% higher Cmax of DTG compared with subjects with genotypes associated with normal UGT1A1 activity (**1/*1*, **1/*36*) (ING116265, Appendix Table 1). Increases in DTG exposure due to UGT1A1 polymorphisms are not considered clinically significant. No DTG dose adjustment according to UGT1A1 polymorphism is needed;
- **HBV/HCV co-infection:** HCV co-infection has no effect on DTG PK exposure. There were limited PK data for subjects with HBV co-infection. There is no drug interaction between DTG and commonly used or recently approved drugs for the treatment of HBV or HCV (Section 3.1.6.2). DTG can be used in HBV or HCV co-infected subjects.

Results from subgroup analysis of integrated efficacy (m2.7.3) and integrated safety (m2.7.4, Section 5.1.1) indicated that there was no apparent or consistent difference in efficacy and safety by age, gender, or race, supporting the conclusions of no dose adjustment for DTG by these intrinsic factors. Although no differences in DTG systemic exposure is seen with HBV/HCV co-infection, differences in the safety profile of DTG for HBV and HCV co-infected subjects are observed (m2.7.4, Section 5.1.2) and are likely due to the intrinsic nature of these diseases and to the more robust virologic and immunologic activity of DTG, especially in treatment-experienced subjects, rather than direct toxicity of DTG. Therefore, dose adjustment is also unnecessary due to this intrinsic factor.

3.1.6. Extrinsic Factors

A total of 21 Phase I DDI studies in healthy subjects have been performed and completed to assess the interaction between DTG and various drugs, including ARV medications for HIV treatment and non-ARV medications expected to be used concomitantly with DTG.

3.1.6.1. Non-clinical transporter data

In vitro, DTG is an inhibitor of the basolateral renal OCT2 and the renal apical transporters: MATE1 transporter (IC_{50} = 6.34 μM) and MATE2-K (IC_{50} = 24.8 μM). DTG has a low potential to affect the transport of MATE2-K substrates. In vitro incubation with DTG concentrations that were observed in vivo after a 50-mg oral dose produced a 90% inhibition of OCT2. These in vitro results indicate the potential for a drug interaction in vivo with cationic compounds that are renally cleared by these transporters, such as the endogenous substrate, creatinine, the antiarrhythmic drugs, dofetilide and pilsicainide, and the anti-diabetic drug, metformin. Caution should be used when considering co-administration of narrow therapeutic index cationic drugs in which a significant part of their clearance is by renal proximal tubule secretion by OCT2 or MATE1 (see Section 3.1.6.2 for details).

3.1.6.2. Drug-drug interactions

Due to different routes of metabolism and elimination and minimal effect of DTG and 3TC on drug metabolizing enzymes or transporters, no clinically significant drug interactions are expected between DTG and 3TC. The primary route of elimination of DTG is metabolism with UGT1A1 as the primary route and CYP3A as the secondary route. The primary route of elimination of 3TC is renal excretion. Although DTG is an inhibitor of OCT2 and has the possibility to increase the exposure of 3TC as OCT2 may be involved in active secretion of 3TC in the urine [Moore, 1996], no clinically relevant drug interaction has been observed between DTG and 3TC. This is supported by the cross-study comparison demonstrating that the PK of 3TC when given as a ABC/3TC FDC tablet co-administered with DTG from the pivotal bioequivalence study ING114580 (m2.7.1) were similar to those obtained when given as ABC/3TC FDC alone in Study CAL10001, a bioequivalence study for Epzicom/Kivexa (m2.7.1). These data suggest that DTG does not have an effect on 3TC exposure. Therefore, no PK drug interaction study was conducted between the individual components of DTG and 3TC.

Effect of Dolutegravir on the Pharmacokinetics of Co-administered Drugs

In vivo drug interaction studies with sensitive substrates for CYP3A4 (MDZ) and CYP2B6 (EFV) confirmed the low propensity of DTG to alter the PK of agents metabolized by either CYP3A4 or CYP2B6 by demonstrating a lack of effect of DTG on the PK of MDZ and EFV. Drug interaction studies also indicated no clinically meaningful effect of DTG on TDF (a renal OAT1, OAT3, MRP2, and MRP4 substrate), RPV (a CYP3A substrate), methadone (primarily metabolized by CYP2B6 and CYP2C19 with CYP3A as a minor route), DCV (CYP3A4 and Pgp substrate), and an OC containing NGMN and EE, which have complex metabolism, including oxidation, reduction, and conjugation (Table 1).

In vitro, metabolic or transporter-related DDI studies have been completed with DTG and the results for the PK parameters of DTG are presented in Table 1.

As noted in Section 3.1.6.1, DTG inhibited the renal transporter OCT2, a mechanism that is consistent with a benign increase in serum creatinine. Based on this observation, DTG may reduce the excretion of dofetilide, metformin, or pilsicainide, thereby increasing plasma concentrations to toxic levels. Co-administration of DTG and dofetilide or pilsicainide is contra-indicated. A drug interaction study (201167) showed that plasma exposures of metformin were significantly increased when co-administered with DTG, and the magnitude of the effect was DTG dose-dependent (Table 1). Co-administration of DTG 50 mg q24h with metformin 500 mg q12h increased metformin AUC(0-τ) by 79% and Cmax by 66%. Additionally, when co-administered with DTG 50 mg q12h; plasma metformin Cmax and AUC(0-τ) were approximately 111% and 145% higher, respectively. Metformin is primarily excreted unchanged in the urine mainly through tubular secretion. In vitro, DTG inhibits OCT2 and MATE 1 which is known to be involved in the tubular secretion of metformin. Thus, an increase in plasma exposure of metformin when co-administered with DTG is not unexpected. However, the extent of increase in metformin plasma exposure is more than would be expected based on in vitro IC_{50} values of OCT2 (1.93 μM) and MATE 1 (6.34 μM) inhibition. Taken together, these findings suggest that mechanisms other than inhibition of metformin renal elimination through inhibition of OCT2 and MATE 1 may be involved in the observed drug interaction. Therefore, a dose adjustment of metformin should be considered when starting and stopping co-administration of DTG/3TC FDC with metformin to maintain glycemic control. Monitoring of blood glucose when initiating concomitant use and after withdrawal of DTG is recommended.

Effects of Co-administered Drugs on the Pharmacokinetics of Dolutegravir

In general, the exposure to DTG can be affected by modulators of the enzymes UGT1A1 and CYP3A4, and by drugs containing divalent cations such as Mg or Al. A summary of the effects of co-administered drugs on DTG PK are presented in Table 2.

Table 1 Summary of Effects of Dolutegravir on Pharmacokinetics of Co-administered Drugs

Concomitant drug	Concomitant drug dose	DTG dose	N	GM Ratio (90% CI) Co-administered drug +DTG / co-administered drug alone			Study	Conclusion
				C24/Cτ	AUC	Cmax		
MDZ (CYP 3A4 substrate)	3 mg single dose	25 mg once daily (suspension)	10	NA	0.945 (0.815, 1.095)	NA	ING111322	No effect on MDZ
TDF	300 mg once daily	50 mg once daily	15	1.186 (1.042-1.350)	1.119 (1.012-1.238)	1.094 (0.974-1.228)	ING111604	No TDF dose adjustment
Methadone	Individualized dose	50 mg BID	11	Total methadone 0.99 (0.91, 1.07) R-methadone 0.95 (0.89, 1.02) S-methadone 1.02 (0.93, 1.12)	0.98 (0.91, 1.06) 0.95 (0.89, 1.02) 1.01 (0.93, 1.09)	1.00 (0.94, 1.06) 0.97 (0.91, 1.03) 1.03 (0.97, 1.10)	ING115698	No methadone dose adjustment
Oral Contraceptive (EE/NGMN)	NGMN 0.25 mg EE 0.035 mg	50 mg BID	15	0.932[c] (0.846, 1.027) 1.019[c] (0.934, 1.112]	0.975 (0.910, 1.044) 1.032 (0.964, 1.105)	0.890 (0.815, 0.973) 0.988 (0.907, 1.077)	ING111855	No OC dose adjustment
RPV	25 mg once daily	50 mg once daily	16	1.214 (1.070, 1.378)	1.063 (0.976, 1.158)	1.102 (0.992, 1.224)	LAI116181	No RPV dose adjustment
DCV	60 mg once daily	50 mg once daily	12	1.06 (0.876, 1.292)	0.978 (0.831, 1.152)	1.033 (0.843, 1.246)	201102	No DCV adjustment

Concomitant drug	Concomitant drug dose	DTG dose	N	GM Ratio (90% CI) Co-administered drug +DTG / co-administered drug alone			Study	Conclusion
				C24/Cτ	AUC	Cmax		
Metformin	500 mg BID	50 mg once daily	15	NA	1.79 (1.65, 1.93)	1.66 (1.53, 1.81)	201167	Metformin dose adjustment [a]
		50 mg BID		NA	2.45 (2.25, 2.6)	2.11 (1.91, 2.33)		
EBR/GZR	EBR 50 mg once daily	50 mg single dose	12	0.98 (0.93, 1.03)	0.98 (0.93, 1.04)	0.97 (0.89, 1.05)	Zepatier USPI	No EBR/GZR dose adjustment
	GZR 200 mg once daily		12	0.86 (0.79, 0.93)	0.81 (0.67, 0.97)	0.64 (0.44, 0.93)		
SOL/VEL	SOL 400 mg once daily	50 mg once daily	24	NA	0.92 (0.85, 0.99)	0.88 (0.80, 0.98)	Vosevi USPI	No SOL/VEL dose adjustment
			24	0.99 [b, c] (0.97, 1.01)	0.99 [b] (0.97, 1.01)	1.01 [b] (0.93, 1.10)		
	VEL100 mg once daily		24	0.88 [c] (0.82, 0.94)	0.91 (0.84, 0.98)	0.94 (0.86, 1.02)		

Data Source: ING111322, Table 11.15; ING111604, Table 11.10; ING115698, Table 11.8; ING111855, Table 3.6, Table 3.10; LAI116181, 201102, Table 10.5 Table 11.15,; 201167, Table 10.051, Table 10.052, Zepatier USPI, 2018, Vosevi USPI, 2017

EBR = Elbasvir; GZR = Grazoprevir; SOL = Sofosbuvir; VEL = Velpatasvir

a. Subjects should be monitored when starting and stopping co-administration of DTG with metformin.
b. GS-331007, active metabolite of prodrug sofosbuvir
c. Cmin

Table 2 Summary of Effects of Co-administered Drugs on Dolutegravir Pharmacokinetics

Co-administered Drug	Co-administered Drug Dose	DTG Dose	N	Geometric Mean Ratio (90% CI) of DTG PK Parameters with/without Co-administered Drugs No Effect = 1.00			Data Source	DTG Dose Recommendation
				Cτ/C24	AUC	Cmax		
TDF	300 mg once daily	50 mg once daily	15	0.920 (0.816-1.036)	1.005 (0.908-1.113)	0.969 (0.867-1.083)	ING111604 Table 11.6	No dose adjustment
DRV/RTV	600/100 mg BID	30 mg once daily	15	0.620 (0.555-0.694)	0.782 (0.722-0.848)	0.892 (0.825-0.965)	ING111405 Table 11.6	No dose adjustment
LPV/RTV	400/100 mg BID	30 mg once daily	15	0.944 (0.848-1.052)	0.973 (0.911-1.039)	1.000 (0.937-1.066)	ING111405 Table 11.6	No dose adjustment
ETV	200 mg BID	50 mg once daily	15	0.121 (0.093-0.157)	0.294 (0.257-0.337)	0.484 (0.433-0.542)	ING111603 Table 11.6	Not recommended
ETV/LPV/RTV	200/400/ 100 mg BID	50 mg once daily	8	1.278 (1.130-1.445)	1.105 (1.017-1.201)	1.072 (1.020-1.128)	ING112934 Table 11.6	No dose adjustment
ETV/DRV/RTV	200/600/ 100 mg BID	50 mg once daily	9	0.629 (0.523-0.758)	0.750 (0.691-0.814)	0.882 (0.781-0.997)	ING112934 Table 11.6	No dose adjustment
Multivitamins	One-a-Day	50 mg single dose	16	0.679 (0.560-0.824)	0.668 (0.553-0.806)	0.646 (0.540-0.774)	ING111602 Table 11.4	No dose adjustment
Maalox	20 mL	50 mg single dose	16	0.256 (0.211-0.311)	0.264 (0.218-0.318)	0.276 (0.231-0.331)	ING111602 Table 11.4	DTG should be taken 2 hours before or 6 hours after antacid
Maalox 2 hrs after	20 mL	50 mg single dose	16	0.703 (0.579-0.853)	0.743 (0.615-0.897)	0.821 (0.686-0.984)	ING111602 Table 11.4	
Calcium carbonate (fasted)	1200 mg	50 mg single dose	12	0.61 (0.47, 0.80)	0.61 (0.47, 0.80)	0.63 (0.50, 0.81)	ING116898 Table 3.5	DTG should be taken 2 hours before or 6 hours after supplement if taken without food; or alternatively, take with food
Calcium carbonate (fed)	1200 mg	50 mg single dose	11	1.08 (0.81, 1.42)	1.09 (0.84, 1.43)	1.07 (0.83, 1.38)	ING116898 Table 3.5	
Calcium carbonate 2hrs prior (fasted)	1200 mg	50 mg single dose	11	0.90 (0.68, 1.19)	0.94 (0.72, 1.23)	1.00 (0.7, 1.29)	ING116898 Table 3.5	
Ferrous Fumarate (fasted)	324 mg	50 mg single dose	11	0.44 (0.36, 0.54)	0.46 (0.38, 0.56)	0.43 (0.35, 0.52)	ING116898 Table 3.5	DTG should be taken 2 hours before or 6 hours after supplement if taken without food; or alternatively, take with food
Ferrous Fumarate (fed)	324 mg	50 mg single dose	11	1.00 (0.81, 1.23)	0.98 (0.81, 1.20)	1.03 (0.84, 1.26)	ING116898 Table 3.5	
Ferrous Fumarate 2hrs prior (fasted)	324 mg	50 mg single dose	10	0.92 (0.74, 1.13)	0.95 (0.77, 1.15)	0.99 (0.81, 1.21)	ING116898 Table 3.5	

Co-administered Drug	Co-administered Drug Dose	DTG Dose	N	Geometric Mean Ratio (90% CI) of DTG PK Parameters with/without Co-administered Drugs No Effect = 1.00			Data Source	DTG Dose Recommendation
				Cτ/C24	AUC	Cmax		
ATV/RTV	300/100 mg once daily	30 mg once daily	12	2.206 (1.972-2.468)	1.617 (1.500-1.743)	1.336 (1.254-1.423)	ING111854 Table 11.6	No dose adjustment
ATV	400 mg once daily	30 mg once daily	12	2.802 (2.523-3.113)	1.911 (1.802-2.026)	1.495 (1.404-1.591)	ING111854 Table 11.6	No dose adjustment
OMP	40 mg once daily	50 mg single dose	12	0.954 (0.752-1.209)	1.00 (0.808, 1.25)	0.915 (0.754-1.111)	ING112941 Table 11.4	No dose adjustment
TPV/RTV	500/200 mg BID	50 mg once daily	14	0.239 (0.212-0.270)	0.409 (0.379-0.443)	0.535 (0.500-0.572)	ING113096 Table 11.6	DTG 50 mg BID[a]
EFV	600 mg once daily	50 mg once daily	12	0.245 (0.179-0.336)	0.431 (0.346-0.536)	0.608 (0.506-0.730)	ING114005 Table 11.10	DTG 50 mg BID[a]
FPV/RTV	700/100 mg BID	50 mg once daily	12	0.510 (0.413-0.629)	0.651 (0.542-0.782)	0.763 (0.632-0.921)	ING113068 Table 11.12	No dose adjustment
RIF	600 mg once daily	50 mg BID[b]	11	1.220 (1.005, 1.480)	1.327 (1.152, 1.529)	1.184 (1.026, 1.366)	ING113099 Table 11.5	DTG 50 mg BID
		50 mg BID[c]	11	0.277 (0.228, 0.336)	0.460 (0.384, 0.552)	0.565 (0.489, 0.652)		
RBT	300 mg once daily	50 mg once daily	9	0.700 (0.566, 0.866)	0.947 (0.816, 1.098)	1.156 (0.978, 1.365)	ING113099 Table 11.6	No dose adjustment
Prednisone	60 mg once daily	50 mg once daily	12	1.167 (1.062, 1.281)	1.111 (1.030, 1.198)	1.062 (0.991, 1.139)	ING115696 Table 11.5	No dose adjustment
BCV	800 mg TID	50 mg once daily	13	1.080 (0.911, 1.281)	1.068 (0.948, 1.203)	1.052 (0.960, 1.153)	ING115697 Table 3.7	No dose adjustment
TVR	750 mg TID	50 mg once daily	15	1.368 (1.290, 1.450)	1.253 (1.196, 1.314)	1.185 (1.111, 1.264)	ING115697 Table 3.8	No dose adjustment
RPV	25 mg once daily	50 mg once daily	16	1.223 (1.149, 1.302)	1.121 (1.053, 1.194)	1.130 (1.055, 1.210)	LAI116181 Table 11.5	No dose adjustment
CBZ	300 mg BID	50 mg once daily	14	0.274 (0.240, 0.313)	0.512 (0.477, 0.549)	0.666 (0.610, 0.726)	200901 Table 10.3	DTG 50 mg BID
DCV	60 mg once daily	50 mg once daily	12	1.4446 (1.246, 1.677)	1.327 (1.106, 1.594)	1.294 (1.070, 1.565)	201102 Table 10.6	No dose adjustment
EBR/GZR	EBR 50 mg + GZR 200 mg once daily	50 mg single dose	12	1.14 (0.95, 1.36)	1.16 (1.00, 1.34)	1.22 (1.05, 1.40)	Zepatier USPI	No dose adjustment

Co-administered Drug	Co-administered Drug Dose	DTG Dose	N	Geometric Mean Ratio (90% CI) of DTG PK Parameters with/without Co-administered Drugs No Effect = 1.00			Data Source	DTG Dose Recommendation
				Cτ/C24	AUC	Cmax		
							Table 9	

Data Source: see table.

a. Caution should be given to INSTI-resistant subjects.
b. Comparison was between DTG 50 mg BID + RIF (test treatment) vs DTG 50 mg once daily (reference treatment).
c. Comparison was between DTG 50 mg BID + RIF (test treatment) vs DTG 50 mg BID (reference treatment).

3.2. Lamivudine

3.2.1. Absorption

Oral absorption of 3TC has been studied in in vitro models and in humans. An in vitro study using the Caco-2 human intestinal model demonstrated that the transport rate was linearly related to the concentration of 3TC, suggesting a passive diffusion process. The apparent permeability of 3TC was 3.2 x 10^{-7} cm/sec compared with that of the paracellular transport marker mannitol of 1 x 10^{-7} cm/sec. This suggests that in addition to paracellular transport, transcellular transport may also be important for the passive diffusion of 3TC across the Caco-2 cell [redacted].

3TC is a highly soluble drug with a rapid dissolution rate. In a single dose cross-over study, absolute oral BA was determined as 86%, 88% and 87% after administration of a 100-mg dose as tablet, capsule, and solution formulations respectively [NUCA1003, see m2.7.1; Yuen, 1995]. In a cross-over study in HIV positive patients, absolute bioavailability was on average approximately 80 to 85% following a single oral dose (NUCB1001, see m2.7.1). In the absence of food, 3TC is absorbed rapidly from the gastrointestinal tract, reaching peak serum concentration (Cmax) approximately 1 hour after dosing [Glaxo report number NUCA1001 UCP/92/015; Van Leeuwen, 1992; Angel, 1993]. Consistent with the single entity, following oral administration of the DTG/3TC FDC, 3TC absorption was rapid with a median tmax of 1 hour. After single and multiple administration of a therapeutic oral dose (2 mg/kg-4 mg/kg/day), Cmax was determined to be 1 to 1.9 μg/mL [Glaxo report number UCR/95/001; Pluda, 1995].

Food has a modest impact on 3TC Cmax (~30-40% lowering) and prolongation of tmax (~3.2 hours) but makes no difference to overall AUC or Cmin concentrations, therefore no dose recommendations are necessary when 3TC is co-administered with food. Similar to the single entity, food resulted in ~32% lower 3TC Cmax and a tmax prolongation to 2.75 hours for the DTG/3TC FDC and no impact on AUC.

3.2.2. Distribution

In vitro, the binding of 3TC to human plasma proteins, at therapeutic concentrations (<0.1 μg/mL), is low (36%); however, at concentrations of 1 to 100 g/mL binding falls to <10%. In vitro studies showed that over the concentration range of 0.1 to 100 μg/mL, the amount of 3TC associated with erythrocytes ranged from 53 to 57% and was independent of concentration.

3TC penetrates freely into tissues, and has a large apparent Vd. After IV administration at 0.25 to 8 mg/kg, the mean apparent Vd is 1.3 L/kg, indicating that the drug penetrates into total body fluid [Glaxo report number UCP/925/015; Van Leeuwen, 1992].

A study of 6 HIV-infected adult patients showed that 3TC penetrated into CSF in low to moderate amounts. After administration of 8 to 20 mg/kg/day, the mean CSF:serum ratio was 0.06 2 hours after dosing, with CSF concentrations ranging from 0.41 to 1.43 μmol/L [Study NUCB2001; Van Leeuwen, 1995].

In a study of 27 HIV-infected women who received 3TC 300 mg once daily, 3TC achieved greater genital tract exposures than blood plasma after a single dose and under steady-state conditions, with median genital tract exposures (AUC ratio) of 241% after a single dose and 411% after multiple doses relative to blood plasma [Dumond, 2007].

Concentrations of 3TC in seminal plasma were greater than in blood plasma in 8 HIV-1-infected men after receiving 3TC 150 mg BID [Taylor, 2000] and in 12 HIV-1-infected men after receiving 3TC 150 mg BID + ZDV + APV [Pereira, 2002]. Median 3TC concentrations were 2305.8 ng/mL in seminal plasma and 880.5 ng/mL in blood plasma 0 to 2 h after dosing and 2497.7 ng/mL in seminal plasma and 168.4 ng/mL in blood plasma >2 h after dosing [Pereira, 2002].

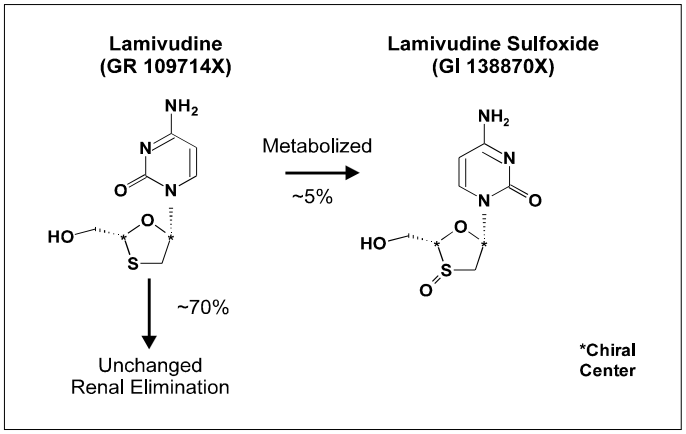
3TC penetrates into amniotic fluid, breast milk, umbilical cord blood, and neonatal serum.

3.2.3. Metabolism

3TC showed no inhibition of the metabolism of MDZ (CYP3A substrate) in in vitro studies [GlaxoSmithKline document number GDM/94/124]. Studies were also conducted to assess the potential roles of the anion or cation transport systems in active renal excretion of 3TC. Probenecid (a competitive inhibitor of organic anion transport in the kidney) had no effect on CLr of 3TC in the isolated rat perfused kidney model implying 3TC is not actively secreted to a significant degree by the organic anion transport system.

3TC is largely excreted in the urine as unchanged drug. Approximately 70% of the dose is recovered over a 24-hour period after oral or IV administration, and hepatic metabolism of 3TC is a minor route of elimination (NUCB1001, see m2.7.1). Approximately 5 to 10% of the parent compound is converted to the pharmacologically inactive trans-sulphoxide metabolite (NUCB1001, see m2.7.1) (Figure 1), which is excreted in the urine within 12 hours of a single oral dose in healthy subjects only [NUCB1003]. The amount of trans-sulphoxide formed increases as renal function declines such that the percentage ratio of 3TC to metabolite can reach 50% in severely renally impaired patients [NUCB1003].

Figure 1 Conversion of Lamivudine to Trans-Sulphoxide Metabolite



3.2.4. Excretion

Renal clearance greatly exceeds CrCl, which is consistent with net renal tubular secretion. The mean CL of 3TC after oral administration has been reported as 22.6 L/hour [Yuen, 1995]. In other studies, CL/F has been determined as 320.9 mL/min, with CLr estimated as approximately 200 to 350 mL/min [Van Leeuwen, 1992; Johnson, 1999; Heald, 1996]. See Section 3.2.6.1 for potential for interactions on renal excretion.

Little accumulation of plasma 3TC occurs during multiple dosing. After BID administration at 12 hourly intervals for 15 days, the accumulation ratio between Day 15 and Day 1 was 1.48, which is in agreement with predictions from single-dose data, assuming an elimination half-life of 5 to 7 hours (NUCA2001).

The terminal elimination half-life of 3TC was determined to be 2 to 4 hours in early studies with a sub-optimal sampling scheme and assay sensitivity. In subsequent studies, the value has increased to 5 to 7 hours, which is the dominant value that dictates the observed accumulation. Longer elimination half-lives of 18 to 19 hours have been reported, depending on the length of the sampling period (ING114580, ING114581, 204857, 204994).

In a study of 10 asymptomatic HIV-positive patients, the mean half-life of the active moiety, 3TC-TP, was found to range from 16 to 19 hours (NUCB4001). Intracellular triphosphate concentrations were comparable following either 150 mg BID or 300 mg once daily [Yuen, 2004]. Pooling of the diphosphate was observed confirming that the rate-limiting step was conversion of the di- to the triphosphate. The pooling of the diphosphate metabolite and the long triphosphate half-life support the suitability of 3TC for once daily dosing.

3.2.5. Intrinsic Factors

Effects of intrinsic factors on 3TC PK were evaluated in either Phase I studies or through population PK modeling:

Renal impairment: Two studies (NUCB1003, NUCA1004) demonstrated that there was a linear relationship between 3TC clearance and renal function (assessed as CrCl) where a reduction in renal function produced a higher exposure to 3TC; therefore, dose modification of 3TC is required in patients where CrCl falls below 50 mL/min. When data from the two renal impairment studies were combined, the regressional analysis was very similar to that for either study alone indicating that the two renally impaired populations, i.e., HIV-positive and non-HIV-positive patients were essentially similar.

Hepatic impairment: Hepatic impairment did not impact significantly on 3TC clearance, so no dose modification is required for patients with moderate or severe hepatic impairment (NUCB1002) (unless accompanied by renal impairment where CrCl <50 mL/min).

Gender and Race: Available data in women and men indicate that there is no appreciable difference by gender in the PK properties of 3TC. A study in Japanese healthy subjects (LA-02) showed no statistical or clinical difference between males and

females. This is consistent with the fact that 3TC is well absorbed and excreted largely unchanged via the kidneys. PK studies carried out in healthy Japanese subjects (LA-01, LA-02) showed parameter estimates in line with those seen in subjects from other ethnic groups. Likewise, a study in Chinese healthy subjects (NUCB1009) showed no statistical or clinical difference between males and females or in comparisons of the PK parameter estimates to Caucasian data. Although no differences in PK parameters in HBV-infected patients as a result of gender or race are expected, two population-based PK analyses were carried out in patients with HIV and also those with HBV infection. Population estimates for CL/F and V/F obtained were in line with values obtained in previous PK studies. The most significant covariant was renal function, again consistent with previous data.

Age:

Elderly: In elderly Japanese patients (LB-05), the age-related reduction in CLr resulted in a moderate (40%), but clinically insignificant, increase in daily exposure. Other parameters were not significantly affected and dose modification is not required on the basis of age alone, unless accompanied by significant impairment in renal function.

Children and Adolescents: Significant differences in CL and CL/F have been described between pediatric and adult patients. When the relationship of Clo and age for the combined data from studies NUCA2002 and NUCA2005 (Day 1 data only) was adjusted for body size (weight), as age increases, Clo approaches adult oral Clo (approximately 0.5 L/h/kg) values. This occurs at adolescence (approximately 12 years). Due to the larger CL values in pediatric patients compared with adults relatively larger doses are required to achieve similar exposure. The comparative 3TC exposure following doses of 4 mg/kg/day in adults compared with 8 mg/kg/day in pediatric patients up to 12 years old, support the recommendation to transition pediatric patients to adult dosing recommendations when the total daily dose reaches the dose recommended for adults (i.e., 300 mg once daily). This occurs at approximately 40 kg body weight (typically at adolescence >12 years old).

3.2.6. Extrinsic Factors

3.2.6.1. Drug-drug interactions

Non-clinical transporter data

Although 3TC is a substrate of BCRP and Pgp in vitro, inhibitors of these efflux transporters are unlikely to affect the disposition of 3TC due to its high bioavailability. 3TC is an in vitro substrate of MATE1, MATE2-K, and OCT2. TMP (an inhibitor of these drug transporters) has been shown to increase 3TC plasma concentrations; however; the resulting increase was of such magnitude that a dose adjustment is not recommended as it is not expected to have clinical significance. 3TC is a substrate of the hepatic uptake transporter OCT1. As hepatic elimination plays a minor role in the clearance of 3TC, drug interactions due to inhibition of OCT1 are unlikely to be of clinical significance.

A mechanistic kidney PK model, as part of the SimCYP PBPK simulator, was used to assess the effect of OCT1 and OCT2 inhibition by 3TC on metformin systemic exposure at the clinically efficacious exposures [m4.2.2.6]. At therapeutic exposures, no change in metformin exposure (exceeding the 1.25x bioequivalence threshold) was predicted with 3TC. These simulations suggest that 3TC is not predicted to perpetrate systemic DDIs with metformin.

Potential for Metabolic Interactions

The potential of 3TC to participate in DDIs is very low, given it is renally cleared and subjected to negligible (hepatic) metabolism (5-10%).

Potential for Interactions on Absorption

The transport of 3TC across Caco-2 cell [redacted] in the presence of several drugs was studied to investigate the transport mechanism of 3TC and potential drug interactions on the gastrointestinal absorption of 3TC and other drugs commonly used in HIV-infected patients [Report UCP/92/028]. The transport was not affected by the presence of AZT, ddC, ddI, acyclovir, probenecid, trimethoprim, sulfamethoxazole, ranitidine or cimetidine. 3TC did not affect the transport of ddI, ddC, or AZT in the same model.

A small number (5) of DDI studies from the 3TC single agent development program have demonstrated no clinically significant drug interactions between 3TC, ABC, ZDV, and ddI (CNAA1002, NUCA1005, NUCA2005). There was no significant DDI and no dose modification is required when 3TC is co-administered with ABC, ZDV, or ddI. No contraindication or dose adjustment of 3TC is required when co-administered with TMP or SMX at normal doses (NUCA1007). The results of a clinical DDI study [204857; Appendix Table 1] showed that co-administration of 3TC with increasing amounts of SBT lowered the 3TC exposures in a dose-dependent manner. SBT had the greatest impact on Cmax and AUC(0-24) suggesting that sorbitol's effect was primarily on absorption and bioavailability of 3TC. SBT is an osmotic laxative and is thought to reduce absorption/bioavailability of drugs with low permeability by increasing gastrointestinal motility and decreasing small intestine transit time. Therefore, when possible, it is recommended to avoid chronic co-administration of SBT-containing medicines with 3TC and to consider more frequent monitoring of HIV-1 viral load when chronic co-administration cannot be avoided.

Potential for Interactions on Renal Excretion

3TC is predominantly cleared by the kidney via glomerular filtration and active tubular secretion of unchanged drug. The organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporters (MATE1 and MATE2-K) have been shown to be clinically important for the active renal secretion of 3TC. OCT2 facilitates 3TC uptake from the blood into the kidney as demonstrated in vitro in transfected human embryonic kidney (HEK) cells (Km = 248 μM; [Jung, 2008]). The apical kidney transporters, MATE1 and MATE2-K, mediate 3TC efflux out of the kidney into the urine [Muller, 2013].

TMP is an inhibitor of OCT2 (IC_{50} =13 μM), MATE1 (IC_{50} =6.2 μM), and MATE2-K (IC_{50} = 0.66 μM) [Muller, 2013], and has been shown to increase 3TC plasma

concentrations in HIV patients. In Study NUCA1007, co-administration of TMP/SMX with 3TC increased 3TC AUC∞ by ~40%, and decreased CL/F and Clr by 30% and 35%, respectively. 3TC had no effect on the PK of TMP or SMX. This interaction is not considered clinically significant, as no dose adjustment of 3TC is needed.

No clinical drug interaction studies have been conducted with 3TC and cimetidine, which is also a MATE1/2-K and OCT2 inhibitor. Cimetidine unbound plasma concentrations are 3.6 to 7.8 μM, which are of a similar magnitude to TMP unbound plasma concentrations (4.66 μM). Cimetidine, however, is a less potent OCT2 and MATE2-K inhibitor than TMP, with Ki values of 95 to 146 μM (OCT2), 1.1 to 3.8 μM (MATE1), and 2.1 to 6.9 μM (MATE2-K) [Ito, 2012]. Although a cimetidine-mediated PK interaction with 3TC is possible, a more marked and clinically significant drug interaction compared to TMP is unlikely to occur. Although DTG inhibits OCT2 (IC_{50} =1.9 μM), a DTG-mediated drug interaction with 3TC is also not expected based on DTG's significantly lower unbound systemic concentrations (0.088 μM) and weaker MATE inhibition (IC_{50} = 6.3 μM [MATE1] and 25 μM [MATE2-K]). This is consistent with clinical studies that have shown that DTG does not alter 3TC PK..

No clinically significant drug interactions were observed between 3TC, ABC, ZDV, and ddI (CNAA1002, NUCA1005, NUCA2005), and therefore no significant DDI and no dose modification is required when 3TC is co-administered with ABC, ZDV, or ddI.

Potential for Pharmacodynamic Interactions

In vitro studies have shown RBV can reduce the phosphorylation of pyrimidine nucleoside analogues such as 3TC. However, no evidence of a PK or PD interaction (e.g., loss of HIV-1/HCV virologic suppression) was seen when RBV was co-administered with 3TC in HIV-1/HCV coinfected subjects.

3.3. Dolutegravir/Lamivudine Fixed-dose Combination

3.3.1. Historical Dolutegravir Data Supporting the [redacted] FDC

The [redacted] FDC formulation was bioequivalent for DTG AUC(0-∞) and Cmax, however, AUC(0-t) was ~16% higher for the [redacted] FDC compared with the reference and the GLS mean ratio upper limit of the 90% CI was above the 1.25 limit for BE (1.2507) (See m2.7.1 Section 2.1.1.1). This 16% increase in AUC(0-t) is not clinically significant based on the following:

- A sensitivity ad-hoc analysis conducted to exclude 2 subjects who had below LLQ concentrations at the last sample collection time showed that DTG AUC(0-t) met the GLS mean ratio BE criteria (See m2.7.1 Section 2.1.1.1).

- An additional ad-hoc analysis showed that DTG AUC(0-72) met the GLS mean ratio BE criteria (See m2.7.1 Section 2.1.1.1).

- Substantially higher steady state AUC values were obtained with 50 mg BID doses compared with once daily doses in a registrational Phase 3 study

ING112574 [Tivicay Product Information 2017] without additional safety concerns.

- No DTG dose adjustments are recommended when co-administered with 400 mg once daily ATV, despite a 91% increase in AUC [Tivicay Product Information 2017].

- DTG can be taken without regard to food despite an ~66% increase in AUC in the presence of a high-fat meal [Tivicay Product Information 2017].

3.3.2. Historical Lamivudine Data Supporting the [redacted] FDC

The [redacted] FDC formulation has a 32% higher (mean) 3TC Cmax (m2.7.1). However, this higher rate of absorption does not translate into a higher extent of absorption (AUCs were bioequivalent), does not impact efficacy, and does not confer any additional safety risk in comparison to 3TC 300 mg SE. The rationale for this conclusion is presented in the sub-sections that follow.

3.3.2.1. Cross-study Comparisons of Lamivudine Cmax and AUC

A cross-study comparison indicates that the 3TC Cmax (geometric mean of 3.22 μg/mL) observed with the DTG/3TC proposed commercial formulation was of a similar magnitude to that observed with Epivir in various SE studies such as NUCA1006, NUCB1004, and NUCA1005 (3.09 μg/mL, 3.33 μg/mL, and 3.15 μg/mL, respectively). In addition, similar Cmax values (3.67 μg/mL and 3.42 μg/mL) were also observed under fasted conditions in BE studies for generic 3TC formulations (EMA, 2009, and MHRA, 2016, respectively) (See m2.7.1 Section 3.3)

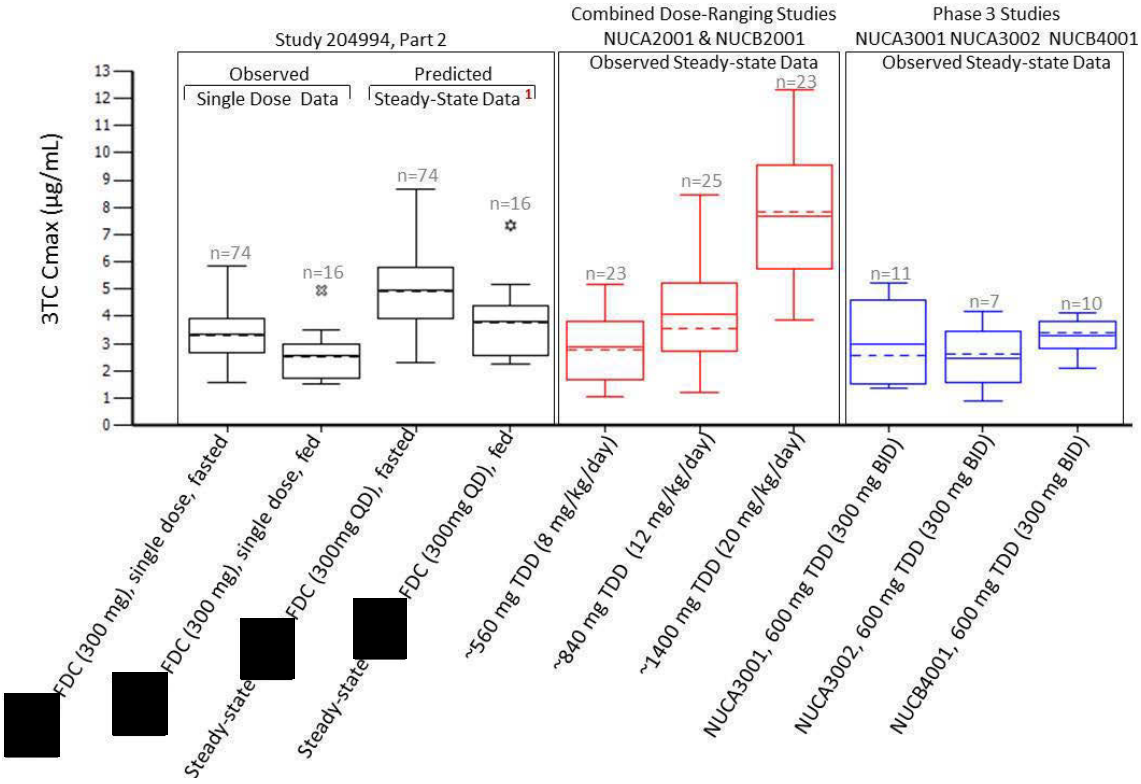
3TC demonstrates linear, time-invariant PK with Cmax and AUC values that increase in proportion to the dose. A comparison of predicted steady-state 3TC Cmax for the [redacted] FDC tablet (300 mg QD) to observed steady-state Cmax values from historical Epivir Phase I/IIa and Phase III studies is shown in Figure 2. The steady-state Cmax of the [redacted] FDC was estimated by multiplying the observed Cmax (in either the fasted or fed state) by 1.48, which is the previously reported accumulation ratio for a 3TC 300 mg once daily regimen (NUCA2001). In the pivotal BE study 204994, the 3TC terminal elimination t1/2 of the [redacted] FDC was similar to that of Epivir (See m2.7.1, Section 2.1.1.1). Therefore, 3TC accumulation following administration of the FDC is expected to be similar to that observed with the SE in Study NUCA2001.

Figure 2 shows the following:

- The predicted 3TC steady-state Cmax for the [redacted] FDC in the fasted state (which represents the scenario for highest exposure) is similar to the observed range of steady-state Cmax values from doses ≥12 mg/kg/day (840 mg daily dose for a 70-kg subject) given in BID divided doses to subjects for 24 weeks in the NUCA2001 and NUCB2001 dose-ranging studies.
- The predicted steady-state 3TC Cmax for the [redacted] FDC in the fed state overlaps with the steady-state Cmax range observed for 300 mg BID (BID)

(600 mg daily dose) doses in the long-term safety and efficacy Phase III studies NUCA3001, NUCA3002, and in study NUCB4001. The safety data from NUCA3001 and NUCA3002 are discussed in m2.7.4, Section 5.6.2.

Figure 2 Cross-study Comparison of Lamivudine Cmax



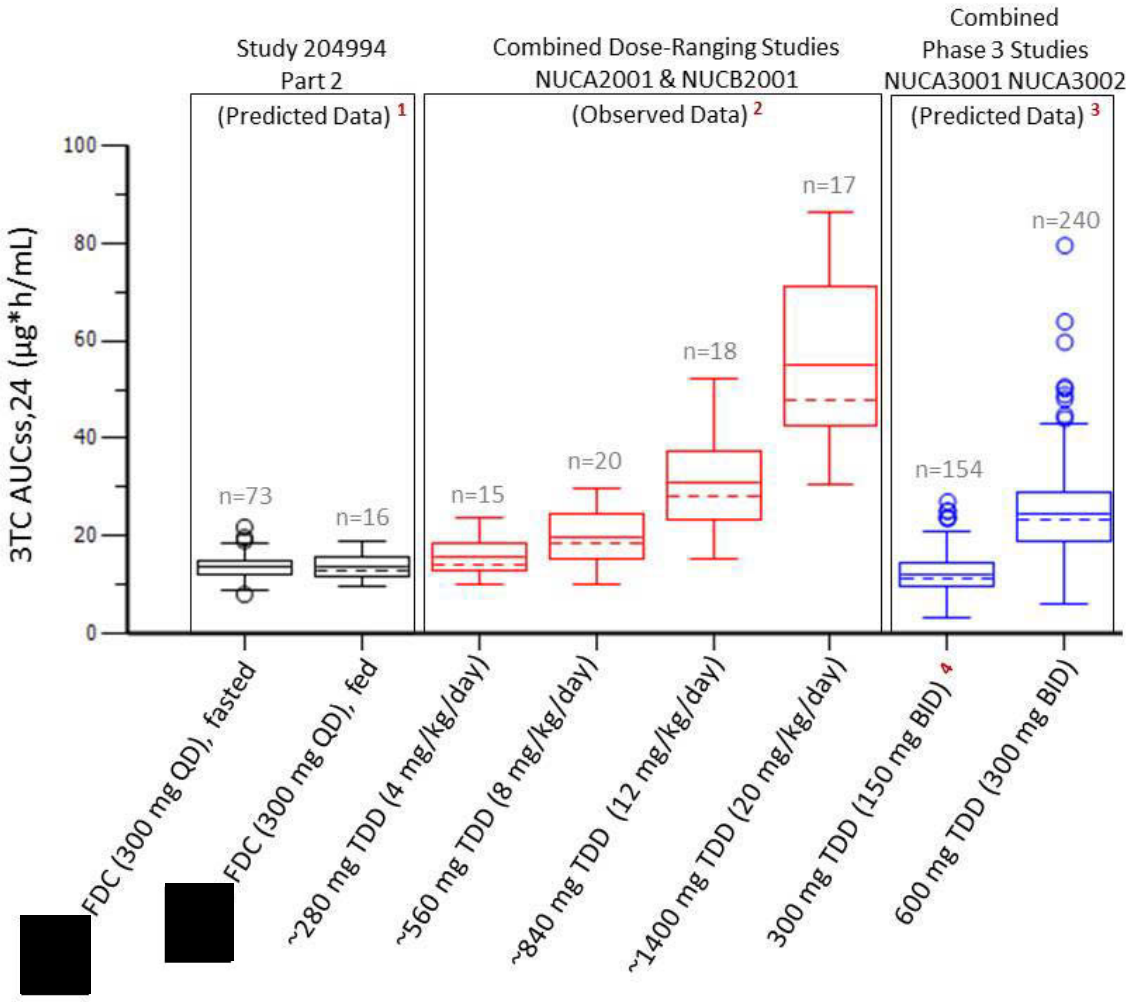
Box Plot: the dashed line represents the median; the solid line is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile and the highest value within 1.5 IQR of the upper quartile, where IQR is the interquartile range, or the middle 50%. The data points beyond the IQR tails are shown as outliers.
1. The steady-state Cmax for the [redacted] FDC was calculated by multiplying the observed Cmax values following the single dose by the accumulation index of 1.48 observed with the daily administration of 3TC (as a SE) (Study NUCA2001). In the pivotal BE study 204994, the 3TC terminal elimination t1/2 for the [redacted] FDC was similar to that of Epivir (m2.7.1 Section 2.1.1.1). Therefore, the 3TC accumulation following daily FDC administration is expected to be similar to that of 3TC administered as a SE.

A comparison of predicted steady-state 3TC AUC for the [redacted] FDC tablet to the observed steady-state AUC values from Phase I/IIa and to the predicted steady-state AUC from Phase III studies is shown in Figure 3. Based on the PK principle that the relationship between steady-state AUC for a dosing interval [i.e., AUC(0-τ)] and AUC(0-∞) following single-dose administration are equal, the 3TC AUC(0-∞) values observed in Study 204994 are shown for the [redacted] FDC in fasted and fed state [although a high-fat meal did not affect the AUC(0-∞) of 3TC].

Data in Figure 3 shows the following:

- Predicted 3TC steady-state AUC for the [redacted] FDC is similar to the predicted steady-state AUC values from the long-term safety and efficacy Phase III studies NUCA3001 and NUCA3002, at 150 mg BID (300 mg daily dose).
- Predicted steady-state AUC values for the [redacted] FDC tablet are below the predicted steady-state AUC values from 300 mg BID (600 mg daily dose) in NUCA3001 and NUCA3002, and from doses ≥8 mg/kg/day (560 mg daily dose) given to participants for 24 weeks in NUCA2001 and NUCB2001 dose-ranging studies. The safety data from these studies are discussed in m2.7.4, Section 5.6.2.

Figure 3 Cross-study Comparison of 3TC steady-state AUC(0-24)



Box Plot: The dashed line represents the median; the solid line is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5 IQR of the lower quartile and the highest value within 1.5 IQR of the upper quartile, where IQR is the interquartile range, or the middle 50%. The data points beyond the IQR tails are shown as outliers.

1. For study 204994, the steady-state AUC(0-24) for the [redacted] FDC is equal to the AUC(0-∞) following single dose.
2. The steady-state AUC(0-24) for studies NUCA2001 and NUCB2001 were calculated as 2x Day 15 AUC(0-t) (AUC from the time of dosing to the last measurable concentration, where t=8 or 12 hours).
3. The steady-state AUC(0-24) for studies NUCA3001 and NUCA3002 were predicted (as daily dose/(CL/F)) using a population PK model for 3TC disposition in adults (RM1996/00214/00).
4. The steady-state AUC(0-24) for the 150 mg BID dose is predicted to be equal to the steady-state AUC(0-24) for the 300 mg QD dose (based on AUCss,24 = daily dose/(CL/F)).

Taken together, the cross-study comparisons for 3TC Cmax and AUC indicate that the steady-state 3TC exposure following the [redacted] FDC is expected to overlap with 3TC exposures from historical dose-ranging and registrational Phase III studies. The safety data associated with these studies is described in detail m2.7.4, Section 5.6.2. In brief, several dose-ranging, pivotal and open-label studies have demonstrated no dose-related increase in the overall incidence of AEs and there were no significant safety and efficacy differences between the standard 3TC 300 mg/day and the higher 3TC 600 mg/day.

Additionally, data from the 3TC dose ranging studies where doses as high as 20 mg/kg/day (700 mg BID) were given to participants for 24 weeks, demonstrated no dose-related increase in the overall incidence of AEs or the overall incidence of study-drug related AEs.

3.3.2.2. Lamivudine Mechanism of Action and Intracellular Lamivudine-Triphosphate Pharmacokinetics

For NRTIs, intracellular levels of triphosphate moieties are associated with toxic activities [Andersen, 2004]. Data in this section demonstrate that saturation of the intracellular 3TC phosphorylation and a plateauing of intracellular 3TC-TP occur at higher plasma exposures and therefore, any increase in Cmax associated with the [redacted] FDC is unlikely to translate into an increased safety risk due to plateauing of intracellular 3TC-TP.

For all NRTIs, intracellular NRTI triphosphate moieties mediate both antiviral and toxic activities [Andersen, 2004]. 3TC is the negative (cis) enantiomer of 2',3'-dideoxy-3'-thiacytidine, a dideoxy pyrimidine which requires intracellular triphosphorylation to the active form, 3TC-TP. The active triphosphate competes with the corresponding endogenous nucleoside triphosphate, dCTP, for binding to the viral reverse transcriptase. Once incorporated into viral DNA, chain termination results due to absence of a 3'-hydroxy group to which 3' – 5'- phosphodiester linkages are normally made [Hart, 1992]. This process interferes with DNA synthesis thus eliciting anti-HIV activity via the inhibition of HIV reverse transcriptase [Mitsuya, 1990].

Interaction with the host mitochondrial DNA synthesis mediated via the inhibition of mitochondrial DNA polymerase gamma has been implicated as the primary cause underlying many of the adverse effects of the NRTI class [Kakuda, 2000]. However, clinically, 3TC appears to produce fewer side effects than the other nucleoside analogues, and has shown little evidence of mitochondrial toxicity [Perry, 1997]. The inhibition constants of 3TC-TP for both RNA- and DNA-dependent DNA polymerisation activity by HIV RT are similar to the Ki for mammalian mitochondrial DNA polymerase gamma. However, DNA polymerase gamma, unlike HIV RT, has a 5'-3' exonuclease DNA repair function which accepts 3TC-TP as a substrate, excising it from the growing mitochondrial DNA chain and thus preventing disruption of mitochondrial DNA synthesis. Toxicity is dependent on the relative time required to replicate the mitochondrial genome based on the probability of incorporating 3TC-TP and the time it takes for the proofreading exonuclease to remove it after incorporation [Lee, 2003]. This may explain 3TC's lack of propensity for causing mitochondrial toxicity as well as its broad therapeutic index.

3.3.2.3. Conclusions for Historical Lamivudine Data

Based on the results of the pivotal fasted BE study (204994), the [redacted] tablet formulation which utilizes the [redacted] was selected for development. The [redacted] FDC tablet demonstrated BE for DTG AUC and Cmax and for 3TC AUC. However, the [redacted] had a 32% higher 3TC Cmax compared with the reference (m2.7.1). Although the 3TC Cmax parameter did not meet

BE, the difference in rate of absorption should not significantly alter the clinical safety profile for the reasons summarized below:

- For 3TC, the best predictor for efficacy is AUC(0-24) given the long half-life of the active intracellular 3TC-3TP moiety. The data from Study 204994 show that AUC values (extent of absorption) are equivalent for the [redacted] FDC and co-administration of the single entities in the fasted state. Therefore, a faster rate of absorption leading to a moderate increase in 3TC Cmax is not expected to impact efficacy.
- 3TC is generally well tolerated, with no major safety concerns relating to its use in HIV infected patients, and has a good long-term safety profile. The cumulative exposure to 3TC oral solid formulation is estimated to be >2.5 million patient years. Several previously submitted dose-ranging, pivotal and open-label studies have demonstrated no dose-related increase in the overall incidence of AEs and that there were no significant safety and efficacy differences between the standard 3TC 300 mg/day and the higher 3TC 600 mg/day doses. The sample sizes of the studies which investigated the safety and efficacy in HIV-infected participants receiving 3TC 300 mg/day or higher (i.e., twice the standard 3TC dose) from several 3TC studies ranged from 9103 to 16,596 patients (see m2.7.4, Section 5.6.2).
- Data from the 3TC dose ranging studies (NUCA2001 and NUCB2001) demonstrated no dose-related increase in the overall incidence of AEs or the overall incidence of study-drug related AEs at doses up to 840 mg daily dose. In these studies, the Cmax following 560 mg daily dose or 840 mg daily dose administration overlapped with the predicted steady-state Cmax for the [redacted] FDC. A description of these analyses is provided in m2.7.4, Section 5.6.2.
- Several previously submitted registrational pivotal Phase II/III studies (NUCA3001, NUCA3002, and NUCB3002) demonstrated that the Cmax for the 3TC 600 mg/day dose was consistent with the Cmax observed with the DTG/3TC FDC in the pivotal BE study (204994). These studies also showed no significant safety and efficacy differences between the 3TC 300 mg/day and the 3TC 600 mg/day (see m2.7.4, Section 5.6.2). The overall differences at the individual study level between treatment groups were small and statistically nonsignificant when comparing the frequencies of AEs, drug-related AEs, SAEs, Grade 3/4 clinical and laboratory abnormalities, and withdrawals due to AEs over the ≥24-week treatment period. Results from the NUCB3001 study, which examined a comparison of 3TC 300 mg BID in combination with ZDV in comparison with ZDV monotherapy, also support the overall safety of the 3TC 600 mg/day.

The data from two large rollover, open-label studies, NUCA3004 and NUCB3004, also reported comparable safety findings for participants receiving 3TC 300 mg BID (in NUCA3004 vs. those receiving 3TC 150 mg BID). While there may be small differences at individual AE levels, overall the safety profiles are comparable for these studies which include more than 16,000 participants who received 3TC 300 mg/day and more than 9,000 participants who received 3TC 600 mg/day.

3.3.3. Management of Drug-drug Interactions for Dolutegravir/Lamivudine Fixed-dose Combination

Recommendations for the management of expected DDIs for the DTG/3TC FDC are presented in Table 3. These recommendations are based on DDI studies from the DTG or 3TC SE development programs.

Table 3 Recommendations for the Management of DTG/3TC FDC Based on Expected Drug-drug Interactions for DTG and 3TC Single Entity Development Programs

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine or Concomitant Drug	Clinical Comment
Carbamazepine (CBZ)	Co-administration of DTG with CBZ resulted in decreases in DTG Cmax, AUC, and Cτ by approximately 33%, 49%, and 73%, respectively. Interaction of CBZ with 3TC was not studied.	Metabolic inducers may significantly decrease DTG plasma concentrations, resulting in loss of therapeutic effect. Therefore, a dose of DTG tablet should be administered daily ~12 hours after the DTG/3TC FDC in patients requiring co-administration of DTG/3TC FDC and CBZ. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and CBZ.
Etravirine (ETV)	Co-administration of DTG and ETV resulted in decreased steady-state plasma DTG AUC(0-τ), Cmax, and Cτ by 71%, 52%, and 88%, respectively. Interaction of ETV with 3TC was not studied.	ETV without boosted PIs decreased plasma DTG concentration, which may result in loss of virologic response and possible resistance to DTG. Therefore, since the recommended adult dose of DTG is 50 mg BID when co-administrated without boosted PIs, a second dose of DTG tablet should be administered daily ~12 hours after the DTG/3TC FDC in patients requiring co-administration of DTG/3TC FDC and ETV. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and ETV.
Efavirenz (EFV)	Co-administration of EFV with DTG did not affect EFV exposure. Co-administration of DTG with EFV resulted in a 57%, 39%, and 75% decreased plasma DTG AUC(0-τ), Cmax, and Cτ, respectively. Interaction of EFV with 3TC was not studied.	EFV may significantly decrease DTG plasma concentrations, resulting in loss of therapeutic effect. To manage this interaction, a second dose of DTG tablet should be administered daily ~12 hours after the DTG/3TC FDC in patients requiring co-administration of DTG/3TC FDC and EFV. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and EFV.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine or Concomitant Drug	Clinical Comment
Omeprazole (OMP)	Co-administration with OMP had no significant effect on plasma DTG AUC(0-τ), AUC(0-∞), Cmax, or C24. Interaction of OMP with 3TC was not studied.	DTG/3TC FDC can be co-administered with OMP without dose adjustment No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and OMP.
Rifampin (RIF)	Co-administration of DTG with RIF resulted in decreases in DTG AUC(0-τ), Cmax, and Cτ by 54%, 43%, and 72%, respectively. Interaction of RIF with 3TC was not studied.	RIF may significantly decrease DTG plasma concentrations, resulting in loss of therapeutic effect. Therefore, to manage this interaction, a second dose of DTG tablet should be administered daily ~12 hours after the DTG/3TC FDC during the period of RIF co-administration. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and RIF.
Tipranavir (TPV)/RTV	Co-administration of DTG with TPV/RTV resulted in a 59%, 46%, and 76% decrease in plasma DTG AUC(0-τ), Cmax, and Cτ, respectively. TPV ↔ RTV ↔ Interaction of TPV/RTV with 3TC was not studied.	TPV/RTV may decrease DTG concentrations. To manage this interaction, a second dose of DTG tablet should be administered daily ~12 hours after the DTG/3TC FDC in patients requiring co-administration of DTG/3TC FDC and TPV/RTV. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and TPV/RTV.
Antacids containing aluminium hydroxide, magnesium hydroxide, and/or calcium carbonate	Co-administration of DTG with aluminium and magnesium-containing antacids (Maalox) decreased DTG AUC, Cmax, and C24 by 74%, 72%, and 74%, respectively. Interaction of Maalox with 3TC was not studied.	Use with caution as co-administration may significantly decrease DTG plasma concentrations, resulting in loss of therapeutic effect. DTG/3TC FDC should be administered 2 hours before or 6 hours after taking antacid products. No interaction with 3TC is expected based on consideration of the absorption and elimination pathways of 3TC and magnesium-containing antacids (Maalox).
Calcium or iron supplements	Co-administration of DTG with calcium carbonate reduced DTG AUC(0-∞), Cmax, and C24 by 39%, 37%, and 39%, respectively. Co-administration of DTG with ferrous fumarate reduced DTG AUC(0-∞), Cmax, and C24 by 54%, 57%, and 56%, respectively. Interaction of calcium or iron supplements with 3TC was not studied.	For other Fe and Ca-containing products (e.g., vitamin supplements) 2 alternatives are available: 1. DTG/3TC FDC to be administered 2 hours before or 6 hours after taking the product. 2. Take DTG/3TC FDC and Fe/Ca together with a meal to overcome Fe/Ca effect on DTG absorption.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine or Concomitant Drug	Clinical Comment
Metformin	Co-administration of DTG with metformin resulted in increases in metformin AUC(0-τ) and Cmax by 79% and 66%, respectively. Cmin not evaluated. Interaction of metformin with 3TC was not studied.	Co-administration of DTG/3TC FDC may increase metformin plasma concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of DTG/3TC FDC with metformin to maintain glycemic control. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and metformin.
Rifabutin (RBT)	Co-administration of DTG with RBT resulted in a 16% increase in DTG Cmax, no change in AUC(0-τ), and a 30% reduction in Cτ. RBT ↔ Interaction of RBT with 3TC was not studied.	No dose adjustment is needed when DTG/3TC FDC is co-administered with RBT. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and RBT.
Didanosine (ddI)	No PK drug interactions were observed among 3TC, ZDV, and ddI. Co-administration of ZDV and ddI did not alter the PK of 3TC. Interaction of ddI with DTG was not studied.	No dose adjustment of DTG/3TC FDC is necessary. No interaction of DTG with ddI is expected.
Methadone	Co-administration of DTG with methadone resulted in decreased methadone AUC(0-τ) and Cτ by 2% and 1%, respectively, and no effect on Cmax. Interaction of methadone with 3TC was not studied.	DTG did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when initiating co-administration with DTG/3TC FDC. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and methadone.
Atazanavir (ATV)	Co-administration of DTG with ATV resulted in an increase in plasma DTG AUC(0-τ), Cmax, and Cτ by 91%, 50%, and 180%, respectively. ATV ↔ Interaction of ATV with 3TC was not studied.	ATV may increase DTG plasma concentrations. No dose adjustment is needed when DTG/3TC FDC is co-administered with ATV. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and ATV.
ATV/ritonavir (RTV)	Co-administration of DTG with ATV/RTV resulted in an increase in plasma DTG AUC(0-τ), Cmax, and Cτ by 62%, 34%, and 121%, respectively. ATV↔ RTV↔ Interaction of ATV/RTV with 3TC was not studied.	ATV/RTV may increase DTG plasma concentrations. No dose adjustment is needed when DTG/3TC FDC is co-administered with ATV/RTV. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and ATV/RTV.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine or Concomitant Drug	Clinical Comment
Fosamprenavir (FPV)/RTV	Co-administration of DTG with FPV/RTV decreased DTG plasma AUC(0-τ), Cmax, and Cτ by 35%, 24%, and 49%, respectively. FPV ↔ RTV ↔ Interaction of FPV/RTV with 3TC was not studied.	FPV/RTV decreases DTG concentrations, but based on limited data, did not result in decreased efficacy in Phase III studies. No dose adjustment is necessary in INI-naïve patients. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and FPV/RTV.
Lopinavir/RTV (LPV + RTV)	Co-administration of DTG with LPV/RTV decreased plasma DTG AUC(0-τ) and Cτ by 4% and 6%, respectively. There was no effect of LPV/RTV on DTG Cmax. LPV ↔ RTV ↔ Interaction of LPV/RTV with 3TC was not studied.	LPV/RTV did not change DTG plasma concentrations to a clinically relevant extent. No dose adjustment is needed when DTG/3TC FDC is co-administered with LPV/RTV. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and LPV/RTV.
Darunavir (DRV)/RTV	Co-administration of DTG with DRV/RTV decreased plasma DTG AUC(0-τ), Cmax, and Cτ by 22%, 11%, and 38%, respectively. DRV ↔ RTV ↔ Interaction of DRV/RTV with 3TC was not studied.	DRV/RTV did not change DTG plasma concentrations to a clinically relevant extent. No dose adjustment is needed when DTG/3TC FDC is co-administered with DRV/RTV. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and DRV/RTV.
Tenofovir disoproxil fumarate (TDF)	**Effect of TDF on DTG:** Co-administration of DTG with TDF decreased plasma DTG Cmax and Cτ by 3%, and 8%, respectively. TDF had no effect on DTG AUC(0-τ). **Effect of DTG on TDF:** Co-administration of DTG with TDF increased plasma TDF AUC(0-τ), Cmax, and Cτ by 12%, 9%, and 19%, respectively. Interaction of TDF with 3TC was not studied.	TDF did not change DTG plasma concentrations to a clinically relevant extent. No dose adjustment is needed when DTG/3TC FDC is co-administered with TDF. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and TDF.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine or Concomitant Drug	Clinical Comment
Daclatasavir (DCV)	**Effect of DCV on DTG** Co-administration of DTG with DCV increased DTG AUC(0-τ), Cmax, and Cτ by 33%, 29%, and 45%, respectively. **Effect of DTG on DCV** Co-administration of DTG with DCV increased DCV Cmax, and Cτ by 3% and 6%, respectively, and resulted in no change in DCV AUC(0-τ). Interaction of DCV with 3TC was not studied.	DCV did not change DTG plasma concentrations to a clinically relevant extent. DTG did not change DCV plasma concentrations. No dose adjustment is needed when DTG/3TC FDC is co-administered with DCV. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and DCV.
Elbasvir (EBR)/grazoprevir (GZR)	The following data on the interaction of DTG with elbasvir/grazoprevir was obtained from the Zepatier USPI. **Effect of DTG on EBR/GZR** Co-administration of DTG with EBR/GZR decreased EBR AUC, Cmax, and C24 by 2%, 3%, and 2%, respectively. Co-administration of DTG with EBR/GZR decreased GZR AUC, Cmax, and C24 by 19%, 36%, and 14%, respectively. Co-administration of DTG with EBR/GZR increased DTG AUC, Cmax, and C24 by 16%, 22%, and 14%, respectively. Interaction of EBR/GZR with 3TC was not studied.	Based on DDI trial results, no dose adjustment is needed when DTG/3TC FDC is co-administered with EBR/GZR. No clinically relevant DDI is expected when EBR/GZR is co-administered with 3TC.
Sofosbuvir (SOF/velpatasvir (VEL)/ voxilaprevir (VOX)	The following data on the interaction of DTG with SOF/VEL was obtained from the Vosevi USPI. **Effect of DTG on SOF/VEL/VOX** Co-administration of DTG with SOF/VEL/VOX decreased SOF AUC and Cmax by 8% and 12%, respectively, and had no effect on GS-331007 AUC, Cmax or Cmin. Co-administration of DTG with SOF/VEL decreased VEL AUC, Cmax, and Cmin by 9%, 6%, and 12%, respectively. The effect of DTG on VOX PK and the effect of SOF/VEL/VOX on DTG PK were not reported. Interaction of SOF/VEL/VOX with 3TC was not studied.	DTG did not change SOF/VEL plasma concentrations to a clinically relevant extent. No interaction with 3TC and SOF/VEL/VOX or DTG and VOX is expected based on consideration of the elimination pathways of the drugs. No dose adjustment is needed when DTG/3TC FDC is co-administered with SOF/VEL/VOX.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Lamivudine or Concomitant Drug	Clinical Comment
Rilpivirine (RPV)	**Effect of RPV on DTG** Co-administration of DTG with RPV resulted in no change in DTG AUC(0-τ) and Cmax, and a 22% increase in Cτ. **Effect of DTG on RPV** Co-administration of DTG with RPV resulted in no change in RPV AUC(0-τ) and Cmax, and a 21% increase in Cτ. Interaction of RPV with 3TC was not studied.	There was no significant drug interaction between DTG and RPV. No dose adjustment is needed when DTG/3TC FDC is co-administered with RPV. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and RPV.
Oral contraceptives (Ethinyl estradiol [EE)] and Norelgestromin [NGMN]) or Norethindrone	**Effect of DTG on EE** Co-administration of DTG with EE increased EE AUC(0-τ) and Cmin by 3% and 2%, respectively, whereas Cmax decreased by 1%. **Effect of DTG on NGMN** Co-administration of DTG with NGMN resulted in decreased NGMN AUC(0-τ), Cmax, and Cmin by 2%, 11%, and 7%, respectively. Interaction of EE and NGMN with 3TC was not studied.	DTG did not change EE and NGMN/norethindrone plasma concentrations to a clinically relevant extent. No dose adjustment of OCs is necessary when co-administered with DTG/3TC FDC. No interaction with 3TC is expected based on consideration of the elimination pathways of 3TC and EE and NGMN.
Sorbitol (SBT)	**Effect of SBT solutions on 3TC** Co-administration of 3TC with SBT decreased 3TC plasma exposures: 3.2 g SBT decreased 3TC Cmax and AUC0-∞ by 28% and 14%; 10.2 g SBT decreased 3TC Cmax and AUC0-∞ by 52% and 32%; 13.4 g SBT decreased 3TC Cmax and AUC0-∞ by 55% and 36%, respectively Interaction of SBT with DTG was not studied	Co-administration of 3TC and sorbitol-containing medicines may decrease 3TC concentrations. To manage this interaction, an all-tablet regimen should be used when possible to avoid a potential interaction with sorbitol and DTG/3TC FDC. No interaction with DTG is expected with SBT.
Trimethoprim (TMP)/sulfamethoxazole(SMX) (Co-trimoxazole)	**Effect of TMP/SMX on 3TC**: Co-administration of 3TC with TMP/SMX increased 3TC AUC by ~40%. **Effect of 3TC on TMP/SMX:** 3TC did not affect the PK of TMP or SMX	Unless the patient has renal impairment, no dosage adjustment of 3TC is necessary. DTG/3TC FDC is not recommended for subjects with CrCl of <50 mL/min

↑ = Increase; ↓ =decrease; ↔ = no significant change
Elbasvir/grazoprevir [Zepatier Product Information, 2018]
Sofosbuvir/velpatasvir/voxilaprevir [Vosevi Product Information. November 2017]

3.3.4. Extrapolation of Adult Dolutegravir/Lamivudine Data to Adolescents

According to the "Guideline on the clinical development of medicinal products for the treatment of HIV infection" [EMA, 2016] and with the "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products" Draft Guidance for Industry [FDA, 2014], extrapolation of efficacy between populations is possible provided that drug exposure is shown to be similar in both cases.

A systematic extrapolation framework in support of the use of the adult DTG 50 mg/3TC 300 mg fixed dose combination (FDC) tablet in adolescents ≥12 to <18 years weighing at least 40 kg was presented in the Adolescent Extrapolation Report for GSK3515864 [GlaxoSmithKline document number 2018N363795_00] and consists of:

- Extrapolation between populations from adults to adolescents
- Extrapolation from the DTG 50mg (Tivicay) plus 3TC 300 mg (Epivir) single entities administered concurrently to the DTG/3TC [redacted] FDC.

The extrapolation of efficacy from adult to adolescent populations is supported by the following:

- HIV disease dynamics, the virologic and immunologic principles underlying the use of ART, and the PK/PD relationship are considered sufficiently similar between adults and adolescents.
- DTG and 3TC PK exposures in adolescents are similar to those in adults to permit extrapolation of efficacy data from PK correlation.
- The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are adult doses that have already been authorized as individual agents in adolescents ≥12 years of age weighing ≥40 kg (DTG) or in pediatric patients weighing ≥25 kg (3TC).
- Week 48 analysis of GEMINI-1 and GEMINI-2 Phase III studies conducted with the SE tablets Tivicay and Epivir showed that DTG plus 3TC is highly efficacious and well tolerated in HIV-infected, ART-naïve adult patients (see m2.7.3and m2.7.4), and confirmed the interim week 24 data that was included in the Adolescent Extrapolation Report for GSK3515864 [GlaxoSmithKline document number 2018N363795_00].

The extrapolation from the DTG plus 3TC single entities administered concurrently to the DTG/3TC [redacted] FDC is supported by an acceptable PK bridge between the DTG/3TC FDC and the single entities used in GEMINI-1 and GEMINI-2 Phase III trials. The bridging between DTG and 3TC single entities and the DTG/3TC FDC is supported by the following:

- Data from the pivotal bioequivalence Study 204994 showed that in a fasted state, the DTG AUC(0-∞), AUC(0-t), and Cmax and 3TC AUC(0-∞) and AUC(0-t) from the [redacted] DTG/3TC FDC formulation were bioequivalent to those from the reference DTG and 3TC single entities (m2.7.1, Section 2.1.1). Although the [redacted] FDC had a 3TC Cmax ~32% higher than the reference, this elevated 3TC Cmax (which reflects

a faster rate of absorption of the 3TC component) is not clinically significant based on historical clinical safety data from clinical trials that evaluated higher 3TC doses/exposures (see m2.7.4, Section 5.6.2).

- The effect of food on plasma exposures of DTG and 3TC following administration with a high-fat meal was similar to the prior food effect observed with Epivir and Tivicay and is not clinically significant (m2.7.1, Section 2.4.1). This supports the recommendation that the DTG/FDC [redacted] tablet can be administered with or without food, consistent with the recommendations for Tivicay and Epivir.

- The bioequivalence and food effect results provide an acceptable PK bridge between the DTG/3TC [redacted] FDC and single entities used in GEMINI-1 and GEMINI-2 Phase III studies thus ensuring similarity in terms of efficacy and safety and supporting the adults and adolescent indication for the DTG/3TC FDC product.

Taken together, the totality of evidence supports the complete extrapolation from adults to adolescents and from the individual DTG plus 3TC to the DTG/3TC FDC and the recommendation for the use of DTG/3TC [redacted] FDC as a once-daily complete regimen administered with or without food for the treatment of HIV-1 infection in ART-naïve adolescents ≥12 years to <18 years of age, weighing at least 40 kg.

4. SPECIAL STUDIES

Please note that m2.7.2.4, Special Studies (Summary of Microbiology/Virology), is provided as a standalone module.

5. CONCLUSIONS

The main characteristics of clinical pharmacology related to the DTG/3TC FDC product are summarized below based upon information obtained from the SE development programs for DTG and 3TC, food effect, and BE studies of the DTG/3TC FDC.

- The [redacted] DTG/3TC FDC tablet was bioequivalent for DTG AUC and Cmax and for 3TC AUC; however, the [redacted] had an approximately 32% higher 3TC Cmax than Epivir. The higher 3TC Cmax, which reflects differences in the rate of absorption but not extent of absorption, does not significantly affect patient safety and antiviral efficacy based on historical clinical efficacy and safety data at higher 3TC doses/exposures.
- The data from the pivotal BE Study 204994, combined with data from the 3TC historical studies, provides an acceptable PK bridge to the SEs used in GEMINI-1 and GEMINI-2 Phase III trials and supports the proposed submission for the [redacted] FDC tablet.
- The DTG/3TC FDC may be taken with or without food (m2.7.1). This is consistent with the prescribing information for the DTG and 3TC SEs.
- DTG/3TC FDC can be used once daily in adolescents (12 to <18 years of age weighing at least 40 kg) with or without food.

- DTG and 3TC each have a generally favorable drug interaction profile with few clinically relevant interactions that require a dose adjustment, dose separation, or contraindication.
- CBZ, ETV, RIF, EFV, and TPV/RTV have been shown in studies to decrease DTG exposures. Therefore, to manage this interaction, a second dose of DTG tablet should be administered daily approximately 12 hours after the DTG/3TC FDC in patients requiring co-administration of DTG/3TC FDC and these drugs.
- Co-administration of DTG and antacid products may significantly decrease DTG plasma concentrations resulting in loss of therapeutic effect, therefore, DTG/3TC FDC should be administered 2 hours before or 6 hours after taking antacid products.
- Co-administration of DTG and drugs that contain divalent metal cations may result in decreased DTG plasma concentrations. Co-administer DTG/3TC FDC at least 2 hours before or 6 hours after taking the product, or alternatively, co-administer DTG/3TC FDC and Fe/Ca together with a meal.
- DTG/3TC FDC is not recommended for use in patients with severe hepatic impairment.
- DTG/3TC FDC is not recommended for use in patients with CrCl less than 50 mL/min.

6. APPENDIX

Appendix Table 1 Summary of Completed Clinical Pharmacology Studies that were Previously Submitted as Part of the Tivicay or Epivir Registration and are "Key" Studies to the DTG/3TC FDC Submission

Study	Study Design	Population	Treatment Details	Main Conclusions
Single-dose PK/Mass Balance				
ING111853 (DTG) GSK Document Number: RM2009/00293/00 Status: Complete	Open-label, single-dose study	Healthy adult subjects	DTG 20 mg (^{14}C-labeled and unlabeled); oral suspension; single dose; fasted.	Following oral administration, the total mean recovery of DTG was 95.6% of the administered dose, with a mean recovery of 64.0% in feces and 31.6% in urine. DTG was the predominant circulating compound in plasma. Low mean blood:plasma concentration ratios indicated minimal association of radioactivity with the blood cellular components.
NUCA1001 (3TC) GSK Document Number: UCP/92/015 Status: Complete	Randomized, open-label, single-center, two-way crossover	HIV-infected patients	3TC 50 mg (2 x 25 mg) capsules fasted or fed	Cmax and tmax were decreased and delayed when 3TC was administered with food, while AUC∞ and the amount of unchanged drug excreted in the urine (Ae) were not significantly affected.
Repeat-dose PK				
ING111322 (DTG) GSK Document Number: RM2008/00375/00 Status: Complete	Part 1: double-blind, randomized, placebo-controlled, repeat-dose, escalation study	Healthy adult subjects	Part 1: DTG 10, 25, and 50 mg; oral suspension; once daily; 10 days; fasted.	Following repeat-dose administration, plasma concentrations of DTG reached steady state by approximately 5 days of dosing. DTG AUC and Cτ increased proportionally between 10 and 50 mg once daily. The increase in DTG Cmax was slightly less than dose-proportional. Accumulation was observed in AUC, Cmax, and Cτ following repeat-dose administration of DTG once daily, with accumulation ratios estimated to be 1.24 to 1.42, 1.16 to 1.36, and 1.29 to 1.53, respectively, across 10 to 50 mg once daily dose levels. DTG showed time-invariant PK.
ING116195 GSK Document Number:	Phase I, open-label, non-blinded, prospective, PK study	Healthy HIV-1-negative men	DTG 50 mg oral; once daily; 8 days	Plasma concentrations of DTG were consistent with previously published data. Penetration of DTG into seminal fluid was <7% BP, with

Study	Study Design	Population	Treatment Details	Main Conclusions
2012N146451_00 Status: Complete				SF C24h below the PA IC_{90}. Although the AUC of DTG in rectal mucosal tissue was <20% of blood plasma, rectal mucosal tissue C24h was approximately 2-fold higher than the PA IC_{90}. Rectal mucosal fluid was not a strong surrogate for rectal mucosal tissue concentrations, and demonstrated high intra- and inter-subject variability.
ING115465 GSK Document Number: 2012N145137_00 Status: Complete	Phase I, open-label, PK study	Healthy adult female subjects	DTG 50 mg tablet oral; once daily; 5-7 days	DTG plasma PK parameters after single and repeat dose were similar to those previously reported. DTG exposure in CVF was 6% of plasma exposure at steady-state. There was no accumulation after repeat dosing. Delayed tmax was observed in CVF (tmax=6hr) compared with plasma (tmax =2hr). DTG exposure in CVF was 10% of plasma exposure at steady state. There was higher accumulation in cervical tissue after repeat dosing than in plasma (R=1.9 in cervical tissue vs. 1.4 in plasma) DTG exposure in vaginal tissue was similar to cervical tissue and represented 9% of plasma exposure. The accumulation in vaginal tissue after repeat dosing was higher than in plasma (R=1.7 in vaginal tissue vs. 1.4 in plasma). Cervical tissue and vaginal tissue exposures were highly correlated, and had concentrations above the PA IC_{90} at steady state in cervical tissue in all women and in vaginal tissue in 7/8 women.
NUCA2001 (3TC) GSK Document Number: UCR/95/001 Status: Complete	Open-label, non-comparative, multiple dose, dose escalation FTIH	HIV-positive adult patients	3TC; Dosage regimen: 0.25 mg/kg BID, 0.5 mg/kg BID, 1.0 mg/kg BID, 2.0 mg/kg BID, 4.0 mg/kg BID, 6.0 mg/kg BID, 10.0 mg/kg BID Daily dose: 0.5 mg/kg/ BID, 1.0 mg/kg/	3TC displayed dose proportional single-dose and repeat-dose PK following oral dosing of 0.5 to 20 mg/kg/day. 3TC is primarily eliminated as unchanged drug in urine; CLr exceeded GFR, suggesting that 3TC CLr involves tubular secretion. At steady state, on average, >70% of an administered dose was accounted for as parent compound in urine, generally within the first 24 h.

Study	Study Design	Population	Treatment Details	Main Conclusions
			BID, 2.0 mg/kg/ BID, 4.0 mg/kg/BID, 8.0 mg/kg/ BID, 12 mg/kg/ BID, 20 mg/kg/ BID	
EPV10001 (3TC) GSK Document Number: RM2000/00258/01 Status: Complete	Open-label, randomized, two-way crossover design study	Healthy adult subjects	3TC 150 mg BID and 300 mg once daily; oral tablet; 7 days	Following 300 mg once daily, 3TC mean Cmax values (CV%) were 2.04 μg/mL (26%) and AUCtau (0-24hr) values (CV%) were 8.87 μg.hr/mL (21%). The PK results demonstrated that plasma 3TC AUC(0-24),ss and intracellular 3TC-TP AUC(0-24), ss, and Cmax,ss were equivalent. Intracellular 3TC-TP trough concentrations (C0,ss and C24,ss) were 18 to 24% lower for the 3TC 300 mg once daily regimen than the 3TC 150 mg BID regimen.
NUCB2001 (3TC) GSK Document Number: GIO/94/001 Status: Complete	Open-label, dose escalating study	HIV-positive adult patients	3TC 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, 20.0 mg/kg/day; oral; capsules and tablets	3TC generally displayed linear, dose-proportional PK following oral dosing of 0.5 to 20 mg/kg Samples of CSF were obtained from 6 patients in this study. The mean ratio of the 3TC concentration in the CSF to that in serum 2 h post-dosing was 0.06. The CSF concentrations ranged from 0.41 to 1.43 .mol/L. This study demonstrated that 3TC penetrates the blood-brain barrier, but the sample size was too small to draw firm conclusions as to the level of penetration into the CSF.
Special Populations: Intrinsic Factors				
Dolutegravir				
ING115381 (DTG) GSK Document Number: 2011N123593_00 Status: Complete	Open-label, single-dose study	Healthy adult Japanese subjects	DTG 50 mg; tablet; oral; single dose.	The PK of DTG following single-dose oral administration to Japanese healthy subjects were similar to previously observed parameters in US healthy subjects, mainly Caucasian. Dose adjustment of DTG in Japanese subjects solely based on PK is not necessary.
ING113097 (DTG) GSK Document Number: 2011N115189_00 Status: Complete	Single-dose, open-label, parallel-group, 2-part, adaptive study	Subjects with mild or moderate hepatic impairment and matched, healthy control subjects with normal hepatic function	DTG 50 mg; tablet; oral; single dose.	Total DTG exposure in plasma was similar between subjects with moderate hepatic impairment and matched healthy subjects. DTG can be taken without dose adjustment in subjects with mild to moderate hepatic impairment.

Study	Study Design	Population	Treatment Details	Main Conclusions
ING113125 (DTG) GSK Document Number: 2011N130599_00 Status: Complete	Single-dose, open-label, PK study	Subjects with severe renal impairment and matched, healthy control subjects with normal renal function	DTG 50 mg; tablet; oral; single dose.	DTG exposure was lower in subjects with severe renal impairment (CrCL< 30 mL/min) than in healthy, matched subjects: AUC(0-∞) and Cmax were 40% and 23% lower, respectively. The moderate reduction in DTG exposure in subjects with severe renal impairment was not considered clinically significant. No dose adjustment of DTG is needed in subjects with mild to severe renal impairment (not on renal replacement therapy).
ING116070 (DTG) GSK Document Number: 2014N201872_00 Status: Complete	Phase IIIb single-arm, open-label, multicenter CSF penetration study	HIV-1infected ART-naïve subjects	DTG 50 mg; tablet; oral; once daily + ABC/3TC 600/300 mg; tablet; oral; once daily; 96 weeks	DTG is present in CSF with average concentrations in CSF at 16.2 ng/mL at Week 2 and 12.6 ng/mL at Week 16, ranging from 3.7 to 23.2 ng/mL. DTG concentrations observed in CSF at both Week 2 and Week 16 exceed the in vitro IC_{50} against wild-type viruses (0.2 ng/mL) for all subjects suggesting that it is possible to achieve therapeutic concentrations of DTG in in the CSF. DTG concentrations in the CSF were similar to the unbound DTG concentrations in plasma, with statistically significant correlations between DTG CSF and plasma, (both total and unbound) concentrations. CSF:plasma concentration ratio of DTG ranged from 0.12% to 2.04%. A regimen of DTG + ABC/3TC was effective in decreasing CSF HIV-1 RNA levels. No direct correlation of DTG CSF concentrations and change from Baseline in CSF HIV-1 RNA levels was observed likely due to combination therapy and the potent antiviral activity across subjects at Week 16. Median decreases in CSF HIV-1 RNA levels at Week 16 were similar to those observed in plasma.
ING112578 (IMPAACT P1093; DTG) GSK Document Number: 2015N235495_01 Status: Ongoing	Phase I/II multi-center, open-label, non-comparative dose-finding study	HIV-1-infected infants, children, and adolescents	DTG tablets (10 mg, 25 mg, and 50 mg) once daily according to the weight-based dosages in order to achieve ~1 mg/kg (comparable dose to 50 mg once daily given to HIV-1-infected adults).	Steady state DTG exposures following 50 mg once daily in HIV-infected adolescents ≥12 to <18 years of age, weighing at least 40 kg, were comparable to those seen in adults receiving the 50 mg once daily dose. Steady state DTG exposures following weight-based dosing of tablet formulations in HIV-infected adolescents and children ≥6 to <12 years of age, weighing at least 15 kg, were comparable to those seen in adults receiving the 50 mg once daily dose.

Study	Study Design	Population	Treatment Details	Main Conclusions
Lamivudine				
NUCB1003 (3TC) GSK Document Number: GCP/95/060 Status: Complete	Single-dose, open-label, study	Subjects with mild/moderate and severe renal impairment and matched, healthy control subjects with normal renal function	3TC 300 mg or 100 mg; capsule; oral; single dose	As renal impairment increases and renal function decreases, there is a concomitant decrease in 3TC CL/F and CLr, an increase in AUC, and an increase in elimination half-life. Below CrCl of 50 mL/min, dose modification is required. In a small (n=6) group of subjects undergoing regular (2-3 times weekly) intermittent hemodialysis PK comparisons between dialysis days and non-dialysis days did not indicate any significant differences.
NUCA1004 (3TC) GSK Document Number: UCP/95/004 Status: Complete	Open-label, parallel-group, single-dose study	HIV-infected adult patients with moderate and end stage renal impairment, and normal renal function	3TC 300 mg; tablet; oral; single dose	All PK parameters, with the exception of tmax, were significantly altered in patients with renal impairment. Patients with end stage renal impairment had greater changes in PK than patients with moderate impairment. In agreement with previous data (NUCB1003), as 3TC is primarily renally cleared, impairment of renal function significantly impacts 3TC exposure, requiring dose modification in patients where CrCl falls below 50mL/min.
NUCB1002 (3TC) GSK Document Number: GCP/95/061 Status: Complete	Open-label, single-dose study	Subjects with moderate or severe hepatic impairment and normal hepatic function	3TC 300 mg; tablet; oral; single dose	Hepatic impairment did not significantly alter plasma 3TC exposure; therefore, dose modification is not required.
LA-01 (3TC) GSK Document Number: JJE/94/001/V2 Status: Complete	Single dose escalation, crossover study	Healthy male Japanese subjects	3TC 50, 100, 300 mg; fasting; 100 mg; fed; tablet; oral; single dose	3TC exposure and excretion of 3TC in urine were in line with those obtained following similar doses in Caucasian subjects when compared with historical data.
LA-02 (3TC) GSK Document Number: JJE/94/002/V3 Status: Complete	Single-blind, placebo-controlled study	Healthy male Japanese subjects	3TC 200 mg; once daily; capsules; oral; 7 days	PK parameter estimates were in line with those obtained following similar doses in either asymptomatic HIV-infected patients or healthy Caucasian subjects when compared with historical data.

Study	Study Design	Population	Treatment Details	Main Conclusions
LB-05 (3TC) GSK Document Number: JJE/97/009 Status: Complete	Open-label, single-dose study	Healthy young males and elderly male Japanese subjects	3TC 100 mg; tablet; oral; single dose	A comparison of mean PK parameters between the treatment groups showed that tmax and AUC0-∞ in the elderly group were 2.7 and 1.4 times higher than those in the young group, respectively, while Clt/F in the elderly group was 0.71 times lower than in the young group. Cmax and t½ in both groups were similar. 3TC does not require dose modification according to age alone; however, normal age-related decline in renal function may reach the point where dose modification is required (CrCl <50 mL/min)
NUCB1009 (3TC) GSK Document Number: GM1998/00231/00 Status: Complete	Open-label, single- and repeat-dose study	Healthy Chinese subjects	3TC 100 mg; once daily; tablets; oral; 7 days	On Day 1 (single dose) and Day 7 (steady state), Cmax was 1371 nglmL and 1440 nglmL, and AUC(0-24) was 4365 ng.hr/mL and 4446 ng.hr/mL, respectively. There was no difference in 3TC PK between male and female Chinese subjects or (by comparison to historical data) Caucasian subjects.
NUCA2002 (3TC) GSK Document Number: UCR/95/004 Status: Complete	Open-label, dose-escalating, study	HIV-positive children and adolescents	3TC single IV dose; Day -2 (48 to 72 h prior to the first oral dose) 1.0 (capsules, oral), 2.0, 4.0, 8.0, 12.0, and 20.0 mg/kg/day; liquid or capsules; ≥24 weeks	The comparative PK properties of 3TC in adult and pediatric patients supports the use of a dose of 8.0 mg/kg/day in infants and children as a dose that provides comparable drug exposure (as measured via AUC) to the adult dose of 300 mg/day (given as 150 mg BID) which is approximately 4.0 mg/kg/day in a 70-kg adult. Although age-related changes in 3TC clearance were consistently observed and require dose modification <13 yrs old (and <37.5 kg), the adolescent age group had similar PK profiles to those seen in adults >18 yrs old. Thus, no dose modification is required for subjects >12 yrs old.
NUCB2020 (3TC) GSK Document Number: GM/1998/00006/00 Status: Complete	Randomized, Phase II, dose ranging study	Children and adolescents with chronic HBV infection	Stratum 1 and 2: 3TC 0.35 mg/kg BID, 3 mg/kg once daily, 1.5 mg/kg BID, 4 mg/kg BID; solution; oral; 4 weeks Stratum 3: 3TC 100 mg;	3TC exhibits linear PK and dose proportionality at doses ranging from 1.5 mg/kg to 4 mg/kg BID. The PK data obtained in the adolescent group were very similar to those seen in adults across all the PK studies carried out with 3TC where renal function is healthy. Adolescents should receive the standard adult dose, as

Study	Study Design	Population	Treatment Details	Main Conclusions
			once daily; tablets; oral; 4 weeks	supported by the PK and efficacy data.
Drug-drug Interactions				
Dolutegravir				
ING111322 (MDZ) GSK Document Number: RM2008/00375/00 Status: Complete	Part 1: double-blind, randomized, placebo-controlled, repeat-dose, escalation study	Healthy adult subjects	Part 1: DTG 25 mg; oral suspension; once daily; 10 days; fasted. MDZ 3 mg; oral single dose on Day -1 and Day 10.	Co-administration of repeat doses of DTG 25 mg once daily with a single dose of 3 mg MDZ resulted in no significant change in MDZ plasma AUC, indicating no induction or inhibition effect of DTG on CYP3A activity. Thus, DTG will not affect exposure of CYP3A substrates following co-administration.
ING111405 (LPV/RTV, DRV/RTV) GSK Document Number: RM2008/00863/00 Status: Complete	Randomized, open-label, 2-period, one-way, two-sequence, croosover, single-sequence, 2-cohort study	Healthy adult subjects	DTG 30 mg; tablet; oral; once daily; 5 days. DTG 30 mg; tablet; oral; once daily + LPV/RTV 400/100 mg; tablet; oral; q12h; 14 days. DTG 30 mg; tablet; oral; once daily + DRV (tablet) /RTV (capsule) 600/100 mg; oral; q12h; 14 days.	Co-administration of LPV/RTV had no effect on plasma DTG PK. Co-administration of DRV/RTV resulted in decreased plasma DTG exposures (DTG AUC(0-∞), Cmax, and Cτ were decreased by 22%, 11%, and 38%, respectively); however, these decreases are not considered to be clinically significant. DTG can be co-administered with DRV/RTV or LPV/RTV with no dose adjustment.
ING111602 (Antacid, Multivitamins) GSK Document Number: UM2009/00142/00 Status: Complete	Open-label, single-dose, randomized, 4-period crossover study	Healthy adult subjects	DTG 50 mg; tablet; oral; single dose. DTG 50 mg; tablet; oral; single dose + multivitamin; tablet; oral; single dose. DTG 50 mg; tablet; oral; single dose + Maalox Advanced Maximum Strength; 20mL suspension; single dose. DTG 50 mg; tablet; oral; single dose 2 hrs prior to Maalox Advanced Maximum Strength 20mL; suspension; single dose.	Concurrent administration of a multivitamin decreased DTG AUC, Cmax, and C24 by 33%, 35%, and 32%, respectively, on average. The decrease is not considered clinically relevant and DTG may be taken concomitantly with a multivitamin without dose adjustment. Concurrent administration of Maalox decreased DTG AUC, Cmax, and C24 by 74%, 72%, and 74%, respectively, on average. Administration of Maalox 2 hours after DTG decreased DTG AUC, Cmax, and C24 by 26%, 18%, and 30%, respectively, on average. Concomitant administration of DTG and antacids should be avoided. It is recommended that DTG should be administered 2 hours before or 6 hours after antacids.

Study	Study Design	Population	Treatment Details	Main Conclusions
ING111603 (ETV) GSK Document Number: RM2008/00859/00 Status: Complete	Open-label, repeat-dose, 2-period, single-sequence study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily + ETV 200 mg; tablet; oral; q12h; 14 days.	Co-administration of DTG and ETV resulted in decreased steady-state plasma DTG AUC(0-τ), Cmax, and Cτ by 71%, 52%, and 88%, respectively. Co-administration of DTG and ETV is not recommended.
ING111604 (TDF) GSK Document Number: RM2008/00793/00 Status: Complete	Open-label, repeat-dose, single-sequence, 3-period study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. TDF 300 mg; tablet; oral; once daily; 7 days. DTG 50 mg; tablet; oral; once daily + TDF 300 mg; tablet; oral; once daily; 5 days.	PK parameters of DTG and TDF during combination therapy were similar to those when either drug was given alone, demonstrating no drug interaction. Therefore, these 2 drugs can be taken together without dose adjustment
ING111854 (ATV, ATV/RTV) GSK Document Number: UM2009/00075/00 Status: Complete	Randomized, open-label, repeat-dose, 2-period, single-sequence, 2-cohort study	Healthy adult subjects	Period 1: DTG 30 mg; tablet; oral; once daily; 5 days; fed. Period 2: DTG 30 mg; tablet; oral; once daily + ATV (capsule) /RTV (capsule) 400/100 mg; once daily; 14 days. DTG 30 mg; tablet; oral; once daily + ATV 400 mg; capsule; oral; once daily; 14 days.	Co-administration of DTG with ATV/RTV resulted in an increase in plasma DTG AUC(0-τ), Cmax, and Cτ by 62%, 34%, and 121%, respectively. Co-administration of DTG with ATV resulted in an increase in plasma DTG AUC(0-τ), Cmax, and Cτ by 91%, 50%, and 180%, respectively. Although co-administration of ATV/RTV or ATV with DTG resulted in increased DTG plasma exposure, this effect is not considered clinically significant based on accumulated toxicity data in animals, and safety and tolerability data in humans receiving DTG to date. Therefore, it is recommended that no dose adjustment is necessary when DTG is co-administered with ATV/RTV or ATV.
ING111855 (EE/NGMN) GSK Document Number: 2012N134648_00 Status: Complete	Randomized, 2-period, double-blind study	Healthy adult female subjects	DTG 50 mg or placebo; oral; tablet; once daily; Days 1-11 and DTG 50 mg or placebo; tablet; oral; once daily; Days 12-21. EE/NGMN; tablet; oral; once daily; Days 1-21.	Co-administration with DTG had no effect on the PK of NGMN and EE in healthy female subjects receiving Ortho-Cyclen. DTG and common oral contraceptives can be co-administered without dose adjustment.
ING112934 (ETV/LPV/RTV, ETV/DRV/RTV)	Randomized, open-label, repeat-dose, 3-period,	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days.	Co-administration of DTG with ETV/LPV/RTV had no effect on DTG AUC(0-τ) and Cmax, while increasing Cτ

Study	Study Design	Population	Treatment Details	Main Conclusions
GSK Document Number: UM2009/00077/00 Status: Complete	single-sequence, 2-cohort adaptive study		DTG 50 mg; tablet; oral; once daily + ETV/LPV/RTV 200/400/100 mg; tablet; oral; q12h; 14 days. DTG 50 mg; tablet; oral; once daily + ETV (tablet) DRV (tablet)/RTV (capsule) 200/600/100 mg; oral; once daily; 14 days.	by 28% and t½ by 36%. Co-administration of DTG with ETV/DRV/RTV resulted in decreased plasma DTG exposures, with plasma DTG AUC(0-τ), Cmax, and Cτ on average 25%, 12%, and 37% lower when co-administered with ETV/DRV/RTV compared with DTG given alone. These effects of ETV/LPV/RTV and ETV/DRV/RTV on DTG exposures are not considered clinically relevant. Co-administration of LPV/RTV and DRV/RTV attenuated the effect of ETV on DTG exposure. DTG may be co-administered with ETV without a dosage adjustment if the subject is receiving concomitant LPV/RTV or DRV/RTV.
ING112941 (OMP) GSK Document Number: RM2009/00534/00 Status: Complete	Part 1: Randomized, open-label, 2-sequence, 3-treatment crossover study	Healthy adult subjects	Part 1: DTG 50 mg; tablet; oral; single dose; fasted. DTG 50 mg; tablet; oral; single dose; within 30 minutes after the start of a high-fat meal. DTG 50 mg; tablet; oral; single dose + OMP 40 mg; capsule; oral; once daily; fasted; 5 days.	Co-administration with OMP had no significant effect on plasma DTG AUC(0-τ), AUC(0-∞), Cmax, and C24. DTG can be co-administered with OMP without dose adjustment.
ING113068 (FPV/RTV) GSK Document Number: 2010N110708_00 Status: Complete	Part A: open-label, repeat-dose, 2-period, single-sequence	Healthy adult subjects	Part A: DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily + FPV 700 mg; tablet / RTV 100 mg; capsule; oral; q12h; 10 days.	Amprenavir concentrations in combination with DTG were similar to literature values suggesting that DTG does not have a significant effect on amprenavir exposure. Co-administration of FPV/RTV decreased DTG plasma exposures: AUC(0-τ), Cmax, and Cτ decreased by 35%, 24%, and 49% , respectively. The effect of FPV/RTV on DTG exposure is not considered clinically significant, therefore no DTG dose adjustment is necessary when co-administered with FPV/RTV. However, caution should be given to INSTI-resistant subjects.
ING113096 (TPV/RTV) GSK Document Number: RM2010/00261/00	Randomized, open-label, repeat-dose, 3-period, single-sequence, study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. TPV/RTV 500/200 mg; capsule; oral; BID; 7 days	Co-administration of DTG with TPV/RTV resulted in a 59%, 46%, and 76% decrease in plasma DTG AUC(0-τ), Cmax, and Cτ, respectively. DTG 50 mg BID dosing is recommended when co-administered with TPV/RTV

Study	Study Design	Population	Treatment Details	Main Conclusions
Status: Complete			DTG 50 mg; tablet; oral; once daily and TPV/RTV 500/200 mg; capsule; oral; BID; 5 days	based on clinical efficacy data.
ING113099 (RIF, RBT) GSK Document Number: 2011N119786_00 Status: Complete	Randomized, open-label, 2-period, single-sequence, 2-cohort study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 7 days. DTG 50 mg; tablet; oral; BID; 7 days then DTG 50 mg; tablet; oral; BID + RIF 600 mg; capsule; oral; once daily; 14 days. DTG 50 mg; tablet; oral; once daily for 7 days then DTG 50 mg; tablet; oral BID+ RBT 300 mg; capsule; oral; once daily; 14 days.	Co-administration of DTG 50 mg BID with RIF 600 mg once daily resulted in decreased DTG plasma exposures compared with DTG 50 mg BID alone: AUC(0-τ), Cmax, and Cτ were reduced by 54%, 43%, and 72%, respectively. However, DTG exposure, AUC(0-24), Cmax, and Cτ, from co-administration of DTG 50 mg BID with RIF 600 mg once daily was 33%, 18%, and 22% higher than those of DTG 50 mg once daily alone, respectively. Co-administration of DTG 50 mg once daily with RBT 300 mg once daily resulted in a 16% increase in DTG Cmax, no change in AUC(0-τ), and 30% reduction in Cτ compared with DTG 50 mg once daily alone. This combination should be used with caution in INI-resistant HIV-1 infected subjects. DTG may be given at 50 mg BID with RIF in HIV-1 infected subjects who are not INI-resistant. No dose adjustment is needed when DTG is co-administered with RBT.
ING114005 (EFV) GSK Document Number: RM2010/00328/00 Status: Complete	Open-label, repeat-dose, 3-period, single-sequence study	Healthy adult subjects	DTG 100 mg; tablet; oral; single dose. DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily in AM + EFV 600 mg; tablet; oral; once daily in PM; 14 days.	Co-administration of EFV with DTG did not affect EFV exposure. Co-administration of DTG with EFV resulted in a 57%, 39%, and 75% decreased plasma DTG AUC(0-τ), Cmax, and Cτ, respectively. DTG 50 mg BID is recommended when co-administered with EFV based on clinical efficacy data
ING115696 (Prednisone) GSK Document Number: 2011N126791_00 Status: Complete	Open-label, repeat-dose, 2-period, single-sequence study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily; Days 1-10 + prednisone; tablet; oral; once daily (60 mg Days 1-	DTG PK parameters were similar between Day 5 and Day 10 in Period 2. Co-administration of prednisone 60 mg once daily x 5 days + 5 days of taper with DTG (Day 10 in Period 2) resulted in an increase in the mean DTG AUC, Cmax and Cτ by 11%, 6%, and 17%, respectively. Steady state was reached for DTG following 5 days co-

Study	Study Design	Population	Treatment Details	Main Conclusions
			5; 50 mg Day 6; 40 mg Day 7; 30 mg Day 8; 20 mg Day 9; 10 mg Day 10).	administration of DTG with prednisone. No dose adjustment is needed for DTG when co-administered with prednisone.
ING115697 (TVR, BCV) GSK Document Number: 2012N140471_01 Status: Complete	Randomized, open-label, 2-period, single-sequence, 2-cohort study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily + TVR 750 mg; tablet; oral; q8h; 10 days. DTG 50 mg; tablet; oral; once daily + BCV 800 mg; capsule; oral; q8h; 10 days.	Co-administration of DTG with BCV had no effect on plasma exposure of DTG. Co-administration of DTG with TVR resulted in increased DTG plasma exposures: AUC(0-τ), Cmax, Cτ, increased by 25%, 19%, 37%, respectively. Co-administration of BCV or TVR with DTG had no clinically significant effect on DTG PK. Plasma BCV and TVR PK data for the DTG-TVR and DTG-BCV combination treatment were similar to historical TVR data, indicating no effect of DTG on BCV or TVR exposure.
ING115698 (Methadone) GSK Document Number: 2012N133261_00 Status: Complete	Open-label, repeat-dose, 2-period, single-sequence study	Healthy adult subjects enrolled in a methadone maintenance program	Stable methadone dose; oral solution; once daily; 3 days. Stable methadone dose; oral solution + DTG 50 mg; tablet; oral; BID; 5 days.	Co-administration of methadone with repeat doses of 50 mg DTG had no effect on total, R-, and S-methadone PK. No dose adjustment in methadone is required when given in combination with DTG.
LAI116181 (RPV) GSK Document Number: 2011N130484_00 Status: Complete	Cohort 1: Open-label, repeat-dose, single-sequence, 3-period study	Healthy adult subjects	Cohort 1: Treatment A = DTG 50 mg; tablet; oral; q24h; 5 days. Treatment B = RPV 25 mg; tablet; oral; q24h; 11 days. Treatment C = RPV 25 mg; tablet; oral; q24h + DTG 50 mg; tablet; oral; q24h; 5 days.	Co-administration of DTG with RPV resulted in no change in DTG AUC(0-τ) and Cmax, and a 22% increase in Cτ. Co-administration of DTG with RPV resulted in no change in RPV AUC(0-τ) and Cmax, and a 21% increase in Cτ. There was no significant drug interaction between DTG and RPV. DTV and RPV can be co-administered without dose adjustment.
ING116898 (Calcium & Iron Supplements) GSK Document Number: 2013N163904_00	A phase 1 open-label, randomized, 2-cohort, 4-period, crossover study	Healthy adult subjects	Cohort 1: DTG 50 mg; tablet; oral; single dose; fasted. DTG 50 mg; tablet; oral;	Under fasted conditions, co-administration of calcium carbonate reduced DTG exposure by 37 to 39% and ferrous fumarate reduced DTG exposure by 54 to 57%. Co-administration of DTG with calcium carbonate or ferrous fumarate under fed conditions or dosing DTG

Study	Study Design	Population	Treatment Details	Main Conclusions
Status: Complete			single dose + calcium carbonate 1200 mg; tablet; oral; fasted. DTG 50 mg, tablet; oral; single dose + calcium carbonate 1200 mg; tablet; oral; fed. DTG 50 mg, tablet, oral, single dose, fasted, 2 hours prior to calcium carbonate 1200 mg, tablet, oral. Cohort 2: DTG 50 mg; tablet; oral; single dose; fasted. DTG 50 mg; tablet; oral; single dose + 324 mg ferrous fumarate; oral, fasted. DTG 50 mg; tablet; oral; single dose + 324 mg ferrous fumarate; oral; fed. DTG 50 mg; tablet; oral; single dose; fasted; 2 hours prior to 324 mg ferrous fumarate; oral,	2 hours prior to these supplements showed DTG exposure similar to those when DTG was given alone under fasted conditions. DTG can be given concurrently with calcium or iron supplements with food; without food, DTG should be given 2 hours prior to or 6 hours after calcium or iron supplements.
200901 (CBZ) GSK Document Number: 2013N185729_00	A phase 1, open-label, 3-period, fixed-sequence crossover study	Healthy adult subjects	Period 1: DTG 50 mg; tablet; oral; once daily (Days 1-5) Period 2: CBZ 100 mg;	Co-administration of DTG with CBZ resulted in decreases in DTG Cmax, AUC, and $C\tau$ by approximately 33%, 49%, and 73%, respectively, compared with DTG administered alone.

Study	Study Design	Population	Treatment Details	Main Conclusions
Status: Complete			tablet; oral; BID (Days 1-3); CBZ 200 mg; tablet; oral; BID (Days 4-6); CBZ 300 mg; tablet; oral; BID (Days 7-16) Period 3: DTG 50 mg; tablet; oral, once daily + CBZ 300 mg; tablet; oral; BID (Days 1-5)	DTG dose adjustment from 50 mg once daily to 50 mg BID is recommended when DTG is co-administered with CBZ.
201102 (DCV) GSK Document Number: 2014N203043_00 Status: Complete	A single-center, open-label, 3-period, crossover study	Healthy adult subjects	Treatment A = DTG 50 mg, tablet, oral, q24h x 5 days Treatment B = DCV 60 mg, tablet, oral, q24h x 5 days Treatment C = DCV 60 mg, tablet, oral, q24h + DTG 50 mg, tablet, oral, q24h x 5 days	Plasma exposure of DCV did not appear to be meaningfully affected when co-administered with DTG compared with DCV administered alone. Co-administration of DTG 50 mg q24h with DCV 60 mg q24h increased DTG AUC(0-τ), Cmax, and Cτ by approximately 33%, 29%, and 45%, respectively, compared with DTG administered alone. DTG and DCV can be co-administered without dose adjustment.
201167 (Metformin) GSK Document Number: 2014N203038_00 Status: Complete	Phase I, open-label, parallel group, 3-period, fixed-sequence study	Healthy adult subjects	Cohort 1: Period 1: Metformin IR 500 mg, tablet, oral, q12h (Days 1-5); fed Period 2: Metformin IR 500 mg, tablet, oral, q12h + DTG 50 mg, tablet, oral, q24h (Days 1-7); fed Period 3: Metformin IR 500 mg, tablet, oral, q12h (Days 1-10); fed Cohort 2: Period 1: Metformin IR 500 mg, tablet, oral, q12h (Days 1-5); fed Period 2: Metformin IR 500 mg, tablet, oral, q12h	Co-administration of DTG 50 mg q24h with metformin 500 mg q12h resulted in increases in metformin AUC(0-τ) and Cmax by 79% and 66%, respectively, compared with metformin administered alone. Co-administration of DTG 50 mg q12h with metformin 500 mg q12h resulted in increases in metformin AUC(0-τ) and Cmax by 145% and 111%, respectively, compared with metformin administered alone. Effects were DTG dose dependent. Subjects should be monitored when starting and stopping co-administration of DTG with metformin and a dose adjustment of metformin should be considered to maintain glycemic control

Study	Study Design	Population	Treatment Details	Main Conclusions
			+ DTG 50 mg, tablet, oral, q12h (Days 1-7); fed Period 3: Metformin IR 500 mg, tablet, oral, q12h (Days 1-10); fed	
Lamivudine				
CNAA1002 (ABC, ZDV) GSK Document Number: GM1997/00203/00 Status: Complete	Open-label, randomized, seven-period, crossover study	HIV-infected patients	1: ABC 600 mg 2: ZDV 300 mg 3: 3TC 150 mg 4: ABC 600 mg + ZDV 300 mg 5: ABC 600 mg + 3TC 150 mg 6: ZDV 300 mg + 3TC 150 mg 7: ABC 600 mg + ZDV 300 mg + 3TC 150 mg Single dose; oral; fasted; 7 days	The PK of ABC following a single, oral dose was unaffected by co-administration with ZDV and/or 3TC. Plasma ZDV Cmax was reduced approximately 20% when co-administered with ABC or ABC/3TC, but there was no change in ZDV AUC(0-∞). This difference is not considered to be clinically significant. Plasma 3TC Cmax was reduced approximately 35% and AUC approximately 15% when given with ABC or ABC+ZDV versus 3TC given alone. These differences are not considered to be clinically significant. No dosage adjustments are recommended when ABC, ZDV, and 3TC are co-administered.
NUCA1005 (ZDV) GSK Document Number: UCP/94/042 Status: Complete	Open-label, randomized, 4-way crossover study	HIV-infected patients	Treatment A: ZDV 200 mg; tablet; oral; single dose Treatment B: 3TC 300 mg; tablet; oral; single dose Treatment C: 3TC 300 mg; tablet; oral; 5 doses + ZDV 200 mg; tablet; oral; single dose Treatment D: ZDV 200 mg; tablet; oral; TID; 9 doses + 3TC 300 mg; tablet; oral; single dose	The study showed a small non-statistically significant increase in ZDV exposure (about 13% and 28% for AUC(0-∞) and Cmax, respectively), when co-administered with 3TC 300mg, which was not considered clinically significant. The t½ for the primary metabolite of ZDV, ZDV glucuronide, was significantly reduced by ~25%, possibly because of a slower formation rate. This was not felt to be clinically significant as ZDV glucuronide has little or no reported activity/toxicity.
NUCA1007 (TMP/SMX) GSK Document Number: UCP/94/043	Randomized, open-label, two-way crossover study	HIV-infected patients	Treatment A: 3TC 300 mg; tablet; oral; single dose Treatment B: TMP/SMX DS (TMP 160 mg + SMX 800 mg); tablet; oral; once	PK analysis of 3TC concentrations for 3TC alone versus combined with co-trimoxazole (TMP/SMX) showed an increase in 3TC AUC of approximately 45%, a 30% decrease in clearance (CL/F), and a 35% decrease in CLr. The differences in AUC(0-∞), CL/F, and CLr were

Study	Study Design	Population	Treatment Details	Main Conclusions
Status: Complete			daily; 5 days; 3TC 300 mg; tablet; oral; single dose + dose 5 of TMP/SMX on Day 5.	considered to be statistically significant but not clinically meaningful with normal doses of TMP/SMX. The 90% CIs for CL/F, CLr, and AUC(0-∞) did not fall within the 70 - 142% criterion (log-transformed analysis). This increase was not considered clinically significant in light of the dosing of co-trimoxazole for prophylaxis (once daily) and the safety profile of 3TC. Also, 3TC did not affect the PK of co-trimoxazole or alter the amount of N4-acetyl-SMX excreted in the urine to a statistically significant degree. No contraindication or dose adjustment of 3TC when combined with TMP or SMX at normal doses. High doses of TMP/SMX should be administered with caution as it would be anticipated that there would be more significant increases in 3TC exposure.
NUCA2005 (ZDV, ddI) GSK Document Number: RM1997/00767/00 Status: Complete	Open-label randomized study	HIV-infected children	**Arm A** Regimen 1: 3TC 4 mg/kg Q12h; ZDV 180 mg/m^2 Q6h; ddI 135 mg/m^{2}Q12h Regimen 2: 3TC 4 mg/kg Q12h; ZDV 90 mg/m^2 Q6h; ddI 135 mg/m^{2}Q12h **Arm B** Regimen 1: 3TC 4 mg/kg Q12h; ZDV 180 mg/m^2 Q6h Regimen 2: 3TC 4 mg/kg Q12h; ddI 135 mg/m^{2}Q12h Regimen 3: 3TC 4 mg/kg Q12h; ZDV 90 mg/m^2 Q6h; ddI 135 mg/m^{2}Q12h	No PK drug interactions among 3TC, ZDV, and ddI were observed in this study. Children appeared to have different PK profiles from adolescents for 3TC and ddI, but similar PK profiles for ZDV.
204857 (SBT) GSK Document Number: 2016N282881_00	Open-label, randomized, 4-way crossover study	Healthy adult subjects	Treatment A: 3TC 300 mg; solution; oral; single dose Treatment B: 3TC 300 mg; solution; oral; single dose + oral solution containing	Co-administration of single doses of 3TC and sorbitol solutions under fasted conditions resulted in decreased 3TC plasma exposures. Sorbitol had a dose-dependent effect on 3TC PK with a 28%, 52%, and 55% reduction in Cmax, a 20%, 39%, and 44% reduction in AUC0-24, and

Study	Study Design	Population	Treatment Details	Main Conclusions
Status: Complete			Sorbitol 3.2 g; single dose Treatment C: 3TC 300 mg; solution; oral; single dose + oral solution containing sorbitol 10.2 g; single dose Treatment D: 3TC 300 mg; solution; oral; single dose + oral solution containing sorbitol 13.4 g; single dose	a 14%, 32%, and 36% reduction in AUC0-∞ when co-administered with 3.2 g, 10.2 g, and 13.4 g sorbitol, respectively.
Pharmacodynamics				
Dolutegravir				
ING111856 (TQT) GSK Document Number: RM2010/00046/00 Status: Complete	Randomized, partial-blind, single-dose, 3-period, crossover study	Healthy adult subjects	DTG 250 mg; oral suspension; single dose Placebo; oral suspension; single dose Moxifloxacin 400 mg; tablet; oral; single dose	DTG had no effect on cardiac repolarization at a supratherapeutic dose of 250 mg suspension. The study was sensitive enough to detect the effect of moxifloxacin, the positive control, on QTcF, which confirmed that this study was valid for assessing the effects of DTG on cardiac repolarization.
ING114819 (Effect of DTG on Renal Functions) GSK Document Number: 2010N110959_00 Status: Complete	Open-label, randomized, 3-arm, parallel, placebo-controlled study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 14 days DTG 50 mg; tablet; oral; q12h; 14 days Placebo; tablet; oral; once daily; 14 days Omnipaque 300 (647 mg/mL of iohexol) 5 mL; solution; IV Aminohippurate Sodium 2 g/10 mL (20%) of Loading Dose: 8 mg/kg, Maintenance Dose: 12 mg/min; solution; IV	Administration of DTG caused a 10 to 14% reduction in plasma CrCl, which is consistent with previous clinical studies. DTG had no effect on GFR or ERPF.
Population PK				
Dolutegravir				
Population PK Analysis of DTG in HIV-Infected Treatment-Naïve Patients	DTG concentration-time, dosing, demographic, and covariate data from the	ARV-naïve and experienced (INSTI inhibitor-naïve) HIV-	DTG 10 and 50 mg tablet; oral; once daily for 10 days	<u>Population PK Modelling</u>: The PK of DTG in subjects with HIV following repeat-oral administration were adequately described by a 1-

Study	Study Design	Population	Treatment Details	Main Conclusions
GSK Document Number: 2012N149219_00 Status: Complete	following studies were combined: proof of concept (PoC: ING111521), Phase IIb (SPRING-1: ING112276), and Phase III (SPRING-2: ING113086)	infected patients, not currently receiving ART HIV-infected treatment-naïve patients	DTG 10, 25, and 50 mg tablet; oral; once daily with either ABC/3TC (600 mg/300 mg) or TDF/FTC (300 mg/200 mg) FDC for 96 weeks DTG 50 mg tablet; oral; once daily with either ABC/3TC (600 mg/300 mg) or TDF/FTC (300 mg/200 mg) FDC	compartment model with first-order absorption and absorption lag-time and first-order elimination. Weight, smoking status, age, and total bilirubin were predictors of CL/F; weight was a predictor of V/F, and gender was a predictor of F. The effect of these covariates was not considered clinically significant, therefore, no DTG dose adjustment by these covariates is necessary. For a typical 4[redacted]-year-old male, non-current smoker subject that weighed 70 kg with total bilirubin of 9 μmol/L, the estimated mean (95% CI) parameter values were: CL/F=0.901 (0.864, 0.938) L/h, V/F=17.4 (16.5, 18.3) L, Ka=2.24 (1.56-2.92) h-1, and ALAG=0.263 (0.0942, 0.432) h. Race/ethnicity, HCV co-infection, CDC classification, albumin, CrCL, ALT, or AST did not influence the PK of DTG in this analysis. There were limited PK data on subjects with HBV co-infection (n=8, 1%) and subjects of ≥65 years of age (n=1). The PK of DTG were dose proportional for the range of doses between 25 and 50 mg, but a greater-than-dose-proportional PK was found at the 10-mg dose due to its 24% higher oral BA compared with the 25 and 50 mg doses. Inter-individual variability for CL/F and V/F was relatively low (23.5% and 13.7%), but was high for Ka (50.1%). Inter-occasion variability on CL/F was 17% over the course of studies. <u>PK-PD Relationship:</u> There was no correlation between DTG exposure (AUC0-τ, Cmax, and Cmin) and antiviral response and CD4+ cell count change from Baseline.

Study	Study Design	Population	Treatment Details	Main Conclusions
				There was no correlation between DTG exposure (AUC(0-τ), Cmax, and Cmin) and safety measures except for change from Baseline in serum creatinine and CrCL. Change from Baseline in serum creatinine and CrCL appeared correlated with DTG exposure, however, it was not clinically significant due to the small magnitude of change.
Population PK Analysis of DTG in HIV-1 Infected Treatment-Experienced Adults GSK Document Number: 2012N149456_01 Status: Complete	DTG concentration-time, dosing, demographic, and covariate data from the following studies were combined: ING112961 (VIKING, Phase IIb RAL-resistant), ING112574 (VIKING-3, Phase III INSTI-resistant), ING111762 (SAILING, Phase III, treatment-experienced and INSTI-naïve), and ING116529 (VIKING-4, Phase III, treatment-experienced and INSTI-resistant).	HIV-1 infected, ARV-experienced adults with RAL resistance HIV-1 infected, ART-experienced adults with INSTI resistance HIV-1 infected, ARV-experienced, INSTI-naïve adults	DTG 50 mg once daily and BID with continuation of the current failing ARV regimen for 10 days, then in combination with OBT for a minimum of 24 weeks. DTG 50 mg BID with continuation of the current failing ARV regimen for 7 days, then in combination with OBT for a minimum of 24 weeks. DTG 50 mg once daily with an investigator-selected background regimen for 48 weeks DTG 50 mg BID or placebo with continuation of the current failing ARV regimen for 7 days, then 50 mg BID in combination with OBT for a minimum of 24 weeks	The PK of DTG following repeat oral administration in HIV-1-infected, treatment-experienced adults were adequately described by a 1-compartment model with first-order absorption, absorption lag-time, and first-order elimination. The structural model resembled PK in HIV-1-infected, treatment-naïve adults. Weight, smoking status, concomitant use of metabolic inducers (DRV-RTV, FPV-RTV, ETV or EFV without RTV-boosted PIs, or TPV-RTV) as part of background ARV classified by their level of induction, concomitant use of metabolic inhibitors (ATV-RTV) as part of background ARV, and albumin level were predictors of CL/F; weight and albumin level were predictors of V/F; and gender and concomitant use of metal cation-containing vitamin/mineral supplements were predictors of F. The estimated effect size of the metabolic inducers or inhibitors in the final model was consistent with observations in Phase 1 drug interaction studies and supports the use of Phase 1 data for informing the need for dosage adjustments. The effect of weight, gender, smoking status, albumin, concomitant use of mild metabolic inducers (DRV-RTV or FPV-RTV) and inhibitors (ATV or ATV-RTV) as part of background ARV, and concomitant use of metal cation-containing vitamin/mineral supplements are unlikely to be clinically significant due to the small magnitude of effects.

Study	Study Design	Population	Treatment Details	Main Conclusions
				For a typical 70-kg male, non-current smoker, not currently receiving metabolic inducers or inhibitors as part of background ARV, not taking any metal cation-containing vitamin/supplements, with albumin of 43 g/L, the estimated mean (95% CI) parameter values CL/F=1.00 (0.942, 1.06) L/hr, V/F=18.9 (17.8, 20.0) L, Ka=1.99 (1.62, 2.36) hr-1, and ALAG=0.333 (fixed) hr. Race/ethnicity, HCV co-infection, CDC classification, mild to moderate renal or hepatic impairment as judged by estimated CrCL, ALT, or AST did not influence the PK of DTG in this analysis. The PK of DTG appeared to be dose proportional between 50 mg once daily and 50 mg BID regimens. Inter-individual variability for CL/F was relatively low (CV=28%). Inter-individual variability for V/F and Ka could not be estimated due to lack of PK samples during the absorption phase. Inter-occasion variability on CL/F was moderate, at 29.5% over the course of studies in treatment-experienced subjects, somewhat higher than that estimated in treatment-naïve subjects (17%).
Population Pharmacokinetic Analysis of DTG in HIV-1 Infected Treatment-Experienced Pediatric Subjects in Study ING112578 (IMPAACT P1093) - Addendum GSK Document Number: 2016N305378_00	Update to the Population PK model parameters following the inclusion of 47 additional pediatric DTG samples from 11 subjects in Study P1093	HIV-1 infected treatment-experienced pediatric subjects	DTG once daily at approximately 1.0 mg/kg according to weight-based fixed doses, using 10 mg, 25 mg, and 50 mg tablets	The DTG PK data in HIV-1 infected treatment-experienced children and adolescents were adequately described by a one-compartment model with first-order absorption, absorption lag time and first-order elimination. Absorption rate constant, absorption lag time, and RBA were formulation-specific. Allometric scaling based on body weight was incorporated as predictors of CL/F and V/F. No other covariates were identified. For a typical 70 kg subject, the estimated mean (95% CI)

Study	Study Design	Population	Treatment Details	Main Conclusions
Status: Complete				parameter values were 1.05 (0.901, 1.20) L/hr, V/F=19.0 (17.1, 20.9) L, Ka tablet=0.808 (0.159, 1.46) hr^{-1}, Ka granule=1.43 (1.09, 1.77) hr^{-1}, ALAG tablet=0.620 (-0.107, 1.35) hr, and F granule=1.50 (1.28, 1.72). The model parameter estimates with the additional 47 observations were similar to the previous analysis. Dosing of DTG tablets on a weight-band basis (20, 25, 35, 50 mg) in children of at least 6 years of age provides comparable exposure to that observed in adults (50 mg daily) whilst higher PK variability in pediatric subjects was observed. Simulations implementing alternative posology showed increased exposure compared to simulation results using study-defined dosing regimens, but were still within the exposure range to that observed in adults receiving 50 mg BID. Alternative PK models for DTG, refining the absorption structural component as well as the error structural component, did not provide any distinct improvement in describing the PK profile compared to the current final model.
Lamivudine				
Population Pharmacokinetic Analysis in HIV-infected Patients (ZDV naive and ZDV experienced) GSK Document Number: RM1996/00214/00 Status: Complete	3TC (3TC) concentration-time, dosing, demographics and covariate data from the following two studies were combined: Protocols NUCA3001 and NUCA3002	NUCA3001: ZDV-naive (≤4 weeks of prior ZDV treatment), HIV-1-infected patients with CD4+ cell counts of 200-500 cells/mm^3. NUCA3002: ZDV-experienced (≥24 weeks of previous ZDV treatment), HIV-1-infected patients with CD4+ cell counts of 100-300 cells/mm^3.	NUCA3001: 3TC 300 mg BID, ZDV 200 mg TID, 3TC 150 mg BID plus ZDV 200 mg TID, or 3TC 300 mg BID plus ZDV 200 mg TID. NUCA3002: 3TC 150 mg BID plus ZDV 200 mg TID,	3TC population PK estimates were similar to values previously reported in HIV-infected patients and were not significantly influenced by covariates of gender, race, age, weight, renal function, surrogate markers of HIV disease (CD4+, CDC Classification, and HIV-1 RNA PCR) or ZDV co-administration. CDC Classification significantly influenced 3TC volume; however, when CDC Classification was combined with CrCl as a covariate of clearance, no significant differences were observed. Weight significantly influenced 3TC clearance; gender and race marginally influenced clearance. When gender and

Study	Study Design	Population	Treatment Details	Main Conclusions
			3TC 300 mg BID plus ZDV 200 mg TID, and zalcitabine 0.75 mg TID plus ZDV 200 mg TID.	race were corrected for weight no significant differences in clearance were observed. Renal function (CrCl) significantly influenced 3TC clearance. This is supported by the findings of Reports UCP/95/004 and GCP/95/060. However, dosage adjustments could not be determined based on the populations findings since most patients had normal renal function and only three patients had estimated CrCl <60 mL/min. ZDV PK parameters were not significantly different when co-administered with 3TC (150 mg or 300 mg BID); this analysis supports the findings of Report UCP/94/042.
Population Pharmacokinetic Analysis of Pooled Lamivudine Data from Six Pediatric Studies to Support Once Daily Dosing in HIV-Infected Children GSK Document Number: 2013N181170_00 Status: Complete	Population PK analysis of data from 6 clinical trials in paediatrics: ARROW (COL105677) PK Substudy Part 1; PENTA-13 (EPV40002); PENTA-15 (COL104929); ARROW PK Substudy 2; NUCA2002; and NUCA2005	HIV-1 infected pediatric subjects ARROW Part 1: [redacted] to 1[redacted] years PENTA-13: [redacted] to 1[redacted] years PENTA-15: [redacted] to [redacted] months ARROW Part 2: children weighing 12 to 15 kg[redacted] to [redacted] years NUCA2002: [redacted] months to 1[redacted] years NUCA2005: [redacted] to 1[redacted] years	ARROW Part 1: 3TC BID PO dosing: 12-20 kg: 75 mg BID >20-25 kg: 150 mg AM, 75 mg PM >25 kg: 150 mg BID 3TC QD PO dosing 12-20 kg: 150 mg QD >20-25 kg: 225 mg QD >25 kg: 300 mg QD PENTA-13: 10 mg/mL 3TC oral solution (n=14) or EPIVIR tablets (n=5) 4 mg/kg 3TC BID 8 mg/kg 3TC QD (up to 300 mg/day max) PENTA-15: 10 mg/mL 3TC oral solution	The PK of oral 3TC in 6 studies of HIV-1 infected children aged [redacted] months to 1[redacted] years were best described by a 1-compartment model with first-order absorption and elimination and a lag time. Body weight had a significant effect on CL and V with an exponential relationship. 3TC solid dosage forms had higher absolute bioavailability than the oral solution. Simulations support the use of 3TC oral solution regimens of 4 mg/kg BID or 8 mg/kg once daily in children of at least 3 months of age and scored tablet dosing in children ≥14 kg according to the weight bands defined in the Epivir label or the WHO 2010 pediatric dosing recommendations when administered either once or BID. Predicted plasma 3TC AUC(0-24), Cmax, and $C\tau$ values for oral solutions of 4 mg/kg BID or 8 mg/kg once daily to children <14 kg results in plasma 3TC exposure similar to observed exposure in children [redacted] months to 1[redacted] years of age receiving the oral solution and within the range of values observed in adults receiving 3TC 150 mg BVID and 300 mg once daily. Predicted plasma 3TC AUC(0-24) and Cmax for once and

Study	Study Design	Population	Treatment Details	Main Conclusions
			4 mg/kg 3TC BID 8 mg/kg 3TC QD ARROW Part 2: 3TC oral solution 10 mg/mL PK Day 1: 6 mL (60 mg) 3TC oral solution PO BID PK Day 2: 75 mg (as ½ Combivir scored tablet) PO BID NUCA2002: 3 TC oral solution (1 & 10 mg/mL) 3TC capsules (2.5, 10, 25, 100 mg) 3TC injection (10 mg/mL) IV infusion x 1 h, followed by repeat PO dose: 0.5 to 10 mg/kg 3TC BID [a] NUCA2005: 3TC oral Solution (10 mg/mL) 3TC tablets (75, 100, 150, 300 mg) 4 mg/kg 3TC BID PO Arm A (<6 wks prior ART): 3TC + ZDV + ddI Arm B (>6 wks prior ART): 3TC + ZDV OR 3TC + ddI OR 3TC + ZDV + ddI	BID dosing of scored tablets according to weight bands in the current Epivir label or WHO recommendations were higher compared with observed exposures in children receiving the oral solution because higher mg/kg doses of scored tablets are administered and scored tablets had higher estimated bioavailability than oral solution. Predicted plasma 3TCAUC(0-24) and Cmax for once and BID dosing of scored tablets according to weight bands in the current EPIVIR label or WHO recommendations were consistent with exposures observed in ARROW and higher than observed in adults receiving 3TC 150 mg BID and 300 mg once daily.
Pharmacogenetics				
ING116265 (PGx432	Meta-analysis of 9 clinical	Healthy adult subjects	DTG 50 mg tablet; oral;	Subjects with genotypes conferring poor metabolizer

Study	Study Design	Population	Treatment Details	Main Conclusions
Evaluation of the effect of UGT1A1 polymorphisms on DTG PK)	pharmacology studies with DTG steady-state PK data from 50 mg once daily		once daily; 5 days	status of UGT1A1 (*28/*28; *28/*37; *37/*37) had a 32% lower clearance, 46% higher AUC, and 32% higher Cmax of DTG compared with subjects with genotypes associated with normal UGT1A1 activity (*1/*1, *1/*36). Subjects with genotypes conferring intermediate and poor metabolizer status of UGT1A1 had a 23% lower clearance of DTG and 31% higher AUC compared with subjects with genotypes associated with normal UGT1A1 activity. Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the PK of DTG. Increases in DTG exposure due to UGT1A1 polymorphisms are not considered clinically significant based on the accumulated safety data for DTG.

a. In NUCA2002 some subjects received IV lamivudine after the repeat dose PO administration

Appendix Table 2 Summary of Completed Clinical Pharmacology Studies that were Previously Submitted as Part of the Tivicay or Epivir Registration and are "Supportive" Studies to the DTG/3TC FDC Submission

Study	Study Title	Main Conclusions
Bioequivalence/Bioavailability		
ING114580 (DTG/ABC/3TC) GSK Document Number: 2012N145882_00 Status: Complete	An evaluation of the bioequivalence of a combined formulated tablet (50mg/600mg/300mg dolutegravir/abacavir/lamivudine) compared to one dolutegravir 50mg tablet and one Epzicom (600mg/300mg abacavir/lamivudine) tablet administered concurrently and the effect of food on bioavailability of the combined formulation in healthy adult subjects	Bioequivalence was demonstrated between the FDC tablet formulation and the separate co-administered tablet formulations of DTG plus Epzicom. Administration of the FDC tablet with a high-fat meal resulted in increases in plasma DTG Cmax and AUC, but these are not considered clinically significant. The effects of food on ABC and 3TC exposures were very similar to prior effects seen with Epzicom, which may be taken with or without food. These results support the recommendation that the FDC tablet can be given without regard to meals.
CAL10001 (3TC) GlaxoSmithKline Document Number: RM2002/00116/01 Status: Complete	An evaluation of the bioequivalence of a combined formulated tablet (600 mg /300 mg abacavir/lamivudine) compared to Ziagen (abacavir) 2 x 300 mg tablets and Epivir (lamivudine) 2 x 150 mg tablets administered concurrently and the effect of food on absorption of the combined formulation in healthy adult subjects.	Following administration of the fixed dose combination of ABC/3TC (600 mg/300 mg) in the fed state, a lack of effect of food on the rate and extent of BA of 3TC was demonstrated. The extent of BA of ABC was unaffected in the fed state, compared with the fasted state, but the rate of BA was reduced. No significant food effect was observed for either ABC or 3TC administered as a FDC tablet.
Repeat-dose Pharmacokinetics		
NUCB4001 (3TC) GSK Document Number: GM1997/00337/00 Status: Complete	A study to investigate the pharmacokinetics of lamivudine (3TC™) phosphorylation in peripheral blood mononuclear cells from HIV positive asymptomatic patients.	3TC serum AUC(0-12) demonstrated dose proportionality between 150 mg and 300 mg (both given BID); serum 3TC Cmax increased slightly greater than proportional with dose, with a point estimate (90% CI) of 1.13 (0.98, 1.30). Based on intracellular AUC(0-12), 3TC-DP was the most predominant anabolite, at approximately 50 to 55% of total intracellular 3TC total phosphate. AUC of 3TC-MP and 3TC-TP were 30-35% and 15-20%, respectively of total intracellular 3TC. Cmax values for 3TC-MP and 3TC-DP were similar; however, values of 3TC-TP were approximately 40% of those for 3TC -MP and -DP. These data are consistent with the rate-limiting step in 3TC phosphorylation from 3TC-DP to the active 3TC-TP. There was a notable delay of approximately 9 to 11 h in intracellular tmax values when compared with serum. The intracellular half-life of 3TC-TP was approximately 15 to 16 h, irrespective of dose. The findings in this study, although exhibiting wide subject variability in intracellular PK parameters, showed no significant statistical differences between doses.

Study	Study Title	Main Conclusions
COL105677 (3TC) GSK Document Number: RM2009/00368/01 Status: Complete	ARROW (COL105677) Substudy: Pharmacokinetic Comparison of Once vs Twice Daily Administration of Abacavir and Lamivudine Scored Tablets in HIV-Infected African Children	For both ABC and 3TC, the AUC(0-24) following once daily dosing were equivalent to those following twice daily dosing over all age groups. As expected, mean Cmax values for ABC and 3TC were approximately 64% and 76% higher, respectively, when once daily administration was compared to twice daily administration
EPV40002 (3TC) GSK Document Number: 2013N185992_00 Status: Complete	Plasma pharmacokinetics of once versus twice daily lamivudine and abacavir-simplification of combination treatment in HIV-1 infected children (PENTA 13)	In HIV-1 infected children ≥ [redacted] to <1 [redacted] years old, both 3TC and ABC given in a q24h regimen are non-inferior to the corresponding q12h regimens. Based on the safety data analysis, there was no increased risk for more toxicity due to the elevated peak levels of both agents when taken once-daily vs. twice-daily. In addition, there was no indication for loss of virological control in this small group of children over 24 weeks of q24h treatment.
PENTA 15 (3TC) GSK Document Number: GM2009/00161/00 Status: Complete	Plasma pharmacokinetic study of once versus twice daily abacavir as part of combination antiretroviral therapy in children with HIV-1 infection aged 3 to <36 months	In HIV-infected children aged [redacted] to [redacted] months, the AUC0-24 for ABC given q24h dosing was demonstrated to be bioequivalent to the AUC0-24 following q12h dosing. In addition, a very similar AUC0-24 was seen for q12h and q24h dosing of 3TC, however, higher than expected variability resulted in the 90% CI falling slightly outside the bioequivalence criteria. As expected, a Cmax approximately two times higher, on once daily compared to twice daily therapy, was observed for both ABC and 3TC. Increased toxicity associated with these elevated peak levels was not observed, in agreement with findings from adult studies.
PK and PK/PD Relationships		
ING111521 (DTG) GSK Document Number: RM2008/00548/00 Status: Complete	A Phase 2a, multicenter, randomized, parallel, double-blind, dose ranging, placebo-controlled study to compare antiviral effect, safety, tolerability and PK of GSK1349572 monotherapy versus placebo over 10 days in HIV-1 infected adults	PK: Following oral dosing using the tablet formulation, DTG was rapidly absorbed with maximal concentration observed at 1.5 to 2 hours post dose. Following repeat-dose administration, plasma concentrations of DTG reached steady state by 7 days of dosing, and accumulation ratios ranged from 1.25 to 1.42 across doses. The increase in DTG exposure (AUC and Cmax) was less than dose proportional following both single- and repeat-dose administration. DTG showed time-invariant PK and moderate %CVb ranging from 16 to 51%. PK/PD Relationship: A mean decrease from Baseline on Day 11 in plasma HIV-1 RNA of 1.51 to 2.46 log_{10} c/mL was observed across the DTG doses tested (2 mg, 10 mg, 50 mg once daily) compared with placebo (0.05 log_{10} c/mL increase). A dose response relationship was observed.

Study	Study Title	Main Conclusions
		The PK/PD analysis showed that greater antiviral activity was associated with higher DTG plasma exposure. The exposure-antiviral activity relationship was best described by an Emax model with Emax fixed to 2.6, Hill factor fixed to 1, and PK parameter on the linear scale. $C\tau$ (concentration at end of dosing interval) was the PK parameter that best predicted Day 11 plasma viral load reduction from baseline or maximum plasma viral load reduction from baseline. DTG exposure from a 10 mg once daily dose is around EC_{90} and DTG exposure from 50 mg once daily is at the plateau of the curve.
ING112276 (DTG) GSK Document Number: 2011N117114_01 Status: Complete	A Phase IIb study to select a once daily oral dose of GSK1349572 administered with either abacavir/lamivudine or TDF/emtricitabine in HIV-1 infected antiretroviral therapy-naive adult subjects. (96-Week results)	PK: DTG exposure, including AUC(0-τ), Cmax, and $C\tau$, increased as dose increased from 10 mg to 50 mg; the increase in DTG exposure is dose proportional from 25 mg to 50 mg, but less than dose proportional from 10 mg to 25 mg. DTG PK parameters demonstrated moderate variability with %CVb estimated at 30 to 50% for AUC(0-τ) and Cmax and 60 to 70% for $C\tau$. DTG 50 mg once daily dose achieved $C\tau$ of 1.2 μg/mL (geometric mean), which is ~18-fold higher than the in vitro PA IC90 of 0.064 μg/mL, supporting the dose selection of DTG 50 mg once daily in Phase III studies in INSTI-naïve subjects. PK and PK/PD Relationships: No dose or exposure-response relationship was found for DTG antiviral activity due to combination therapy. There was a positive correlation between DTG dose/exposure and increase in serum creatinine from Baseline. End of Study: The data from this completed study continue to support the long-term use of DTG 50 mg once daily in combination with other antiretroviral agents for the management of HIV infection. The vast majority of subjects who entered the Open-label phase maintained viral suppression throughout their participation in the study based on an observed analysis. One subject experienced VF during the Open-label phase. The safety profile observed in this Open-label phase was similar to that observed during the Randomized phase, with very few new adverse clinical events or graded laboratory anomalies observed, and no new signals identified. This longer-term end of study data supports the safety of DTG in combination with either ABC/3TC or TDF/FTC once daily in an HIV-infected treatment-naive patient population
ING113086 (DTG)	Phase III, randomized, double blind study of the safety and efficacy of dolutegravir [DTG, GSK1349572] 50 mg once	DTG C0 and moderate variability are consistent with prior studies, with average C0 well above the in vitro PA-IC_{90}, supporting the antiviral response observed in the DTG

Study	Study Title	Main Conclusions
	daily compared to raltegravir (RAL) 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects	treatment group. No relationship was found in DTG C0 between PDVF and non-PDVF subjects. No clinically relevant relationship was observed between concentrations and pre-defined safety assessments/endpoints.
ING111762 (DTG) GSK Document Number: 2011N117609_00 Status: Ongoing	A Phase III randomized, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus RAL 400 mg BID, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, INSTI-naïve, antiretroviral therapy-experienced adults	PK: Trough DTG concentrations observed in treatment-experienced subjects were lower than those observed in treatment-naïve subjects, likely due to drug interactions with concomitant medications, including ARVs, and less optimal compliance. DTG should be given at 50 mg BID when co-administered with TPV/RTV and EFV. DTG can be co-administered with FPV/RTV without dose adjustment. DTG can be co-administered with once daily or BID DRV/RTV without dose adjustment. PK/PD Relationship at Week 24: DTG drug exposure, C0, was a statistically significant predictor of Week 24 efficacy response using data from all subjects, but was not a predictor once subjects with evidence of non-compliance or on moderate/strong inducers were excluded. The only PK/PD relationship observed between DTG and safety measures was a correlation with total bilirubin and serum creatinine, likely due to benign competition between DTG and unconjugated bilirubin for UGT1A1 and an expected effect of DTG on OCT2, respectively. PK and PK/PD Relationships at Week 48: The PK and PK/PD results support the recommendation of DTG 50 mg once daily in the treatment-experienced, INI-naïve subjects. DTG C0_avg was a significant predictor of virologic response. DTG should be given at 50 mg BID when co-administered with TPV/RTV and EFV. DTG can be co-administered with once daily DRV/RTV without dose adjustment. There was no PK/PD relationship with AEs. The only PK/PD relationships observed between DTG and clinical chemistries were a correlation with total bilirubin and serum creatinine, which were not considered clinically significant

Appendix Table 3 Tabular Listing of All Dolutegravir Clinical Pharmacology Studies

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
Pharmacokinetic Studies in HIV-Negative Subjects										
ING114580 (BE) ViiV Healthcare	1 US	Start 20 Jun 2012; Completed 21 Sept 2012; 66/65	To evaluate bioequivalence between a single fixed dose combination (FDC) tablet formulation of DTG 50 mg, ABC 600 mg, 3TC 300 mg and separate tablet formulations of DTG 50 mg plus Epzicom (EPZ; ABC 600 mg/3TC 300 mg), in the fasted state and with food	Open-label, Randomized, 2-part, Crossover	Healthy subjects	Part 1 Treatment A: DTG/ 50 mg/ ABC 600 mg/ 3TC 300 mg/ FDC tablet / oral/ single dose Treatment B: DTG/ 50 mg/ tablet/ oral/ single dose plus ABC/ 600 mg/ 3TC 300 mg/ FDC tablet/ oral/ single dose Part 2 DTG/ 50 mg/ ABC 600 mg/ 3TC 300 mg/ FDC tablet / oral/ single dose with high fat meal	Part 1 65/63 Part 2 12/12	Part 1 43/22 29.3 (1[redacted]-5[redacted]) Part 2 8/4 33.8 (1[redacted]-5[redacted])	DTG, ABC, and 3TC AUC(0-t), AUC(0-∞), Cmax.	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING111207 (Dose Linearity) GSK	1 US	Start 13 Nov 2007; Completed 18 Feb 2008; 25/20	To assess safety, tolerability and PK of single doses of DTG	Double-Blind, Randomized, Placebo-Controlled	18-55 yrs, Healthy subjects, male/ female	DTG 2 to 100 mg; oral suspension; single dose; fasted	25 Enrolled, 13 Completed	20/5; 31.8 yrs (1[redacted] – 5[redacted] yrs)	DTG safety parameters AUC(0-t), AUC(0-∞), Cmax, tmax, C24, and t½ following single dose administration	Completed CPSR
ING111322 (Dose Linearity) GSK	1 US	Start 27 Feb 2008; Completed 12 Jun 2008; Part 1: 32/32, Part 2: 12/12	Part 1: To assess safety, tolerability and PK of repeat doses of DTG Part 2: To assess safety, tolerability and PK of single doses of DTG suspension and single doses of DTG tablets with or without food	Part 1: Double-Blind, Randomized, Placebo-Controlled Part 2: Randomized, 3-Period, Balanced, Crossover	18-50 yrs, Healthy subjects, male/ female	Part 1: DTG 10 to 50 mg; oral suspension; once daily; 10 days; fasted Part 2: DTG 20 mg; oral suspension; singe dose; fasted	Part 1: 32 (includes 5 placebo; 1 subject assigned to placebo received a single dose of DTG in error) Enrolled, 31 Completed Part 2: 12 Enrolled, 12 Completed	Part 1: 27/5; 31.7 yrs (1[redacted]-5[redacted] yrs) Part 2: 12/0; 30.8 yrs (1[redacted]-5[redacted] yrs)	Part 1: DTG safety parameters from pre-dose values DTG PK parameters following single dose administration on Day 1: AUC(0-∞) and AUC(0-24), Cmax, tmax, C24, t1/2, tlag, and CL/F; and AUC(0-τ), C0, Cτ, Cmin, Cmax, tmax, t1/2, and CL/F on Day 10	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						DTG 10 mg x2 (20 mg); tablet; oral; single dose; fasted DTG 10 mg x2 (20 mg); tablet; oral; single dose; fed			Part 2: Single dose plasma DTG PK parameters: AUC(0-t), AUC(0-∞), Cmax, and C24	
ING111853 (Mass Balance) GSK	1 US	Start 17 Feb 2009; Completed 21 Apr 2009; 6/6	To investigate the recovery, excretion, and PK of ^{14}C-DTG	Open-label, single dose study	30-55 yrs, Healthy subjects, male	DTG 20 mg; oral suspension; single dose; fasted	6 Enrolled, 6 Completed	6/0; 37.5 yrs (3[redacted]-4[redacted] yrs)	Percent recovery of total radiocarbon in urine and feces. AUC(0-t), AUC(0-∞), Cmax, tmax, λz, tlag, and t½ of total drug-related material (radiocarbon) in blood and plasma following oral suspension [^{14}C]-DTG dosing AUC(0-t), AUC(0-∞), Cmax, tmax, λz, tlag, CL/F, Vz/F, and t½ of DTG in	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
									plasma following oral suspension [^{14}C]-DTG dosing Collection of samples for use in a separate study for characterization and quantification of DTG-related metabolites in plasma, urine and fecal homogenates	
ING113125 (PK) ViiV Healthcare	1 US	Start 28 Jun 2011; Completed 20 April 2012; 16/16	To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with severe renal impairment	Single dose, open-label, parallel group, 2-part study	18-70 yrs, Severe renal impairment subjects and matched, healthy control subjects with normal renal function, male / female	DTG 50 mg; tablet; oral; single dose	Renal: 8 Enrolled, 8 Completed Healthy: 8 Enrolled, 8 Completed	Renal: 5/3; 56.8 yrs (4[redacted]-6[redacted] yrs) Healthy: 5/3; 56.1 yrs (4[redacted]-6[redacted] yrs)	Plasma DTG tlag, tmax, Cmax, AUC(0-t), AUC(0-∞), %AUCex, t½, CL/F and Vz/F	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING113097 (PK) ViiV Healthcare	1 US	Start 19 Nov 2010; Completed 04 Jun 2011; 16/16	To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with mild or moderate hepatic impairment based on Child-Pugh category	Single dose, open-label, parallel group, 2-part, adaptive study	18-70 yrs, Subjects with mild or moderate hepatic impairment and matched, healthy control subjects with normal hepatic function, male / female	DTG 50 mg; tablet; oral; single dose	Hepatic Impaired: 8 Enrolled, 8 Completed Healthy Controls: 8 Enrolled, 8 Completed	Hepatic Impaired : 5/3; 55.5 yrs (5[redacted]-6[redacted] yrs) Healthy Controls: 5/3; 57.0 yrs (4[redacted]-6[redacted] yrs)	Plasma DTG AUC(0-t), AUC(0-∞), Cmax, C24, apparent t½, apparent clearance (CL/F), and Vz/F	Completed CPSR
ING115381 (PK) ViiV Healthcare	1 US	Start 20 Apr 2011; Completed 27 May 2011; 10/10	To assess safety, tolerability and PK of single doses of DTG in healthy Japanese subjects	Open label, single dose study	20-55 yrs, Healthy Japanese subjects, male /female	DTG 50 mg; tablet; oral; single dose	10 Enrolled, 10 Completed	6/4; 33.4 yrs (2[redacted]-5[redacted] yrs)	Plasma DTG following single dose administration: AUC(0-t), AUC(0-∞), Cmax, and C24	Completed CPSR
ING113099 (Drug Interaction) ViiV Healthcare	1 US	Start 13 May 2011; Completed 28 Nov 2011; 27/24	To assess the potential for a drug interaction between DTG and RIF and between DTG	Randomized, open-label, 2-period, single-sequence, 2 cohort study	18-65 yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 7 days. DTG 50 mg;	Arm 1: 12 Enrolled, 11 Completed Arm 2:	Intent-to-Treat-Expose: 19/7; 44.7 yrs (2[redacted]-5[redacted]	Plasma DTG Cτ, Cmax, and AUC(0-τ), and AUC(0-24) for comparison between once	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			and RBT			tablet; oral; BID; 7 days then DTG 50 mg; tablet; oral; BID + RIF 600 mg; capsule; oral; once daily; 14 days DTG 50 mg; tablet; oral; once daily for 7 days then DTG 50 mg; tablet; oral BID+ RIF 300 mg; capsule; oral; once daily; 14 days	14 Enrolled, 9 Completed	yrs)	daily and BID regimens only	
ING115465 (PK, Investigator sponsored) [redacted]	1 US	Start 30 Aug 2011; Completed 16 Apr 2012; 11/8	To describe first-dose and steady-state DTG PK in cervicovaginal fluid (CVF) and vaginal (VT) and cervical	Open-label, repeat dose study	18-35yrs, Healthy subjects, female	DTG 50 mg; tablet; oral; once daily; 5-7 days	11 Enrolled, 8 Completed	ITT-E: 0/8; Median age: 21 yrs (1[redacted]-2[redacted] yrs)	AUC(0-24), AUClast, AUC∞, Clast, Cmax, tmax, and t1/2 for BP, CVF, CT, and VT after dosing of DTG 50-mg tablet on	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			(CT) tissue compared to blood plasma (BP) in HIV-1-negative women						the first dosing day (Day 1) and at steady-state after 5-7 days of treatment Accumulation ratio of DTG in BP, CVF, CT, and VT CVF:BP, CT:BP, VT:BP, CT:CVF, and VT:CVF DTG AUC ratios	
ING116195 PK, Investigator sponsored) [redacted]	1 US	Start 14 Dec 2011; Completed 22 May 2012; 14/12	To describe DTG exposure in semen and rectal tissue	Open-label, repeat dose study	18-49yrs, Healthy subjects, male	DTG 50 mg; tablet; oral; once daily; 8 days	14 Enrolled, 12 Completed	ITT-E: 12/0; Median: 25.5yrs (2[redacted]-4[redacted] yrs)	AUC(0-24), AUClast, AUC∞, Clast, Cmax, tmax for blood plasma (BP), seminal fluid (SF), rectal mucosal fluid (RF), and rectal mucosal tissue (RT) after dosing of DTG 50 mg tablet on the first dosing day (Day1; PK) and at a steady state 7 and 8	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
									days later. Accumulation of ratio of DTG in BP, SF, RF, and RT SF: BP, RT:BP, and RF: RT DTG AUC ratios	
ING115696 (Drug Interaction) ViiV Healthcare	1 US	Start 01 Sep 2011; Completed 17 Oct 2011; 12/12	To investigate the effects of prednisone on the steady-state PK of DTG	Open-label, repeat dose, 2-period, single-sequence	18-65 yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily; Days 1-10 + prednisone; tablet; oral; once daily (60 mg Days 1-5; 50 mg Day 6; 40 mg Day 7; 30 mg Day 8; 20 mg Day 9; 10 mg Day 10)	12 Enrolled, 12 Completed	5/7; 28.5 yrs (2[redacted]-3[redacted] yrs)	DTG PK parameters on Day 5 and Day 10: AUC(0-τ), Cmax, C0, Cτ, Cmin, CL/F, and t½	Completed CPSR
ING115697 (Drug Interaction)	1 US	Start 13 Mar 2012; Completed	To assess the potential for a drug interaction	Randomized, open-label, 2-period, single-	18-65 yrs, Healthy subjects,	DTG 50 mg; tablet; oral; once daily;	DTG + BCV 16 Enrolled, 13	19/13; 42.5 yrs (1[redacted]-6[redacted]	Plasma steady-state DTG AUC(0-τ), Cmax,	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ViiV Healthcare		23 May 2012; 32/32	between DTG and TVR and between DTG and bocepravir (BCV)	sequence, 2 cohort study	male / female	5 days DTG 50 mg; tablet; oral; once daily + TVR 750 mg; tablet; oral; q8h; 10 days DTG 50 mg; tablet; oral; once daily + BCV 800 mg; capsule; oral; q8h; 10 days	Completed DTG + TVR 16 Enrolled, 15 Completed	yrs)	Cmin, Cτ, following administration of DTG 50 mg once daily (q24h) for 5 days and following co-administration with BCV 800 mg q8h for 10 days or TVR 750 mg q8h for 10 days	
ING115698 (Drug Interaction) ViiV Healthcare	1 Canada	Start 02 Dec 2011; Completed 30 Dec 2011; 11/12	To assess the potential for a drug interaction between DTG and methadone	Open-label, repeat dose, 2-period, single-sequence	18-65 yrs, Healthy subjects enrolled in a methadone maintenance program, male / female	Stable methadone dose; oral solution; once daily; 3 days Stable methadone dose; oral solution + DTG 50 mg; tablet; oral; BID; 5 days	11 Enrolled, 10 Completed	6/5; 34.5 yrs (2[redacted]-4[redacted] yrs)	Steady-state total and R-Methadone PK parameters: AUC(0-τ), Cmax, and Cτ	Completed CPSR

Protocol No. (Study Type) Sponsor	**No. Study Center Location(s)**	**Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment**	**Study Objectives**	**Study Design**	**Diagnosis; Key Inclusion Criteria**	**Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)**	**No. of Subjects by Group Entered/ Completed**	**Gender M/F; Mean Age (Range)**	**Primary Endpoint(s)**	**Study Reporting Status (Type of Report)**
ING111405 (Drug Interaction) GSK	1 US	Start 09 Oct 2008; Completed 12 Dec 2008; 31/30	To assess the potential for a drug interaction between DTG and LPV/ RTV and between DTG and DRV/ RTV	Randomized open-label, 2-period, single-sequence, 2 cohort study	18-50 yrs, Healthy subjects, male / female	DTG 30 mg; tablet; oral; once daily; 5 days DTG 30 mg; tablet; oral; once daily + LPV/RTV 400/100 mg; tablet; oral; q12h; 14 days DTG 30 mg; tablet; oral; once daily + DRV (tablet) /RTV (capsule) 600/100 mg; oral; q12h; 14 days	31 Enrolled, 30 Completed	31/0; 29.4 yrs (1[redacted]-5[redacted] yrs)	Plasma DTG steady-state AUC(0-τ), Cmax, Cτ, Cmin, CL/F, t½ and t1/2 following administration of DTG 30 mg q24h for 5 days and following co-administration with LPV/RTV 400/100 mg q12h or DRV/RTV 600/100 mg q12h for 14 days	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING111602 (Drug Interaction) GSK	1 US	Start 07 Jan 2009; Completed 05 Mar 2009; 16/16	To assess the potential for a drug interaction between DTG and multivitamin and between DTG and Maalox	Open-label, single dose, randomized, 4-period crossover study	18-65 yrs, Healthy subjects, male/ female	DTG 50 mg; tablet; oral; single dose DTG 50 mg; tablet; oral; single dose + multivitamin; tablet; oral; single dose DTG 50 mg; tablet; oral; single dose + Maalox Advanced Maximum Strength; 20 mL suspension; single dose DTG 50 mg; tablet; oral; single dose 2 hrs prior to Maalox Advanced Maximum Strength	16 Enrolled, 16 Completed	16/0; 30.8 yrs (1[redacted]-5[redacted] yrs)	Single dose plasma DTG AUC(0-∞), Cmax, and C24	Completed CPSR

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						20 mL; suspension; single dose				
ING111603 (Drug Interaction) GSK	1 US	Start 16 Oct 2008; Completed 12 Dec 2008; 16/16	To assess the potential for a drug interaction between DTG and ETV	Open-label, repeat dose, 2-period, single-sequence study	18-65 yrs, Healthy subjects, male/ female	DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily + ETV 200 mg; tablet; oral; q12h; 14 days	16 Enrolled, 15 Completed	16/0; 41.5 yrs (1[redacted]-6[redacted] yrs)	Plasma DTG steady-state AUC(0-τ), Cmax, Cτ, Cmin, CL/F, t½ following administration of DTG 50 mg q24h for 5 days and following co-administration with ETV 200 mg q12h for 14 days	Completed CPSR
ING111604 (Drug Interaction) GSK	1 US	Start 11 Aug 2008; Completed 01 Oct 2008; 16/16	To assess the potential for a drug interaction between DTG and TDF	Open-label, repeat-dose, single-sequence, 3-period study	18-65 yrs, Healthy subjects, male/ female	DTG 50 mg; tablet; oral; once daily; 5 days TDF 300 mg; tablet; oral; once daily; 7 days DTG 50 mg; tablet; oral; once daily + TDF 300 mg; tablet; oral;	16 Enrolled, 15 Completed	15/1; 38.6 yrs (2[redacted]-5[redacted] yrs)	Plasma DTG steady-state AUC[0-τ], Cmax and Cτ following administration of DTG 50 mg q24h for 5 days and following co-administration with TDF 300 mg q24h for 5 days	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						once daily; 5 days				
ING111854 (Drug Interaction) GSK	1 US	Start 07 Apr 2009; Completed 09 Jun 2009; 24/24	To assess the potential for a drug interaction between DTG and ATV and between DTG and ATV/RTV	Randomized, open-label, repeat dose, 2-period, single-sequence, 2-cohort study	18-65 yrs, Healthy subjects, male / female	Period 1: DTG 30 mg; tablet; oral; once daily; 5 days; fed Period 2: DTG 30 mg; tablet; oral; once daily + ATV/RTV 300/100 mg; capsule; once daily; 14 days DTG 30 mg; tablet; oral; once daily + ATV 400 mg; capsule; oral; once daily; 14 days	24 Enrolled, 24 Completed	21/3; 37.2 yrs (1[redacted]-6[redacted] yrs)	Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 30 mg q24h for 5 days and following co-administration with ATV/RTV 300/100 mg q24h or ATV 400 mg q24h for 14 days	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING111855 (Drug Interaction) ViiV Healthcare	1 US	Start 13 Dec 2011; Completed 28 Mar 2012; 16/16	To assess the potential for a drug interaction between DTG and oral contraceptives (EE / NGMN)	Randomized, 2-period, double-blind study	18-40 yrs, Healthy subjects, female	DTG 50 mg or placebo; oral; tablet; once daily Days 1-11 and DTG 50 mg or placebo; tablet; oral; once daily Days 12-21 EE / NGMN; tablet; oral; once daily Days 1-21	16 Enrolled, 15 Completed	0/16; 31.1 yrs (2[redacted]-4[redacted] yrs)	AUC(0-τ) of Norelgestromin and EE after Ortho-Cyclen alone and after Ortho-Cyclen with DTG	Completed CPSR
ING112934 (Drug Interaction) GSK	1 US	Start 02 Apr 2009; Completed 20 May 2009; 17/18	To assess the potential for a drug interaction between DTG, ETV, and LPV/RTV or DRV/RTV	Randomized, open-label, repeat dose, 3-period, single-sequence, 2-cohort adaptive study	18-65 yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily + ETV/LPV/RTV 200/400/ 100 mg; tablet; oral; q12h; 14 days DTG 50 mg; tablet; oral;	17 Enrolled, 17 Completed	17/0; 37.6 yrs (2[redacted]-6[redacted] yrs)	Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 50 mg q24h for 5 days, and following co-administration of DTG 50 mg q24h (and 50 mg q12h if appropriate) with ETV/LPV/RTV 200/400/100 mg	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						once daily + ETV (tablet) DRV (tablet) /RTV (capsule) 200/600/ 100 mg; oral; once daily; 14 days			q12h or ETV/DRV/RTV 200/600/100 mg q12h, each for 14 days	
ING112941 (Drug Interaction) GSK	1 US	Start 23 Jul 2009; Completed 28 Sep 2009; Part 1: 14/14, Part 2: 10/10	To evaluate the effect of a high fat meal and OMP on DTG PK and to evaluate the safety and PK of a 250 mg dose of DTG	Part 1: Randomized, open-label, 2 sequence, 3-treatment crossover Part 2: Randomized, double-blind, single dose PK study	18-65 yrs, healthy subjects, male / female	Part 1: DTG 50 mg; tablet; oral; single dose; fasted DTG 50 mg; tablet; oral; single dose; within 30 minutes after the start of a high fat meal DTG 50 mg; tablet; oral; single dose + OMP 40 mg; capsule; oral; once daily;	Part 1: 14 Enrolled, 12 Completed Part 2: 10 Enrolled (includes 2 placebo), 10 Completed	Part 1: 12/2; 40.6 yrs (2[redacted]-5[redacted] yrs) Part 2: 9/1; 38.4 yrs (2[redacted]-5[redacted] yrs)	Plasma DTG following a single dose administration of 50 mg under fasted conditions with and without OMP 40 mg: AUC(0-t), AUC(0-∞), Cmax, tmax, C24, tlag Plasma DTG following a single dose administration of 50 mg under fasted conditions and with a high-	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						5 days Part 2: DTG 250 mg or placebo; oral suspension, single dose; fasted			fat meal: AUC(0-t), AUC(0-∞), Cmax, tmax, C24, and tlag Plasma DTG following a single dose administration of 250 mg under fasted conditions: AUC(0-t), AUC(0-∞), Cmax, tmax, C24, and tlag Safety and tolerability parameters following a single supratherapeutic dose of DTG 250 mg	
ING113068 (Drug Interaction) ViiV Healthcare	1 US	Start 09 Sep 2010; Completed 04 Nov 2010; Part A: 12/12, Part B: 15/15	To investigate the effects of fosamprenavir (FPV)/ RTV on the steady-state PK of DTG and to	Part A: Open-label, repeat dose, 2-period, single-sequence Part B: Open-	18-65 yrs, Healthy subjects, male / female	Part A: DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg;	Part A: 12 Enrolled 12 Completed Part B:	Part A: 10/2; 33.4 yrs (2[redacted]-5[redacted] yrs) Part B:	Part A: Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			evaluate relative BA of tablets with varying particle size	label, single dose, randomized, 3-period, cross over study		tablet; oral; once daily + FPV 700 mg; tablet / RTV 100 mg; capsule; oral; q12h; 10 days Part B: DTG 50 mg using 25 mg tablets with micronized drug substance; oral; single dose DTG 50 mg using 25 mg tablets with unmicronized drug substance; oral; single dose DTG 50 mg using 25 mg tablets with	15 Enrolled, 15 Completed	4/11; 34.7 yrs (2[redacted]-6[redacted] yrs)	DTG 50 mg q24h for 5 days and following co-administration with FPV/RTV 700/100 mg q12h for 10 days Part B: Plasma DTG AUC(0-∞), AUC(0-t), and Cmax following a single dose of DTG 50 mg	

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						intermediate particle size drug substance; oral; single dose				
ING113096 (Drug Interaction) GSK	1 US	Start 15 Feb 2010; Completed 05 Apr 2010; 18/18	To assess the safety, tolerability and PK of repeat dose co-administration of DTG alone, TPV/RTV alone, and DTG in combination with TPV/RTV	Randomized, open-label, repeat dose, 3-period single-sequence, study	18-55 yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 5 days TPV / RTV 500/200 mg; capsule; oral; BID; 7 days DTG 50 mg; tablet; oral; once daily and TPV / RTV 500/200 mg; capsule; oral; BID; 5 days	18 Enrolled, 13 Completed	14/4; 29.3 yrs (1[redacted]-4[redacted] yrs)	Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 50 mg once daily for 5 days and following co-administration with TPV/RTV 500/200 mg BID for 5 days	Completed CPSR

Protocol No. (Study Type) Sponsor	**No. Study Center Location(s)**	**Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment**	**Study Objectives**	**Study Design**	**Diagnosis; Key Inclusion Criteria**	**Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)**	**No. of Subjects by Group Entered/ Completed**	**Gender M/F; Mean Age (Range)**	**Primary Endpoint(s)**	**Study Reporting Status (Type of Report)**
ING114005 (Drug Interaction) ViiV Healthcare	1 US	Start 16 Mar 2010; Completed 26 May 2010; 12/12	To evaluate PK of DTG 100 mg versus 50 mg and the effect of EFV on the PK, safety and tolerability of DTG 50 mg	Open label, repeat dose, 3-period single-sequence	18-65 yrs, Healthy subjects, male / female	DTG 100 mg; tablet; oral; single dose DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily in AM + EFV 600 mg; tablet; oral; once daily in PM; 14 days	12 Enrolled, 12 Completed	12/0; 38.7 yrs (2[redacted]-6[redacted] yrs)	Plasma DTG AUC(0-24), Cmax, and C24, and dose-normalized AUC(0-24), Cmax, and C24 following single dose administration of 100 mg and 50 mg Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 50 mg q24h for 5 days and following co-administration with EFV 600 mg q24h for 14 days	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
LAI116181 (Drug Interaction) ViiV Healthcare	1 US	Start 07 Nov 2011; Completed 20 Feb 2012; Cohort 1: 16/16, Cohort 2: 12/12	To assess the potential for a drug interaction between DTG and RPV	Open label, repeat dose, single-sequence, 3-period study	18-55 yrs Healthy subjects, male / female	Cohort 1: Treatment A = DTG 50 mg; tablet; oral; q24h; 5 days Treatment B = RPV 25 mg; tablet; oral; q24h; 11 days Treatment C = RPV 25 mg; tablet; oral; q24h + DTG 50 mg; tablet; oral; q24h; 5 days Cohort 2: Treatment D = GSK1265744 30 mg; tablet; oral; q24h;12 days Treatment B = RPV 25 mg; tablet; oral; q24h; 12 days	Cohort 1: 16 Enrolled, 16 Completed Cohort 2: 12 Enrolled, 11 Completed	24/4; 31.4 yrs (1[redacted]-5[redacted] yrs)	Plasma DTG AUC(0-τ), Cmax, and tmax, and Cτ, following 50 mg q24h administration with and without RPV 25 mg q24h Plasma GSK1265744 steady-state AUC(0-τ), Cmax, tmax, and Cτ following GSK1265744 30 mg q24h administration with and without RPV 25 mg q24h Plasma RPV steady-state AUC(0-τ), Cmax, tmax, and Cτ following RPV 25 mg q24h administration	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						Treatment E = RPV 25 mg; tablet; oral; q24h + GSK1265744 30 mg; tablet; oral; q24h; 12 days			with and without DTG 50 mg q24h or GSK1265744 30 mg q24h	
ING116898 (Drug Interaction)/ ViiV Healthcare	1 US	Start 31 Dec 2012; Completed 12 Mar 2013; Cohort 1: 11/12, Cohort 2: 10/12	To evaluate the effect of calcium carbonate and ferrous fumarate on DTG PK	Open label, single dose, 4-period crossover study	Healthy adult subjects	Cohort 1: DTG, 50 mg, tablet, oral, single dose, fasted DTG, 50 mg, tablet, oral single dose, +1200 mg calcium carbonate, oral, fasted DTG, 50 mg, tablet, oral, single dose, + 1200 mg calcium carbonate, oral,	Cohort 1: 12 Enrolled, 11 Completed; Cohort 2: 12 Enrolled, 10 Completed	Cohort 1: 8/4; 31.4yrs (2[redacted] - 5[redacted]); Cohort 2: 6/6; 34.9yrs (2[redacted] - 6[redacted])	DTG AUC(0-t), AUC(0-∞), Cmax, C24	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						fed DTG, 50 mg, tablet, oral, single dose, fasted, 2 hours prior to 1200 mg calcium carbonate, oral Cohort 2: DTG, 50 mg, tablet, oral, single dose, fasted DTG, 50 mg, tablet, oral single dose, +324 mg ferrous fumarate, oral, fasted DTG, 50 mg, tablet, oral, single dose, + 324 mg ferrous fumarate, oral,				

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						fed DTG, 50 mg, tablet, oral, single dose, fasted, 2 hours prior to 324 mg ferrous fumarate, oral				
200901 (Drug Interaction) ViiV Healthcare and GSK	1 US	Start 08 Oct 2013; Completed 14 Jan 2014; 16/16	To compare the steady state PK of DTG 50 mg once daily when co-administered with CBZ to those of DTG 50 mg once daily administered alone	Phase I, open-label, 3-period, fixed sequence crossover study	Healthy adult subjects	Period 1: DTG 50 mg, tablet, oral, once daily (Days 1-5) Period 2: CBZ 100 mg, tablet, oral, BID (Days 1-3); CBZ 200 mg, tablet, oral, BID (Days 4-6); CBZ 300 mg, tablet, oral, BID (Days 7-16) Period 3: DTG 50 mg, tablet, oral, once daily + CBZ 300 mg, tablet, oral, BID (Days 1-5)	Period 1: 16 Enrolled, 16 Completed Period 2: 16 Enrolled, 14 Completed Period 3: 14 Enrolled, 14 Completed	14/2; 38.9 yrs (2[redacted] - 5[redacted])	Steady state Cτ, Cmax, AUC(0-τ), CL/F, t½, C0, Cmin	Completed CPSR

Protocol No. (Study Type) Sponsor	**No. Study Center Location(s)**	**Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment**	**Study Objectives**	**Study Design**	**Diagnosis; Key Inclusion Criteria**	**Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)**	**No. of Subjects by Group Entered/ Completed**	**Gender M/F; Mean Age (Range)**	**Primary Endpoint(s)**	**Study Reporting Status (Type of Report)**
201102 (Drug Interaction) ViiV Healthcare	1 US	Start 18 March 2014; Completed 15 May 2014; 12/11	To describe and compare steady-state plasma DTG PK following administration of DTG 50 mg q24h with and without DCV 60 mg q24h and DCV 60 mg q24h with and without DTG 50 mg q24h	Open-label, 3-period, crossover study	Healthy adult subjects	Treatment A: DTG 50 mg, tablet, oral, once daily x 5 days Treatment B: DCV 60 mg, tablet, oral, once daily x 5 days Treatment C: DCV 60 mg, tablet, oral, once daily + DTG 50 mg, tablet, oral, once daily x 5 days	12 Entered, 11 Completed	9/3; 32.3 yrs (2[redacted] - 5[redacted])	Plasma DTG steady state AUC(0-τ), Cmax, Cτ, CL/F and t½	Completed CPSR
201167 (Drug Interaction) ViiV Healthcare and GSK	1 US	Start 19 Feb 2014; Completed 12 May 2014; 15/15	To assess the effect of DTG given once daily or BID on the PK of metformin after repeat dosing	Open label, parallel group, 3-period, fixed sequence study	Healthy adult subjects	**Cohort 1**: Period 1: Metformin IR 500 mg, tablet, oral, BID (Days 1-5) Period 2: Metformin IR 500 mg, tablet, oral, BID + DTG 50 mg, tablet, oral,	**Cohort 1**: Period 1: 15 Enrolled, 15 Completed Period 2: 15 Enrolled, 14 Completed	Cohort 1: 11/4; 37.7 yrs (2[redacted] - 5[redacted]) Cohort 2: 12/3; 33.9 yrs (2[redacted] - 5[redacted])	Steady-state plasma metformin PK parameters in Period 2 as compared with those in Period 1 for each cohort: Cmax and AUC(0-τ). Steady-state plasma DTG PK parameters for	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						once daily (Days 1-7) Period 3: Metformin IR 500 mg, tablet, oral, BID (Days 1-10) **Cohort 2**: Period 1: Metformin IR 500 mg, tablet, oral, BID (Days 1-5) Period 2: Metformin IR 500 mg, tablet, oral, BID + DTG 50 mg, tablet, oral, BID (Days 1-7) Period 3: Metformin IR 500 mg, tablet, oral, BID (Days 1-10)	Period 3: 14 Enrolled, 14 Completed **Cohort 2**: Period 1: 15 Enrolled, 15 Completed Period 2: 15 Enrolled, 14 Completed Period 3: 14 Enrolled, 13 Completed		each cohort: AUC(0-τ), Cmax, C0, Cτ, and CL/F. Steady-state plasma metformin PK parameters in Period 2 as compared with those in Period 1 for each cohort: t½ and CL/F	
ING116265 (PGx) ViiV Healthcare	NA	NA	To evaluate the effects of UGT and CYP polymorphisms on the PK of	Meta-analysis of PGx and PK data from 9 Phase II studies	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days	89 subjects included in the analysis	78/11; 36.9yrs (1[redacted]- 6[redacted])	NA	Completed: Meta-analysis Report

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			DTG							
204994	1 US	Start 27 Mar 2017; Completed 18 Aug 2017; 154/152	To evaluate the bioequivalence of FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state.	R, OL, XO	Healthy adult subjects	**Treatment A:** DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet **Treatment B:** DTG/3TC Tablets, 50 mg/300 mg FDC [redacted] formulation Product Code AH **Treatment C:** DTG/3TC Tablets, 50 mg/300 mg FDC [redacted] formulation Product Code AK	**Part 1:** 78/73 **Part 2:** 76/74	103/51: 30.5 yrs (1[redacted]-5[redacted] yrs)	Plasma DTG and 3TC AUC(0-∞), AUC(0-t), and Cmax	Completed CPSR
Human Pharmacodynamic Studies										
ING111856 (PD) GSK	1 US	Start 28 Sep 2009; Completed 29 Dec 2009; 42/42	To evaluate the effect of DTG on cardiac conduction as assessed by	Randomized, partial-blind, single dose, 3-period, cross-over	18-55 yrs, Healthy subjects, male / female	DTG 250 mg; oral suspension; single dose	42 Enrolled, 38 Completed	17/25; 34.5 yrs (1[redacted]-5[redacted] yrs)	Change from Baseline in QTcF for DTG	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			12-lead ECG compared with placebo and moxifloxacin (Thorough QTc study of DTG)	study		Placebo; oral suspension; single dose Moxifloxacin 400 mg; tablet; oral; single dose				

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING114819 (PD) ViiV Healthcare	1 US	Start 05 Oct 2010; Completed 03 Dec 2010; 38/36	To evaluate the effect of DTG on GFR as measured by iohexol and to evaluate creatinine clearance, extra-glomerular creatinine excretion, and renal plasma flow	Open-label, randomized, 3-arm, parallel, placebo-controlled	18-65 yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 14 days DTG 50 mg; tablet; oral; q12h; 14 days Placebo; tablet; oral; once daily; 14 days Omnipaque 300 (647 mg/mL of iohexol) 5 mL; solution; IV Amino-hippurate Sodium 2 g/10 mL (20%) of Loading Dose: 8 mg/kg, Maintenance Dose: 12 mg/min; solution; IV	38 Enrolled, 34 Completed	28/10; 31.8 yrs (1[redacted]-5[redacted] yrs)	GFR as measured by iohexol plasma clearance at Days -1, 7, and 14	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
Pharmacokinetic and PK/PD Studies in Target Patient Population										
ING111521 (PK and PK/PD) GSK	14 US	Start 25 Jun 2008; Completed 26 Aug 2008; 35/30	To assess the safety, tolerability and efficacy of repeat dose DTG	Dose-ranging, 10-day, repeat dose, placebo-controlled monotherapy study	18-65 yrs, HIV-infected subjects, male/ female	DTG 2, 10, 50 mg tablet; oral; once daily; 10 days; fasted	35 Enrolled (including 7 placebo) 35, Completed	35/0; 38.4 yrs (2[redacted]-5[redacted] yrs)	Change from Baseline in plasma HIV-1 RNA to Day 11 DTG following dose administration on Day 1: AUC(0-∞), AUC(0-24), Cmax, tmax, C24, t½, tlag, and CL/F; and following last repeat administration on Day 10: AUC(0-τ), C0, Cτ, Cmin, Cmax, tmax, t½, and CL/F, if data permit Safety and tolerability parameters	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING116070 (PK) ViiV Healthcare	3 US	Start 24 Jan 2012; Completed 22 May 2014 13/14	To determine plasma (total and unbound) DTG concentration and evaluate the relationship between DTG concentration in plasma and CSF	Phase IIIb single-arm, open-label, multicenter study	≥18 yrs, HIV-infected, ART-naïve subjects, male / female	DTG 50 mg; tablet; oral; once daily + ABC/3TC 600/300 mg; tablet; oral; once daily; 96 weeks	13 Enrolled 11 Completed	13/0; 40.2 yrs (2[redacted]-5[redacted] yrs)	Proportion of subjects with plasma HIV-1 RNA <50 c/mL over time; Proportion of Subjects with CSF HIV-1 RNA <50 c/mL at Week 2 and Week 16; DTG concentration in plasma (bound and unbound) and CSF	Completed synoptic CPSR
ING112276 (PK and PK/PD) ViiV Healthcare	34 centers: 6 France, 4 Germany, 3 Russia, 4 Italy, 5 Spain, 12 US	Start 30 Jul 2009; Completed 10 Oct 2017 205/200	To select a once daily oral dose of DTG administered with either ABC/3TC or TDF/ FTC and to evaluate antiviral activity, safety and PK over time	Phase IIb, Randomized, multicenter, parallel group, dose-ranging	≥18yrs, HIV-infected, ARV-naïve subjects, male / female	DTG 10 mg; tablet; oral + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/ 200 mg; tablet; oral; once daily; 96 weeks DTG 25 mg; tablet; oral + ABC/3TC 600 mg/300 mg	DTG 10 mg: 53 Randomized 27 Completed DTG 25 mg: 51 Randomized 32 Completed DTG 50 mg: 51	177/28; 37.2yrs (2[redacted]- 7[redacted])	Proportion of subjects with HIV-1 RNA <50 c/mL (c/mL) through Week 16 using the TLOVR algorithm. Dose selection will be based primarily on antiviral activity and tolerability in conjunction with immunologic,	Completed: (Week 16 Synoptic CSR) (Week 24 Full CSR) (Week 48 Abbr. CSR) (Week 96 Full CSR)

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						or TDF/FTC 300 mg/ 200 mg; oral; once daily; 96 weeks DTG 50 mg; tablet; oral + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/ 200 mg; oral; once daily; 96 weeks EFV 600 mg + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/ 200 mg; oral; once daily; 96 weeks	Randomized 29 Completed EFV 600 mg: 50 Randomized 39 Completed DTG 50 mg: 138 Enrolled 88 Completed		safety and PK measures will also be considered	End of Study synoptic CSR
ING113086	100 centers: 27 Spain 19 US,12 France, 11 Russia, 10	Start 19 Oct 2010; Completed; 27 Dec 2016 822/788	To assess safety and efficacy of DTG 50 mg once daily to RAL 400 mg BID	Phase III, multicenter randomized, double blind, double-dummy,	≥18yrs, HIV-infected, ART-naïve subjects, male /	DTG 50 mg; tablet; oral; once daily or RAL 400 mg; tablet; oral; once daily +	DTG: 411 Randomized 349 Completed	703/119; 36.0yrs (1[redacted]-7[redacted])	The proportion of subjects with HIV-1 RNA <50 c/mL through Week 48 using a Missing, Switch	Completed: Week 48 Full CSR Week 96

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
	Germany, 7 Canada, 7 Italy, 4 Australia, 3 UK		both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy	active-controlled, parallel group, fully-powered non-inferiority study	female	ABC/3TC 600 mg/300 mg or TDF/ FTC 300 mg/200 m; tablet; oral; once daily; 96 weeks	Open-label Phase: 338 Entered: 294 Completed: RAL: 411 Randomized 332 Completed Open-label Phase: 52 Entered NA Completed		or Discontinuation = Failure (MSDF) algorithm	Full CSR End of Study synoptic CSR
ING111762 (PK and PK/PD) ViiV Healthcare	185 centres: 4 Belgium, 12 France, 4 Greece, 1 Hungary, 7 Italy, 2 Netherlands, 3 Romania, 24 Spain,	Start 26 Oct 2010; Ongoing [a]; 719/688	To evaluate safety and efficacy of DTG 50 mg once daily vs. RAL 400 mg BID, both administered with an investigator-selected	Phase 3, multicentre randomized, double-blind, active-controlled, parallel group, non-inferiority study	≥18 yrs, HIV-infected, ARV-experienced subjects, INSTI-naïve regimen, male / female	DTG 50 mg; tablet; oral; once daily or RAL 400 mg; tablet; oral; BID + Investigator-selected background regimen; 48 weeks	DTG: 354 Randomized 4 Completed, 282 Ongoing [a] RAL: 361 Randomized	485/230 (1[redacted]-7[redacted] yrs)	The proportion of subjects with HIV-1 RNA <50 c/mL through Week 48 using MSDF algorithm as codified by the FDA's "snapshot algorithm. The proportion of	Week 48 Full CSR Complete

Protocol No. (Study Type) Sponsor	No. Study Center Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
	4 UK, 6 Canada, 72 US, 6 Argentina, 2 Australia, 9 Brazil, 5 Chile, 4 Mexico, 12 Russia, 3 South Africa, 5 Taiwan		background regimen				236 Completed, 43 Ongoing [a]		subjects with plasma HIV-1 RNA <50 c/mL will also be assessed at Week 24	
ING112578 (P1093)	Thailand US South Africa	Start 20 Apr 2011; Ongoing[b] 46/168	To select a DTG dose for chronic dosing in infants, children, and adolescents that achieves similar exposure to the DTG adult dose selected from the Phase IIb clinical trial in ART-naïve adult subjects	Phase I/II multi-center, open-label, non-comparative study	HIV-1-infected pediatric subjects ages ≥4 weeks to <18 years	DTG once-a day doses with target dose of ~1 mg/kg and with 4 weight bands, and a maximum dose of 50 mg; 48 weeks	Cohort I: 23 Enrolled, 21 Completed Week 48 8 Ongoing Cohort IIA: 23 Enrolled, 16 Completed Week 48 12 Ongoing	Cohort I: 5/18; 14.0yrs (1[redacted]–1[redacted]) Cohort IIA: 16/7; 9.0yrs ([redacted]– 1[redacted])	Steady-state PK of DTG in combination with OBT to determine the dose of DTG that achieved a targeted AUC24 in this population.	Week 48 Full CSR Complete

a. The number of ongoing subjects reported is based on a data cut-off date of 04 February 2013 in the Week 48 CSR
b. The number of ongoing subjects reported is based on a data cut-off date of 14 February 2015 in the Week 48 CSR

3TC = Lamivudine; ABC = Abacavir; ARV = Antiretroviral; ATV = Atazanavir; BA = Bioavailability ; BCV = Boceprevir; BID = Twice daily; CPSR = Clinical pharmacology study report ; CSR = Clinical study report; DRV = Darunavir; DTG = Dolutegravir ; EE= Ethinyl Estradiol; EFV = Efavirenz; ETV = Etravirine; FPV = Fosamprenavir; FTC = Emtricitabine; IV = Intravenous; LPV= Lopinavir; NA = Not applicable; NGMN = Norgestimate; OMP = Omeprazole ; PD = Pharmacodynamics; PK = Pharmacokinetics; RAL = Raltegravir; RBT = Rifabutin; RIF = Rifampin; RPV = Rilpivirine; RTV = Ritonavir; TDF = Tenofovir disoproxil fumarate; TVR = Telaprevir; TPV = Tipranavir; GFR = Glomerular filtration rate; OBT = Optimized background therapy

Appendix Table 4 Tabular Listing of Included Lamivudine Clinical Pharmacology Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
Pharmacokinetic Studies in Healthy Subjects						
EPV10001	PK and Safety	OL, R, 2- way, XO	Healthy subjects	3TC; 150 mg/Tablet/BID/Oral/7 days 3TC; 300 mg/Tablet/QD/Oral/7 days	63 Enrolled 60 Completed	Completed Full CPSR
CAL10001	BE of ABC/3TC FDC tablet and separate tablets; effect of food on FDC	O, R, XO	Healthy Subjects	ABC/3TC (600 mg/300 mg)/FDC tablet/oral/single dose, fasted ABC (2x300 mg) + 3TC (2x150 mg)/tablets/oral/single dose, fasted ABC/3TC (600 mg/300 mg)/FDC tablet/oral/single dose, fed	30 Enrolled 25 Completed	Completed Full CPSR
Pharmacokinetic Studies in HIV-infected Patients						
NUCA2001	Safety, PK and preliminary activity of 3TC	OL, non-comparative, multiple dose, dose escalation FTIH	HIV-positive patients with advanced ARC or AIDS	3TC; 0.5 mg/kg/ BID/; Oral 3TC; 1.0 mg/kg/ BID/ Oral; 3TC; 2.0 mg/kg/ BID/; Oral; 3TC; 4.0 mg/kg/BID/ Oral; 3TC; 8.0 mg/kg/ BID/; Oral; 3TC; 12 mg/kg/ BID/; Oral; 3TC; 20 mg/kg/ BID/ Oral	97 Enrolled 97 Completed	Completed Full CPSR

Study Identifier **(Identifier of Study Report)**	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)**	**Total No. of Subjects by Group Entered/** **Completed**	**Study Reporting Status (Type of Report)**
NUCA3001/3002	PK of 3TC from trials NUCA3001/ 3002 and characterize the influence of 3TC co-administration on ZDV disposition	R, DB, Multicenter	NUCA3001: HIV-1 infected patients who were ZDV-naïve (<4 weeks) and had CD4 cell counts of 200-500 cells/mm^3 NUCA3002: HIV-1 infected patients who were ZDV-experienced (≥24 weeks) and had CD4 cell counts of 100-300 cells/mm^3	NUCA3001: ZDV Arm: ZDV 200 mg LAM (300 mg) Arm: 3TC 300 mg ZDV+LAM (150 mg): 3TC 150 mg/ZDV 200 mg ZDV+LAM (300 mg) Arm: 3TC 300 mg/ZDV 200 mg NUCA3002: ZDV+ddC (0.75 mg): ZDV 200 mg/ddC 0.75 mg ZDV+LAM (150 mg): 3TC 150 mg/ZDV 200 mg ZDV+LAM(300 mg): 3TC 300 mg/ZDV 200 mg	394 patients in total from both studies	Completed Full CPSR
NUCA1001	Determine the effect of food on the PK of 3TC following a single oral dose of 3TC	R, OL, XO	HIV-infected patients	3TC 50 mg (2 x 25 mg) capsules fasted or fed	13 Entered 12 Completed	Completed Full CPSR
NUCB1001	PK, BA and safety of IV and oral doses of GR109714X (3TC)	OL, XO (3-day washout). Five dosing groups (0.25, 1, 2, 4, 8 mg/kg) each receiving (as single doses) oral and IV 3TC	HIV-positive patients	3TC; 0.25, 1, 2, 4, 8 mg/kg/ single dose/ oral and IV	20 Entered 20 Completed	Completed Full CPSR

Study Identifier **(Identifier of Study Report)**	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)**	**Total No. of Subjects by Group Entered/** **Completed**	**Study Reporting Status (Type of Report)**
NUCA1003	BE and RBA of 3TC 100 mg when administered as a capsule, as a tablet, or as an oral solution	OL, single dose, 4-way, XO (3-14-day washout)	HIV-positive patients	3TC oral formulations of a solution (1 mg/mL, 10% ethanol), capsule, and tablet administered at a 100 mg dose	14 Enrolled 12 Completed	Completed Full CPSR
NUCB4001	PK of 3TC and relationship between serum 3TC and intracellular 3TC-TP PK	OL, R, XO	HIV-positive asymptomatic subjects	A: 3TC/150 mg/BID/Oral/for 14 days B: 3TC/300 mg/BID/Oral/for 14 days	10 Enrolled 10 completed	Completed Full CPSR
CNAA1002	Safety and PK of ABC, ZDV and 3TC alone and in combination	OL, R, XO	HIV-infected patients	ABC 600 mg, ZDV 300 mg, 3TC 150 mg tablets; with each given alone and as each two and three drug combination / oral / single dose	15 Enrolled 13 Completed	Completed Full CPSR
NUCB2001	Safety, PK and preliminary activity of 3TC	OL, non-comparative, multiple dose	HIV-positive asymptomatic and mild ARC patients	3TC: 0.5 mg/kg/day 1.0 mg/kg/day 2.0 mg/kg/day 4.0 mg/kg/day 8.0 mg/kg/day 12 mg/kg/day 20 mg/kg/day (divided doses bid)	105 Enrolled 104 Completed	Complete Full CPSR

Study Identifier **(Identifier of Study Report)**	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)**	**Total No. of Subjects by Group Entered/** **Completed**	**Study Reporting Status (Type of Report)**
Pharmacokinetic Studies in Special Populations						
NUCB1003	PK of a single oral dose of 3TC in patients with renal impairment, and to determine whether 3TC is dialysed freely during dialysis therapy	OL	Healthy subjects and subjects with renal impairment	Healthy Group (normal renal function) and Group 1 (mild/moderate Impairment): 3TC; 300 mg (3 x 100 mg); hard gelatine capsules; oral; single dose. Group 2 (severe Impairment, non-dialysis): 3TC; 100 mg (1 x 100 mg) hard gelatine capsule; oral; single dose. Group 3 (severe Impairment, dialysis): 3TC; 100 mg; oral; single dose on 2 occasions (intra-dialysis and inter-dialysis) separated by a period of at least 1 week.	29 Enrolled 29 Completed Healthy Group: 9 Enrolled 9 Completed Group 1: 8 Enrolled 8 Completed Group 2: 6 Enrolled 6 Completed Group 3: 6 Enrolled 6 Completed	Completed Full CPSR
NUCA1004	Disposition and safety, tolerability of 3TC in HIV-infected subjects with normal and impaired renal function	OL, NR, parallel, single-dose study	HIV-infected subjects with normal and impaired renal function	3TC 300 mg; oral; single dose	16 Enrolled 16 Completed	Completed Full CPSR
NUCB1002	To investigate the PK of a single oral dose of 3TC in subjects with moderate and severe hepatic impairment in comparison with healthy subjects.	OL, single-dose study	Patients with impaired hepatic function	3TC, Single/oral 300 mg, as 3 x 100 mg Tablets with 200 mL water	25 Enrolled 24 Completed	Completed Full CPSR

Study Identifier **(Identifier of Study Report)**	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)**	**Total No. of Subjects by Group Entered/** **Completed**	**Study Reporting Status (Type of Report)**
LA-01	Safety and PK in Japanese subjects	Single doses, XO	Healthy subjects	3TC; 50 mg/Tablet/Oral/Single dose 3TC; 100 mg/Tablet/Oral/Single dose 3TC; 300 mg/Tablet/Oral/Single dose	12 Enrolled 12 Completed	Completed Full CPSR
LA-02	Safety and PK of repeated doses in Japanese subjects	Repeat doses for 7 days	Healthy subjects	3TC; 200 mg/Tablet/QD/Oral/Repeated doses for 1 week	8 Enrolled 8 Completed	Completed Full CPSR
LB-05	To evaluate the safety and PK between elderly and healthy young Japanese subjects	OL, single dose	Elderly and young healthy subjects	3TC; 100 mg/Tablet/Oral/Single dose.	12 Enrolled 12 Completed Elderly subjects: 6 Enrolled 6 Completed Healthy young male subjects: 6 Enrolled 6 Completed	Completed Full CPSR
NUCB1009	To evaluate the PK of single-dose and repeat-dose 3TC and to compare PK parameters in Chinese subjects to historical data	OL, repeat-dose study	Healthy subjects	3TC; 100 mg; QD; single dose; Oral; for 7 days (repeat dose)	24 Enrolled 24 Completed	Completed Full CPSR

Study Identifier **(Identifier of Study Report)**	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)**	**Total No. of Subjects by Group Entered/** **Completed**	**Study Reporting Status (Type of Report)**
NUCA2002	Safety, toxicity, preliminary activity of 3TC and PK	OL, non-comparator, dose escalating, 3 arm	HIV-positive children	3TC; 10 mg/mL/ single dose/IV dose Oral dosing of 3TC for 24 weeks and beyond based on investigators discretion: 3TC; 0.5 mg/; kg/BID/oral 3TC; 1 mg/kg/BID/oral 3TC; 2 mg/kg/BID/oral 3TC; 6 mg/kg/BID/oral 3TC; 10 mg/kg/BID/oral 3TC; 4 mg/kg/BID/oral	102 Enrolled 102 Completed	Completed Full CPSR
NUCB2020	Safety, PK and [HBV] antiviral activity in children and adolescents	DB, PC, dose-ranging study	HBV-infected asymptomatic patients	Children (2-6, 7-12yr): 0.35 mg/kg BID, 1.5 mg/kg BID, 4 mg/kg BID and 3 mg/kg QD Adolescents (>12yr): 100 mg tablet	53 Enrolled (41 children, 12 adolescents) 51 Completed per protocol	Completed Full CPSR

Study Identifier **(Identifier of Study Report)**	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)**	**Total No. of Subjects by Group Entered/** **Completed**	**Study Reporting Status (Type of Report)**
COL105677 (ARROW)	To describe the plasma PK of lamivudine (3TC), zidovudine (ZDV) and abacavir (ABC) when used as whole and half tablets, of either Combivir (ZDV/3TC 300/150 mg scored tablets twice daily), 3TC (150 mg scored tablets, twice and once daily), or ABC (300 mg scored tablets, twice and once daily) in HIV-infected African children, with doses determined according to World Health Organization (WHO) weight bands.	OL, R	Age 3 years to <12 years HIV infected, ART-naive, males/females	3TC: oral, 150 mg scored tablet once or twice daily, 48 weeks (in addition to twice-daily ABC+3TC for ≥36 weeks at entry). WHO weight band-based dosing, specifically: 14 to 20 kg; 1 tablet once daily or 0.5 tablet twice daily (total daily dose 150 mg) >20 to <25 kg; 1.5 tablets once daily or 0.5 tablet morning and 1 tablet evening (total daily dose 225 mg) ≥25 kg; 2 tablets once daily or 1 tablet twice daily (total daily dose 300 mg)	41/41 3TC evaluable PK: 35	Complete Full CPSR
EPV40002 (PENTA 13)	To compare the plasma PK of q24h with q12h 3TC and ABC in HIV-1 infected children ≥2 to <13 years old	OL, PK, single-sequence	HIV-infected, male/female, age 2 to <13 years old,	3TC: oral, 150 mg tablet or 10 mg/ml solution, twice or once daily, 24 weeks Dosing; 4 mg/kg twice daily (maximum 150 mg twice daily) or 8 mg/kg once daily (maximum total daily dose 300 mg)	24/24 3TC evaluable PK: 19	Complete Full CPSR

Study Identifier **(Identifier of Study Report)**	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)**	**Total No. of Subjects by Group Entered/** **Completed**	**Study Reporting Status (Type of Report)**
COL104929 (PENTA 15)	To compare plasma PK parameters of q24h versus q12h dosing of ABC in HIV-1 infected infants and children aged 3 months to 36 months	Single sequence, OL, XO PK	HIV-1–infected children 3 to <36 months, male/female	3TC: oral, 10 mg/ml solution, twice or once daily, 48 weeks Dosing; 4 mg/kg twice daily (maximum 150 mg twice daily) or 8 mg/kg once daily (maximum total daily dose 300 mg)	23/23 3TC evaluable PK: 17	Completed Full CPSR
Pharmacokinetic Interaction Studies						
NUCA1005	PK of both ZDV and 3TC alone and when co-administered.	OL, R, 4-way XO, 3-14-day washout	HIV-infected subjects	ZDV; 200 mg; oral tablet 3TC; 300 mg; oral tablet 3TC; 300 mg/BID/; oral tablet (5 doses) + ZDV; 200 mg/oral tablet (with dose 5 of 3TC) ZDV; 200 mg/; TID/oral tablet (9 doses) + 3TC /300 mg/oral tablet (with dose 7 of ZDV)	12 Enrolled 12 Completed	Completed Full CPSR
NUCA1007	PK of 3TC with and without co-administration of Co-trimoxazole (TMP/SMX)	OL, R, 2-way XO, 7-14-day washout	HIV-infected subjects	Treatment A: 3TC 300 mg tablet Treatment B: TMP 160 mg + SMX 800 mg QD (5 doses) + 3TC 300 mg tablet with dose 5	15 Enrolled 14 Completed	Completed Full CPSR
NUCA2005	Safety, tolerance, toxicity, viral resistance and pharmacokinetics	OL, parallel group	HIV-positive children	ZDV; 90 mg/m^2/dose/QD/oral/ 24 weeks ZDV; /180 mg/m^2/dose/QD/oral/ 24 weeks 3TC;4 mg/kg/dose/ BID/oral/ 24 weeks ddI;135 mg/m^2/dose/BID/24 weeks	65 Enrolled 65 Completed	Completed Full CPSR

Study Identifier **(Identifier of Study Report)**	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)**	**Total No. of Subjects by Group Entered/** **Completed**	**Study Reporting Status (Type of Report)**
204857	PK of 3TC with and without co-administration of SBT	OL, R, XO	Healthy subjects	Treatment A: 3TC 300 mg; solution; oral; single dose Treatment B: 3TC 300 mg; solution; oral; single dose + oral solution containing SBT 3.2 g; single dose Treatment C: 3TC 300 mg; solution; oral; single dose + oral solution containing SBT 10.2 g; single dose Treatment D: 3TC 300 mg; solution; oral; single dose + oral solution containing SBT 13.4 g; single dose	16 Enrolled 16 Completed	Completed Full CPSR

3TC = Lamivudine; ABC = Abacavir; AIDS = Acquired immune deficiency syndrome; ARC = AIDS-related complex; BA = Bioavailability; BID = Twice daily; DB = Double blind; HBV = Hepatitis B virus; HIV = Human immunodeficiency virus; IV = Intravenous; NR = Nonrandomized; QD = Once daily; OL = Open-label; ddC = dideoxycytidine; PC = Placebo control; PK = Pharmacokinetics; R = Randomized; TMP/SMX = Trimethoprim + sulfamethoxazole; ddI = Didanosine; XO = Cross Over; ZDV = Zidovudine; SBT = Sorbitol

Legend to Table 5 Summary Results PK Clinical Pharmacology Studies

Protocol No.	The Study identifier.
Study Design:	Degree of blinding: O=open, SB=single blind, DB=double blind Degree of control: UC=uncontrolled, PLC=placebo, AC=active control Treatment assignment: R=random, NR=nonrandom Treatment sequence: XO=crossover, PRL=parallel, DR=Dose rising
Number of subjects (M/F):	Number of subjects/patients who received study medication; (number of males M/ females F)
Age Mean Range:	Provides the mean and range of ages in years
Treatment Details (Drug/Dose/ Form/Route/ Frequency):	Study treatments are identified Dose (mg) of each treatment as specified in the protocol (od=once daily, bd=twice daily) Number of individual days receiving study medication
Cmax	Maximum observed plasma concentration.
tmax	Time to reach the maximum observed plasma concentration.
AUC(0-t)	Area under the plasma concentration versus time curve from time zero to the last time point that concentrations were quantifiable.
AUC(0-∞)	Area under the plasma concentration versus time curve from time zero to infinity.
t½	Apparent terminal elimination half-life
Others	Add As appropriate

Appendix Table 5 Summary of Single Dose Dolutegravir Pharmacokinetic Parameters

Study	Population/ No. of Subjects Randomized/Entered	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Parameter [a]				
				Cmax (μg/mL)	tmax (h)	AUC (0-∞) (μg.h/mL)	t1/2 (h)	C24 (μg/mL)
204994	Healthy adults/154	Oral Tablet	**Part 1:** **Treatment A:** DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet (Fasted)/73	2.41 (39.0)	2.01 (0.500, 8.01)	43.1 (39.3)	14.7 (15.6)	0.637 (40.2)
			Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH) (Fasted)/73	3.08 (31.9)	2.00 (0.500, 5.01)	54.9 (31.6)	14.7 (15.3)	0.806 (32.8)
			Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH) (Fasted)/16	3.51 (30.3)	1.50 (0.503, 5.00)	62.3 (32.3)	14.5 (8.89)	0.922 (36.1)
			Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH) (High-fat meal)/16	3.79 (21.0)	5.00 (2.00, 12.0)	72.0 (20.0)	14.5 (13.3)	1.19 (25.0)

Study	Population/ No. of Subjects Randomized/Entered	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Parameter [a]				
				Cmax (μg/mL)	tmax (h)	AUC (0-∞) (μg.h/mL)	t1/2 (h)	C24 (μg/mL)
			Part 2: **Treatment A:** DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet (Fasted)/74	2.55 (36.4)	2.50 (0.500, 5.01)	47.2 (40.3)	15.1 (17.8)	0.707 (41.5)
			Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) (Fasted)/74	2.91 (30.6)	2.50 (0.500, 6.00)	54.6 (32.1)	15.0 (18.2)	0.807 (33.8)
			Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) (Fasted)/16	3.10 (35.6)	1.50 (0.751, 3.00)	57.7 (36.0)	15.3 (17.3)	0.836 (38.5)
			Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) (High-fat meal)/16	3.75 (21.3)	5.00 (1.01, 8.00)	76.4 (22.4)	15.5 (16.0)	1.23 (25.7)
ING114580	Healthy adults/65	Oral Tablet	DTG/ 50 mg/ ABC 600 mg/3TC 300 mg/ FDC/65	2.44 (28)	3.0 (1.0-8.0)	44.8 (33)	12.8 (20)	0.73 (35)
			DTG/ 50 mg + ABC/ 600 mg/ 3TC 300 mg/ FDC/65	2.54 (29)	3.0 (0.5-8.0)	47.4 (34)	12.9 (18)	0.76 (38)
ING111322	Healthy adults/32	Oral Suspension	10 mg/ 8	1.24 (12)	0.50 (0.50-1.00)	15.8(12)	11.8 (19)	0.23 (19)
			25 mg/ 10	2.66 (21)	1.00 (0.50-2.00)	43.1(28)	12.6 (17)	0.65 (33)
			50 mg/ 8	4.52 (20)	0.75 (0.50-1.00)	75.8(28)	12.6 (14)	1.18 (32)
ING111521	HIV-infected/ 35	Oral Tablet	2 mg (fasted)/ 9	0.18 (35)	1.5 (0.5-3.0)	2.63 (39)	10.7 (30)	0.03 (49)

Study	Population/ No. of Subjects Randomized/Entered	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Parameter [a]				
				Cmax (μg/mL)	tmax (h)	AUC (0-∞) (μg.h/mL)	t1/2 (h)	C24 (μg/mL)
			10 mg (fasted)/ 7	0.57 (28)	2.0(1.0-6.0)	10.1 (26)	11.8 (22)	0.15 (30)
			50 mg (fasted)/ 10	2.46 (32)	2.1 (1.0-3.97)	40.5 (33)	11.2 (29)	0.59 (31)
ING111602	Healthy adults/16	Oral Tablet	50 mg (alone)/ 16	2.03 (25)	2.5 (0.5-8.0)	35.6 (33)	NR	0.51 (38)
			50 mg (+ multi-vitamin)/ 16	1.31 (25)	2.5 (0.5-8.0)	23.74 (30)	NR	0.34 (33)
			50 mg (+ Maalox)/ 16	0.56 (29)	2.5 (0.5-8.0)	9.40 (36)	NR	0.13 (41)
			50 mg (+ Maalox 2 hrs post dose)/ 16	1.67 (51)	2.5 (0.5-8.0)	26.33 (45)	NR	0.36 (42)
ING111853	Healthy adults/ 6	Oral Suspension	20 mg (fasted)/ 6	2.57 (24)	0.50 (0.50-2.00)	35.9 (12)	15.6 (16)	N/A
ING111856	Healthy adults/42	Oral Suspension	250 mg (fasted)/ 41	12.4 (27)	3.08 (1.52-6.05)	167 (33)	NR	3.86 (48)
ING112941	Healthy adults/14	Oral Tablet	50 mg (fasted)/ 12	1.84 (44)	4.00 (1.00-5.00)	34.7 (57)	14.4 (21)	0.56 (63)
			50 mg (fasted + OMP)/ 12	1.69 (19)	3.00 (1.00-5.03)	34.8 (26)	16.3 (20)	0.53 (27)
		Oral Suspension	250 mg/ 8	14.1 (10)	2.50 (1.50-4.00)	278 (15)	14.5 (10)	4.08 (17)
ING113097	Healthy and moderate hepatic impairment adults/16	Oral Tablet	50 mg (fasted)/ 8 healthy matches	1.80 (49)	3.0 (1.0-4.0)	37.3 (47)	14.9 (24)	0.57 (44)
			50 mg (fasted)/ 8 with moderate hepatic impairment	1.78 (17)	4.0 (2.0-5.0)	38.5 (30)	15.5 (19)	0.59 (36)
ING113125	Healthy and severe renal impairment adults/ 16	Oral Tablet	50 mg (fasted)/ 8 healthy matches	1.86 (45)	2.00 (1.0, 4.0)	37.1 (58)	15.4 (15)	NR
			50 mg (fasted)/ 8 with severe renal impairment	1.50 (34)	2.00 (1.0, 3.0)	23.5 (48)	12.7 (31)	NR
ING114005	Healthy adults/12	Oral Tablet	50 mg (fasted)/ 12	1.83 (35)	2 (1-4)	24.3 (44)[b]	13.6 (24)	0.53 (59)
			100 mg (fasted)/ 12	2.77 (35)	2 (1-4)	34.3 (41)	NR	0.80 (53)
ING115381	Healthy adults (Japanese)/10	Oral Tablet	50 mg(fasted)/ 10	2.14 (47)	NR (2.0-4.0)	43.4 (46)	14.6 (10)	0.67 (45)
ING116898	Healthy adults/12 (Cohort 1)	Oral Tablet	50 mg (fasted)/12	1.98 (46)	3 (0.5-6.0)	35.6 (62)	12.2 (28)	0.542 (66)
			50 mg (fasted, +Calcium Carbonate)/12	1.25 (45)	2 (0.5-12)	21.8 (66)	12.7 (24)	0.332 (74)
			50 mg (fed, Calcium Carbonate)/11	2.13 (30)	3 (1.0-6.02)	39.2 (47)	12.3 (25)	0.588 (54)

Study	Population/ No. of Subjects Randomized/Entered	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Parameter [a]				
				Cmax (μg/mL)	tmax (h)	AUC (0-∞) (μg.h/mL)	t1/2 (h)	C24 (μg/mL)
			50 mg (2 hrs prior to Calcium Carbonate)/11	1.98 (46)	3 (1.0-4.0)	33.8 (57)	12.4 (24)	0.492 (58)
	Healthy adult/11 (Cohort 2)	Oral Tablet	50 mg (fasted)/11	1.77 (41)	3 (1.0-6.0)	33.6 (40)	13.2 (16)	0.528 (41)
			50 mg (fasted, +Ferrous Fumarate)/11	0.742 (56)	4 (2.0-6.0)	15.1 (53)	14.3 (23)	0.227 (56)
			50 mg (fed, Ferrous Fumarate)/10	1.90 (25)	3.5 (1.0-8.0)	34.1 (33)	12.8 (20)	0.540 (42)
			50 mg (2 hrs prior to Ferrous Fumarate)/10	1.79 (52)	2 (0.5-6.0)	32.3 (47)	13.7 (25)	0.489 (48)

a. Data presented are geometric mean (%CVb) except for tmax where median (range) are presented.
b. AUC(0-24) is reported.
NR = Not reported; N/A = Not available

Appendix Table 6 Summary of Repeat Dose Dolutegravir Pharmacokinetic Parameters

Study	Population/ No. of Subjects Randomized/Entered	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter [a]				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg/mL)
ING111322	Healthy adult/ 32	Oral Suspension	10 mg/ 8	QD x 10 days	1.47 (24)	0.50 (0.25-2.00)	16.7 (15)	13.7 (15)	0.35 (20)
			25 mg (+MDZ)/ 10		3.09 (26)	1.00 (0.50-2.00)	38.4 (23)	15.0 (16)	0.84 (33)
			50 mg/ 8		6.16 (15)	1.00 (0.50-2.00)	76.8 (19)	15.3 (8)	1.64 (25)
ING111405	Healthy adult/ 31	Oral Tablet	30 mg/ 30	QD x 5 days (mod. fat meal)	2.80 (15)	NR	36.9 (19)	12.1 (15)	0.77 (29)
			30 mg (+LPV/RTV 400/100 mg)/ 15	QD (+LPV/RTV q12h) x 14 days (mod. fat meal)	2.94 (21)	NR	38.0 (25)	12.2 (22)	0.77 (36)
			30 mg (+DRV/RTV 600/100 mg)/ 15	QD (+DRV/RTV q12h) x 14 days (mod. fat meal	2.38 (20)	NR	27.3 (23)	9.78 (17)	0.45 (37)
ING111521	HIV-infected adult/ 35	Oral Tablet	2 mg/ 9	QD x 10 days	0.22 (25)	1.00 (0.42-3.00)	2.56 (29)	11.1 (24)	0.04 (50)
			10 mg/ 7	QD x 10 days	0.80 (23)	1.48 (0.50-3.00)	10.1 (20)	11.6 (21)	0.19 (25)
			50 mg/ 10	QD x 10 days	3.34 (16)	2.00 (0.97-4.00)	43.4 (20)	12.0 (22)	0.83 (26)
ING111603	Healthy adult/ 16	Oral Tablet	50 mg/ 15	QD x 5 days (mod. fat meal)	4.34 (19)	3.00 (1.00-4.07)	60.4 (22)	12.4 (21)	1.29 (29)
			50 mg (+ETV 200 mg)/ 15	QD (+ETV q12h) x 14 days (mod. fat meal)	2.10 (24)	2.00 (1.00-3.00)	17.8 (39)	6.39 (22)	0.16 (84)
ING111604	Healthy adult/ 15	Oral Tablet	50 mg/ 15	QD x 5 days	3.45 (30)	3.00 (1.00-4.00)	46.6 (32)	N/A	1.08 (39)
			50 mg (+300 mg TDF)/ 15	QD x 5 days	3.34 (26)	3.00 (1.00-4.03)	46.9 (28)	N/A	0.99 (32)
ING111762	HIV-infected adult/ 354	Oral Tablet	50 mg/342 (average)	QD	NR	NR	NR	NR	0.926 (131)[b]
			50 mg/329 (Wk 4)		NR	NR	NR	NR	0.786 (143)[c]
			50 mg/298 (Wk 24)		NR	NR	NR	NR	0.940 (132)[c]
			50 mg/276 (Wk 48)		NR	NR	NR	NR	0.932 (152)[c]
ING113086	HIV-infected adult/ 411	Oral Tablet	50 mg/ 399 (average)	QD	NR	NR	NR	NR	1.18 (60)[b]
			50 mg/ 379 (Wk 4)		NR	NR	NR	NR	1.05 (69)[c]

Study	Population/ No. of Subjects Randomized/Entered	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter [a]				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg/mL)
			50 mg/ 365 (Wk 24)		NR	NR	NR	NR	1.17 (71)[c]
			50 mg/ 351 (Wk 48)		NR	NR	NR	NR	1.13 (72)[c]
ING111854	Healthy adult/ 24	Oral Tablet	30 mg/ 12	QD x 5 days (mod. fat meal)	3.21 (19)	3.00 (1.00-4.00)	45.3 (21)	13.3 (19)	1.00 (30)
			30 mg (+ATV/RTV 300/100 mg)/ 12	QD x 14 days (mod. fat meal)	4.29 (19)	4.00 (2.00-4.00)	73.3 (16)	24.1 (11)	2.21 (16)
			30 mg/ 12	QD x 5 days (mod. fat meal	3.42 (13)	4.00 (1.00-4.00)	45.8 (17)	12.6 (20)	0.95 (29)
			30 mg (+ATV 400 mg)/ 12	QD x 14 days (mod. fat meal	5.11 (20)	4.00 (2.00-4.00)	87.4 (17)	23.8 (21)	2.67 (21)
ING111855	Healthy adult female/ 16	Oral Tablet	50 mg (+OC)/ 15	BID (+ OC QD) x 10 days	7.77 (23)	1.00 (1.0-6.0)	68.6 (27)	NR	4.00 (36)
ING112276	HIV-infected adult/ 155	Oral Tablet	10 mg/ 15	QD x 10 days	1.10 (37)	2.0 (2.0-4.0)	16.0 (40)	NR	0.30 (71)
			25 mg/ 15	QD x 10 days	1.71 (43)	2.0 (2.0-8.0)	23.1 (48)	NR	0.54 (67)
			50 mg/ 15	QD x 10 days	3.40 (27)	2.0 (2.0-4.0)	48.1 (40)	NR	1.20 (62)
ING112934	Healthy adult/ 17	Oral Tablet	50 mg/ 8 (Cohort 1)	QD x 5 days (mod. fat meal)	3.52 (12)	3.50 (2.00-4.00)	47.8 (19)	11.3 (18)	0.97 (33)
			50 mg/ 8 (Cohort 2)	QD x 5 days (mod. fat meal)	3.38 (26)	3.02 (1.00-12.00)	45.2 (22)	10.4 (17)	0.94 (40)
			50 mg (+ ETV 200 mg and LPV/RTV 400/100 mg)/ 8	QD (+ETV and LPV/RTV q12h) x 14 days (mod. fat meal)	3.78 (12)	3.50 (1.00-4.00)	52.8 (18)	15.4 (25)	1.23 (32)
			50 mg (+ ETV 200 mg and DRV/RTV 600/100 mg)/ 9	QD (+ETV and DRV/RTV q12h) x 14 days (mod. fat meal)	2.98 (18)	4.00 (1.00-4.00)	33.9 (22)	10.2 (16)	0.59 (33)
ING113068	Healthy adult/ 12	Oral Tablet	50 mg/ 12	QD x 5 days	2.38 (38)	2.0 (1.0-4.0)	30.6 (39)	12.1 (19)	0.61 (45)
			50 mg (+FPV/RTV 700/100 mg BID)/ 12	QD x 10 days	1.82 (57)	2.0 (1.0-4.0)	19.9 (57)	9.54 (26)	0.31 (64)
ING113096	Healthy adult/ 18	Oral Tablet	50 mg/ 14	QD x 5 days (mod. fat meal)	4.53 (23)	3.00 (2.00-3.00)	64.5 (28)	14.8 (22)	1.48 (40)

Study	Population/ No. of Subjects Randomized/Entered	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter [a]				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg/mL)
			50 mg (+TPV/RTV 500/200 mg)/ 14	QD (+TPV/RTV BID) x 5 days (mod. fat meal)	2.42 (23)	4.00 (1.00-4.00)	26.4 (30)	7.88 (20)	0.35 (54)
ING113099	Healthy adult/ 27	Oral Tablet	50 mg/ 20	QD x 7 days	2.78 (34)	2.0 (1.0-5.1)	35.1 (42)	11.2 (30)	0.63 (72)
			50 mg/ 11	BID x 7 days	5.55 (49)	1.0 (1.0-4.0)	46.3 (55)	9.54 (48)	2.41 (77)
			50 mg (+ RIF 600 mg)/ 11	BID (+RIF QD) x 14 days	3.13 (25)	2.0 (1.0-5.0)	42.6 (31)	4.24 (23)	0.67 (55)
			50 mg (+ RBT 300 mg)/ 9	QD x 14 days	3.41 (23)	3.0 (1.0-4.0)	37.0 (32)	8.64 (22)	0.53 (56)
ING114005	Healthy adult/ 12	Oral Tablet	50 mg/ 12	QD x 5 days	3.08 (30)	2.0 (1.0-4.0)	42.3 (39)	13.9 (23)	0.91 (53)
			50 mg (+EFV 600 mg QD)/ 12	QD x 14 days	1.87 (42)	1.0 (1.0-4.0)	18.2 (50)	7.82 (21)	0.22 (76)
ING114819	Healthy adult/ 38	Oral Tablet	50 mg (+iohexol and PAH infusion)/ 11	QD x 14 days	2.83 (27)	NR	39.1 (38)	NR	0.84 (61)
			50 mg (+iohexol and PAH infusion)/ 11	BID x 14 days	5.50 (34)	NR	51.6 (36)	NR	3.02 (40)
ING115696	Healthy adult/ 12	Oral Tablet	50 mg/ 12	QD x 5 days (mod. fat meal)	4.27 (25)	4.0 (1.0-4.0)	58.6 (32)	13.8 (21)	1.32 (40)
			50 mg (+prednisone)/ 12	QD x 10 days (mod. fat meal) (Day 5)	4.47 (31)	3.5 (1.0-4.0)	65.9 (37)	15.2 (17)	1.59 (47)
			50 mg (+prednisone)/ 12	QD x 10 days (mod. fat meal) (Day 10)	4.54 (29)	3.5 (1.0-4.0)	65.0 (37)	14.6 (24)	1.53 (50)
ING115697	Healthy adult/ 32	Oral Tablet	50 mg/ 16 (Cohort 1)	QD x 5 days (mod. fat meal)	4.62 (21)	2.50 (1.0, 4.0)	61.5 (27)	13.2 (18)	1.31 (38)
			50 mg/ 16 (Cohort 2)	QD x 5 days (mod. fat meal)	4.99 (23)	3.00 (1.0, 4.0)	68.9 (25)	14.5 (19)	1.59 (35)
			50 mg (+BCV 800 mg)/ 13	QD (+q8h BCV) x 10 days (mod. fat meal)	4.82 (17)	3.00 (1.0, 4.0)	65.3 (22)	13.8 (19)	1.40 (36)

Study	Population/ No. of Subjects Randomized/Entered	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter [a]				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg/mL)
			50 mg (+TVR 750 mg)/ 15	QD (+ q8h TVR) x 10 days (mod. fat meal)	5.81 (15)	4.00 (1.1, 4.0)	84.2 (21)	16.7 (18)[d]	2.09 (28)
ING115698	Healthy adult/ 11	Oral Tablet	50 mg (+methadone)/ 11	BID x 5 days	4.88 (35)	NR	44.3 (37)	NR	2.63 (41)
LAI116181	Healthy adult/ 28	Oral Tablet	50 mg/ 16	QD x 5 days (mod. fat meal)	3.46 (30)	3.50 (1.0-4.0)	48.8 (35)	NR	1.07 (45)
			50 mg (+RPV 25 mg)/ 16	QD x 5 days (mod. fat meal)	3.90 (25)	3.50 (1.0-4.0)	54.7 (33)	NR	1.31 (46)
200901	Healthy adult/ 16	Oral Tablet	50 mg/ 16	QD x 5 days (mod. fat meal)	4.16 (14.4)	3.01 (2.00-6.00)	53.8 (21.4)	12.9 (23.8)	1.20 (39.1)
			50 mg (+ CBZ 300 mg/ 14	QD (+ CBZ BID) x 5 days (mod. fat meal)	2.77 (25.0)	2.50 (1.00-6.00)	27.4 (22.1)	7.31 (16.9)	0.325 (45.9)
201102	Healthy adult/ 12	Oral Tablet	50 mg/ 12	QD x 5 days	2.65 (32.0)	2.00 (1.00, 4.00)	35.7 (34.7)	13.9 (32.8)	0.771 (41.3)
			50 mg (+ DCV 60 mg/ 12	QD x 5 days	3.43 (24.5)	2.00 (1.00,3.00)	47.3 (26.3)	16.2 (32.6)	1.11 (36.6)
201167	Healthy adult/ 15	Oral Tablet	50 mg (+ Metformin 500 mg/ 14	QD (+ Metformin BID) x 7 days (mod. fat meal)	3.81 (27.7)	4.00 (1.00, 11.9)	54.6 (25.7)[e]	NR	1.25 (33.7)
			50 mg (+ Metformin 500 mg/ 14	BID (+ Metformin BID) x 7 days (mod. fat meal)	6.81 (19.3)	2.50 (1.00, 4.00)	65.6 (23.8)	NR	4.37 (31.0)

a. Data presented are geometric mean (%CVb) except for tmax where median (range) are presented
b. Data presented as C0avg
c. Data presented as C0
d. N = 14
e. For 1 subject, AUC(0-t) with last observed concentration at 11.93 hr post-dose was used as AUC(0-τ)as there were not enough data points in the terminal phase to estimate AUC(0-τ).

ATV = Atazanavir; BCV = Boceprevir; BID = Twice Daily; CBZ = Carbamazepine; DCV = Daclatasvir; DRV = Darunavir; EFV = Efavirenz; ETV = Etravirine; FPV = Fosamprenavir; LPV = Lopinavir; MDZ = Midazolam; N/A = Not applicable; NR = Not reported; OC = Oral contraceptive; PAH = Para-aminohippurate; QD = Once daily; RBT = Rifabutin; RIF = Rifampin; RPV = Rilpivirine; RTV = Ritonavir; TDF = Tenofovir disoproxil fumarate; TVR = Telaprevir; TPV = Tipranavir

Appendix Table 7 Summary of Lamivudine (3TC) Pharmacokinetic Parameters [a]

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (µg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (µg.h/mL)**	**t½ (h)**
204994	Healthy adults/154	Oral Tablet	**Part 1:** **Treatment A:** DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet; single dose (n=73) (Fasted)	2.67 [d] (29.0)	1.00 (0.500, 4.00)	12.3 [d] (19.9)	17.6 [d] (27.9)
			Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH); single dose (n=73) (Fasted)	3.19 [d] (28.1)	1.00 (0.500, 3.50)	12.8 [d] (19.8)	17.7 [d] (22.9)
			Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH); single dose (n=16) (Fasted)	3.54 [d] (27.1)	1.00 (0.500, 2.00)	13.4 [d] (21.0)	18.4 [d] (21.9)
			Treatment B: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product code AH); single dose (n=16) (High-fat meal)	2.51 [d] (18.7)	3.50 (1.01, 5.00)	12.9 [d] (18.5)	19.1 [d] (30.7)
			Part 2: **Treatment A:**				

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
			DTG 50 mg tablet (clinical image) plus a single Epivir 300 mg tablet; single dose (n=74) (Fasted)	2.44 [d] (28.3)	1.00 (0.500, 4.00)	12.8 [d] (18.6) [e]	19.2 [d] (29.5) [e]
			Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) ; single dose (n=74) (Fasted)	3.22 [d] (29.3)	1.00 (0.500, 3.50)	13.6 [d] (18.0) [e] 13.6 (17.9) [f]	18.6 [d] (26.9) [e] 18.8 (27.7) [f]
			Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK); single dose (Fasted) (n=16)	3.58 [d] (35.2)	1.00 (0.503, 2.51)	14.6 [d] (18.5)	18.1 [d] (24.4)
			Treatment C: DTG/3TC 50 mg/300 mg FDC [redacted] formulation (Product Code AK) single dose (n=16) (High-fat meal)	2.45 [d] (33.9)	2.75 (1.00, 6.00)	13.3 [d] (20.3)	19.8 [d] (20.4)
EPV10001	Healthy Subjects/63	Oral/tablet	3TC 300 mg BID x 7 days/ (n=60)	1.96 (1.84-2.11)	1.0 (1.0-2.0)	8.69 (AUC0-24) (8.28-9.14)	NR
			3TC 150 mg QD x 7days/ (n=60)	1.18 (1.12-1.26))	1.0 (0.83-2.0)	9.21 (AUC0-24) (8.81-9.63)	

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
EPV10001 (Triphosphate) (units are pmol.h/1x10^6 cells)[g]	Healthy Subjects/63	Oral/tablet	3TC 300 mg BID x 7 days (fasted)/ (n=60)	7.74 (6.56-9.14)	NR	86.71 (AUC0-24) (74.38-101.08)	NR
			3TC 150 mg QD x 7 days (fasted)/ (n=60)	8.15 (6.99-9.51)	NR	85.38 (AUC0-24) (73.71-98.89)	NR
CAL10001	Healthy Subjects/30	Oral/tablet	ABC/3TC (600 mg/300 mg): single dose (fasted) FDC/; (n=25)	2.64 (2.37-2.95)	2.00 (1.00-5.00)	12.57 (11.64-13.58)	4.93 (4.63-5.26)
			ABC (600 mg)/2x300 mg tablets + 3TC (300 mg)/ 2x150 mg; single dose (fasted)/ (n=25)	2.82 (2.61-3.05	1.50 (0.75-4.00)	13.18 (12.20-14.24)	4.99 (4.74-5.25)
			ABC/3TC (600 mg/300 mg) FDC; single dose (fasted)/ (n=25)	2.26 (2.07-2.46)	3.00 (1.00-5.00)	12.08 (11.27-12.96)	4.86 (4.57-5.17)
LA-01	Japanese healthy subjects/12	Oral/tablet	3TC 50 mg single dose (fasted)/ (n=6)	0.54 (0.17)[h]	1.1(0.2)[h]	1.78 (0.37)[h]	6.53 (1.35)[h]
			3TC 100 mg single dose (fasted)/(n=6)	1.18 (0.17)[h]	1.1(0.6)[h]	4.00 (0.80)[h]	8.2 (3.2)[h]
			3TC 100 mg + food single dose (n=6)	0.88 (0.16)[h]	1.7 (0.4)[h]	3.91 (0.33)[h]	8.5 (1.8)[h]
			3 TC 300 mg single dose fasted)/ (n=6)	2.90 (0.92)[h]	0.8 (0.4)[h]	10.24 (2.03)[h]	9.3 (4.8)[h]
LA-02	Japanese healthy	Oral/tablet	200 mg single dose	1.56 (0.14)[h]	1.9 (0.7)[h]	7.38 (0.947)[h]	8.7 (2.0)[h]

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
	subjects/8		(n=6) 200 mg repeated dose for 4 days (n=6) 200 mg repeated dose for 7 days (n=6)	 1.52 (0.20) [h] 1.79 (0.64) [h]	 1.8 (0.4) [h] 1.8 (0.4) [h]	 7.15 (0.986) [h] 7.21 (0.128) [h]	 9.6 (1.5) [h] 9.3 (1.3) [h]
LB-05	Elderly and healthy young subjects/ 12	Oral/tablet	Elderly subjects: 100 mg single dose (fasted)/(n=6) Healthy Young subjects: 100 mg single dose (fasted)/ (n=6)	1.67 (0.73) [h] 1.45 (0.68) [h]	1.9 (1.7) [h] 0.7 (0.3) [h]	6.84 (1.05) [h] 4.97 (1.11) [h]	8.17 (0.66) [h] 9.21 (1.23) [h]
NUCA1003	HIV-infected patients/14	IV Oral/solution Oral/Capsule Oral/Tablet	3TC 100 mg IV single dose/ (n=12) 3TC 100 mg Oral solution single dose (fasted)/(n=12) 3TC 100 mg Oral capsule single dose (fasted)/ (n=12) 3TC 100 mg Oral tablet single dose (fasted) (n=12)	1.77 (1.56-2.01) [i] 1.029 (0.87-1.22) [i] 1.07 (0.87-1.32) [i] 1.00 (0.86-1.17) [i]	NR 0.75 (0.75-1.00) 0.75 (0.50-1.50) 0.75 (0.50-1.50) [i]	4.48 (4.04-4.98) [i] 3.84 (3.51-4.21) [i] 3.86 (3.34-4.35) [i] 3.78 (3.50-4.08) [i]	8.30 (6.66-10.59) [i] 8.32 (7.38-9.38) [i] 8.43 (7.78-9.13) [i] 8.30 (7.46-9.23) [i]
NUCA1004	HIV-infected subjects with normal and impaired renal function/16	Oral/tablet	Group 1 (normal renal function- CrCl >60 mL/min): 300 mg single dose (fasted)/	2.52 (2.14-2.97)	1.0 (0.75- 3.00)	10.89 (8.33-14.24)	11.49 (9.02-14.64)

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
			(n=6) Group II (moderate renal impairment-10 mL/min< CrCl <30 mL/min): 300 mg single dose (fasted)/(n=4) Group III (end-stage renal impairment- CrCl <10 mL/min): 300 mg single dose (fasted)/(n=6)	3.54 (2.906-4.32) 5.68 (4.83-6.69)	1.27 (1.02- 4.00) 2.25 (0.75-4.00)	45.66 (32.86-63.43) 14.65 (11.20-191.58)	14.09 (10.47-18.95) 20.73 (16.28-26.41)
NUCA1005	HIV infected subjects/ 12	Oral/tablet	3TC 300 mg single dose (Treatment B) (n=12) 3TC (300 mg with dose 7 of ZDV) +ZDV (200 mg TID) (Treatment D) (n=12)	3.15[i] (2.87-3.45) 3.27[i] (3.58-2.98)	1.0 (Range -NA) 1.0 (Range -NA)	10.78[i] (11.15-10.42) 10.99[i] (10.62-11.37)	6.57[i] (5.99-7.21) 6.49[i] (7.12 -5.92)
NUCA1007	HIV-infected subjects/15	Oral/tablet	3TC 300 mg single dose (fasted)(Treatment A) (n=14) 3TC 300 mg + TMP 160 mg/SMX 800 mg once daily (fasted) (Treatment B) (n=14)	2.73[i] (2.54-2.94) 2.97[i] (2.76-3.19)	NR NR	10.12[i] (9.43-10.87) 14.45[i] (13.46-15.51)	7.2[i] (6.8-7.7) 6.2[i] (5.9-6.6)
NUCA2001	HIV-positive patients with advanced ARC or AIDS/97	Oral, Capsules/Tablets	BID dosing; no food at least 1 hour before and 1 hour after PK dose 3TC: 0.5 mg/kg/day	0.02	0.75 (43)[j]	0.053	3.15

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
			(n=10)	(0.01, 0.02)		(0.40, 0.68)	(2.79, 3.56)
			1.0 mg/kg/day (n=12)	0.31 (0.24, 0.41)	1.0 (39)	1.10 (0.86, 1.40)	3.07 (2.70, 3.50)
			2.0 mg/kg/day (n=14)	0.61 (0.47, 0.08)	0.88 (44)	2.16 (1.80, 2.57)	2.88 (2.62, 3.17)
			4.0 mg/kg/day (n=9)	1.37 (0.99, 0.19)	1.5 (32)	5.21 (4.09, 6.63)	2.64 (2.32, 2.99)
			8.0 mg/kg/day (n=13)	2.34 (1.75, 3.14)	1.0 (53)	8.18 (6.66, 10.04)	2.83 (2.37, 3.39)
			12 mg/kg/day (n=15)	3.19 (2.36, 4.32)	1.5 (44)	13.55 (10.45, 17.56)	2.77 (2.45, 3.13)
			20 mg/kg/day (n=14)	5.66 (4.67, 6.87)	1 (54)	22.27 (18.44, 26.88)	2.82 (2.58, 3.08)

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
NUCA2002	HIV-positive children/102	Oral and IV/ Tablets and Injections	3TC IV doses; single dose, (10 mg/mL):				
			1 mg/kg/day (n=5)	0.659 (0.389, 1.116)	NR	1.360 (0.561, 3.295)	1.48 (0.95, 2.31)
			2 mg/ kg/day (n=9)	1.203 (0.968, 1.496)	NR	1.747 (1.433, 2.129)	1.65 (1.53, 1.78)
			4 mg/ kg/day (n=12)	2.110 (1.503, 2.963)	NR	3.918 (2.868, 5.354)	1.91 (1.56, 2.33)
			8 mg/kg/day (n=12)	3.797 (2.876, 5.012)	NR	7.970 (6.337, 10.024)	1.68 (1.47, 1.91)
			12 mg/kg/day (n=9)	4.952 (3.427, 7.155)	NR	10615 (7.877, 14.304)	1.51 (1.28, 1.77)
			20 mg/kg/ day (n=11)	8.153 (6.212, 10.701)	NR	17.843 (14.392, 22.122)	1.45 (1.22, 1.73)
			3TCoraldoses (PK data from 1st dose):				
			1 mg/kg/day (n=7)	0.189 (0.111, 0.322)	1.21 (0.64)	0.588 (0.366, 0.945)	1.97 (1.34, 2.91)
			2 mg/ kg/day (n=9)	0.417 (0.271, 0.642)	1.17 (0.56)	1.445 (1.045, 1.999)	2.13 (1.79, 2.54)
			4 mg/ kg/day (n=10)	0.601 (0.364, 0.991)	1.95 (1.21)	2.367 (1.549, 3.618)	2.33 (1.84, 2.95)
			8 mg/kg/day (n=12)	1.062 (0.822, 1.372)	2.04 (1.34)	4.457 (3.099, 6.410)	2.01 (1.69, 2.38)
			12 mg/kg/ day (n=9)	1837 (1.028, 3.282)	1.44 (0.53)	6.709 (4.108, 10.958)	1.96 (1.60, 2.41)
			20 mg/kg/ day (n=13)	4.013 (3.022, 5.330)	1.42 (0.91)	12.783 (9.490, 17.220)	1.72 (1.45, 2.04)
NUCA2005	HIV-positive children /65	Oral/Capsule, Oral suspension, Tablet	PK data from 1st (single) dose:				
			8 mg/Kg/day BID, 2 - <12	NR	NR	4.586	NR

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
			yrs, 3TC alone			(3.967-5.297)	
			8 mg/Kg/day BID, 2 - <12 yrs, 3TC + ZDV	NR	NR	4.288 (3646-5045)	NR
			8 mg/Kg/day BID, 2 - <12 yrs, 3TC + ZDV + ddI	NR	NR	4.632 (3.715-5755)	NR
			8 mg/Kg/day BID, >12 - < 18yrs, 3TC alone	NR	NR	7.017 (5.641-8.713)	NR
			8 mg/Kg/day>12 - < 18yrs, 3TC alone + ZDV	NR	NR	6.627 (4999 – 8759)	NR
NUCB2001	HIV-positive asymptomatic and mild ARC patients/105	Oral, Capsules/Tablets	**Day 1** (BID dosing on an empty stomach, 1 hour before eating)				
			0.5 mg/kg/day (n=12)	0.19 [i] (0.15, 0.24)	0.8 (0.5-2.0)	0.51 [i] (0.4, 0.60)	2.30 [i] (2, 2.8)
			1.0 mg/kg/day (n=16)	0.32 [i] (0.26, 0.39)	1.0 (0.5-3.0)	0.94 [i] (0.81, 1.09)	2.6 [i] (2.2, 3.1)
			2.0 mg/kg/day (n=15)	0.62 [i] (0.50, 0.76)	1.0 (0.5-4.0)	1.93 [i] (1.66, 2.24)	2.2 [i] (1.9, 2.6)
			4.0 mg/kg/day (n=14)	1.17 [i] (0.94, 1.44)	1.5 (0.8-2.0)	3.53 [i] (3.02, 4.13)	2.1 [i] (1.8, 2.5)
			8.0 mg/kg/day (n=15)	3.01 [i] (2.45, 3.70)	1.5 (0.5-3.0)	8.88 [i] (7.64, 10.33)	2.1 [i] (1.8, 2.5)
			12 mg/kg/day (n=15)	3.94 [i] (3.21, 4.85)	1.0 (0.5-2.0)	12.78 [i] (10.99, 14.86)	2.4 [i] (2.1, 2.9)
			20 mg/kg/day (n=11)	7.3 [i] (5.7-9.2)	1.0 (0.5-2.0)	22.58 [i] (18.93, 26.93)	2.5 [i] (2.1, 3.1)
			Day 15 (BID dosing on				

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
			an empty stomach, 1 hour before eating) 0.5 mg/kg/day (n=10) 1.0 mg/kg/day (n=11) 2.0 mg/kg/day (n=17) 4.0 mg/kg/day (n=6) 8.0 mg/kg/day (n=12) 12 mg/kg/day (n=8) 20 mg/kg/day (n=5)	 0.24 [i] (0.18, 0.31) 0.34 [i] (0.27, 0.44) 0.98 [i] (0.71, 1.35) 1.47 [i] (1.04, 2.08) 2.79 [i] (2.18, 3.55) 3.78 [i] (2.80, 5.10) 6.84 [i] (4.69, 9.98)	 0.8 (0.5-2.0) 0.8 (0.5-1.5) 1.0 (0.5-2.0) 1.3 (0.5-1.5) 1.0 (0.5-2.0) 1.0 (0.8-2.0) 1.0 (0.8-2.0)	 0.67 [i] (0.53, 0.83) 1.12 [i] (0.90, 1.38) 3.37 [i] (2.58, 4.39) 4.63 [i] (3.48, 6.17) 9.42 [i] (7.69, 11.54) 14.64 [i] (11.43, 18.77) 22.81 [i] (16.66, 31.22)	 3.50 [i] (2.8, 4.3) 3.00 [i] (2.4, 3.7) 3.30 [i] (2.5, 4.3) 3.20 [i] (2.4, 4.3) 2.70 [i] (2.2, 3.3) 3.50 [i] (2.7, 4.5) 2.60 [i] (1.9, 3.6)
NUCB1002	Patients with impaired hepatic function	Oral/tablets	3TC 300 mg single dose (fasted)/(n=8) (healthy) 3TC 300 mg single dose (fasted)/(n=8) (moderate impaired hepatic function) 3TC 300 mg single dose (fasted)/(n=8) (severe impaired hepatic function)	2.64 (2.06-3.39) 2.88 (1.97-4.21) 3.14 (2.51-3.92)	1.31 [j] (0.87) 1.44 (0.82) 1.38 (1.19)	11.77 (10.41-13.3) 11.39 (8.75-14.82) 12.79 (11.39-14.36)	5.42 (4.64-6.32) 5.73 (5.00-6.57) 5.79 (4.89-6.85)
NUCB1003	Healthy subjects and subjects with renal impairment/29	Oral/hard gelatine capsules	Healthy Group (normal renal function): 3TC 300 mg (3 x 100 mg) single dose (fasted)/-	3.80 (3.04-4.75)	1.0 (0.5, 1.6)	15.58 (13.41-18.10)	11.7 (9.3, 14.6)

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
			(n=9) Group 1 (mild/moderate Impairment): 3TC 300 mg (3 x 100 mg) single dose (fasted)/-(n=8) Group 2 (severe Impairment, non-dialysis): 3TC 100 mg (1 x 100 mg) single dose (fasted), –(n=6) Group 3 (severe Impairment, inter-dialysis): 3TC 100 mg (fasted)/(n=6) Group 3 (severe Impairment, intra-dialysis): 3TC 100 mg (fasted)/ (n=6)	5.43 (4.47-6.60) 4.55 (3.65-5.68) 4.93 (3.37-7.22) 3.97 (2.79-5.65)	1.8 (1.0, 4.0) 2.8 (1.0, 4.0) NR NR	42.78 (34.63-52.84) 79.82 (60.72-104.93) 80.21 (60.71-105.97) 60.74 (40.19-91.81)	9.9 (9.2, 10.6) 14.8 (13.2, 16.4) 15.3 (13.3, 17.7) 18.2 (14.4, 22.9)
NUCB1009	Healthy male and female Chinese subjects/24	Oral tablets	100 mg single dose (n=24) 100 mg repeat dose for 7 days (n=24)	1.37[k] (0.41) 1.44[k] (0.39)	0.8926[k] (0.3086) 0.8267[k] (0.3513)	4.37[k] (0.92) 4.45[k] (0.92)	6.35[k] (2.38) 6.85[k] (1.68)
NUCA1001	HIV-infected patients/ 13	Oral, capsule	3TC 50 mg (2 x 25 mg) single dose, capsules/(n=12)				

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
			Fasted Fed	0.513 ±0215 [k] 0.273 ± 0.056 [k]	0.88 ± 0.25 [k] 3.15 + 1.27 [k]	1.677 ± 0.427 [k] 1.548 ± 0.249 [k]	3.3 ± 0.3 [k, l] 3.0 ± 0 [k, m]
NUCB1001	HIV positive patients/ 20	Oral and IV	0.25 mg/kg IV (n=4) (single dose, fasted)	0.38 (0.27, 0.54)	NA	0.75 (0.66, 0.86)	2.60 (1.65, 4.08)
			1 mg/kg IV (n=4) (single dose, fasted)	1.61 (1.40, 1.85)	NA	3.27 (2.42, 4.43)	2.31 (1.64, 3.25)
			2 mg/kg IV (n=4) (single dose, fasted)	3.30 (3.02, 3.60)	NA	6.65 (5.21, 8.48)	2.47 (2.18, 2.80)
			4 mg/kg IV (n=4) (single dose, fasted)	5.60 (4.71, 6.65)	NA	12.79 (9.52, 17.19)	3.11 (1.11, 8.75)
			8 mg/kg IV (n=4) (single dose, fasted)	10.48 (8.36, 13.15)	NA	22.58 (17.54, 29.07)	2.59 (2.25, 2.99)
			0.25 mg/kg PO (n=4) (single dose, fasted)	0.227 (0.85)	NR	0.70 (0.09)	1.904 (NR)
			1 mg/kg PO (n=4) (single dose, fasted)	1.26 (0.35) [k]	NR	3.18 (0.67) [k]	1.615 (NR)
			2 mg/kg PO (n=4) (single dose, fasted)	1.73 (0.61) [k]	NR	4.57(0.20) [k]	1.188 (NR)
			4 mg/kg PO (n=4) (single dose, fasted)	2.65 (0.39) [k]	NR	9.23(1.47) [k]	1.916 (NR)
			8 mg/kg PO (n=4)	5.82 (0.76) [k]	NR	17.95 (2.05) [k]	1.910 (NR)
NUCB2020	HBV-infected asymptomatic patients/53	Oral/solution Oral/tablets	Children (2-6, 7-12yr): 0.35 mg/kg BID Day 1 (n=7)	0.26 (0.19-0.35)	0.51 (0.51-1.02)	0.68 (0.50-0.90)	2.09 (1.92-2.27)

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
			Day 28 (n=7)	0.29 (0.17-0.49)	1.02 (0.51-2.03)	NR	3.40 (2.87-4.03)
			1.5 mg/kg BID Day 1 (n=12)	0.97 (0.75-1.25)	0.51 (0.51-2.03)	2.35 (2.02-2.74)	2.16 (1.95-2.39)
			Day 28 (n=12)	0.80 (0.64-0.99)	1.02 (0.51-2.03)	NR	2.95 (2.12-4.11)
			4 mg/kg BID Day 1 (n=11)	2.17 (1.86-2.55)	0.51 (0.51-4.07)	6.54 (5.91-7.24)	1.95 (1.75-2.17)
			Day 28 (n=11)	2.76 (2.34-3.26)	1.02 (0.51-1.02)	NR	2.52 (2.14-2.97)
			3 mg/kg QD Day 1 (n=11)	1.57 (1.17-2.11)	0.51 (0.51-2.03)	4.16 (3.34-5.17)	2.14 (1.78-2.58)
			Day 28 (n=11)	1.86 (1.44-2.39)	0.51 (0.51-2.03)	NR	7.56 (5.13-11.15)
			Adolescents (1[redacted]-1[redacted] yrs): 100 mg tablet Day 1 (n=12)	1.39 (1.07-1.80)	1.02 (0.51-4.07)	4.67 (4.07-5.29)	2.20 (2.03-2.39)
			Day 28 (n=12)	1.50 (1.23-1.82)	1.02 (0.51-2.03)	NR	6.45 (4.75-8.77)
NUCB4001	Asymptomatic HIV-infected subjects/20	Oral/Tablets	Treatment A 150 mg BID repeat dose (Day 14 fasted PK)/ (n=10)	1.43 [i] (1.143-1.797)	1.0 (1.0-2.0)	6.13 (AUC0-12) [i] (5.05-7.44)	12.4 [i] (10.8-14.3)

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
			Treatment B 300 mg BID repeat dose (Day 14 fasted PK)/ (n=10)	1.62 [i] (1.290-2.029)	1.0 (1.0-2.0)	6.46 (AUC0-12) [i] (5.32-7.83)	11.6 [i] (10.1-13.3)
NUCB4001 (Triphosphate units are pmol.h/10^6 cells) [g]	Asymptomatic HIV-infected subjects/20	Oral/Tablets	150 mg BID repeat dose/(n=10)	2.8 [k] (1.3)	10.2 (7.3)	17.7 (AUC0-12) [k] (6.3)	16.1 [k] (7.7)
			300 mg BID repeat dose (Day 14 fasted PK) /(n=10)	3.4 [k] (1.8)	8.0 (5.6)	25.6 (AUC0-12) [k] (15.1)	19.0 [i] (10.7)
204857	Healthy subjects/16	Oral/Solution	3TC 300 mg single dose (fasted)/(n=16) (Treatment A)	3.34 (2.79-4.01)	0.75 (0.5-1.5)	13.19 (11.73-14.84)	13.87 (12.4-15.5)
			3TC 300 mg single dose + SBT 3.2 g (fasted) /(n=16) (Treatment B)	2.42 (2.04-2.87)	1.0 (0.5-1.5)	11.27 [n] (9.99-12.72)	18.96 [n] (15.1-23.8)
			3TC 300 mg single dose + SBT 10.2 g (fasted) /(n=16) (Treatment C)	1.6 (1.38-1.84)	1.0 (0.5-2.5)	8.93 (7.95-10.03)	21.25 (16.7-27.0)
			3TC 300 mg single dose + SBT 13.4 g (fasted) /(n=16) (Treatment D)	1.52 (1.29-1.78)	1.26 (0.5-3.0)	8.60 [o] (7.45-9.93)	17.33 [o] (13.1-22.9)
CNAA1002	HIV infected patients	Oral/Single doses/fasted ABC 100 mg capsules ZDV 100 mg capsules	3TC 150 mg alone	1.51 (1.27-1.76)	0.75 (0.50-1.50)	5.34 (4.43-6.26)	3.26 (2.92-3.60)
			3TC 150 mg + ABC 600 mg	0.97 (0.72-1.21)	2.00 (1.03-2.50)	4.52 (3.60-5.43)	3.54 (3.20-3.87)

				Parameter			
Study/Location of Study Report	**Population/No. of Subjects Randomized/ Entered**	**Route of Administration/ Dosage Form**	**Dose/No. Of Subjects**	**Cmax (μg/ml)**	**tmax[b] (h)**	**AUC (0-∞)[c] (μg.h/mL)**	**t½ (h)**
		3TC 150 mg tablets	3TC 150 mg + ZDV 300 mg	1.38 (1.13-1.63)	1.00 (0.50-1.50)	5.23 (4.31-6.14)	3.23 (2.90-3.57)
			3TC 150 mg + ABC 600 mg + ZDV 300 mg	0.96 (0.72-1.21)	1.50 (0.75-2.50)	4.77 (3.85-5.68)	3.58 (3.24-3.92)

a. Data are geometric mean (95% CI) unless otherwise stated
b. Tmax is median (range)
c. AUC (0-∞) unless otherwise stated; AUC(0-tau) for repeat dose steady-state values
d. Geometric mean (%CVb)
e. PK parameter estimation for Subject [redacted] (Treatment A, Period 2) did not conform to the prescribed criteria for acceptance (i.e., lambda_z time duration <2x the calculated t1/2 and >20% AUC(0-∞) extrapolated), therefore it was excluded from analysis of AUC(0-∞), CL/F, and t1/2; n=73
f. Sensitivity analysis conducted by including Subject [redacted] Treatment C, Period 1 data
g. The units for Cmax and AUC of 3TC-TP are different from those for 3TC (pmol.h/10^6 cells)
h. Mean (SD)
i. Geometric least square mean (95% CI)
j. Mean (CV%)
k. Arithmetic mean±SD
l. Harmonic mean (t½) = 3.3hr
m. Harmonic mean (t½) = 2.9hr
n. N = 14
o. N = 13

3TC = Lamivudine; AIDS = Acquired immune deficiency syndrome; ARC = AIDS-related complex; BA = Bioavailability; BID = Twice daily; DB = Double blind; HBV = Hepatitis B virus; HIV = Human immunodeficiency virus; IV = Intravenous; NA = Not applicable; NR = Not reported; QD = Once daily; PO = Orally; TMP/SMX = Trimethoprim + sulfamethoxazole; ZDV = Zidovudine; SBT = Sorbitol

Appendix Table 8 Summary of Lamivudine Pharmacokinetic Results for Pediatric Clinical Pharmacology Studies that Evaluated Once Daily Dosing[e]

Protocol No. Study Status	Study Design and Objectives	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Population Treatment Details Drug/Dose/Form (Strength)/Route/ Frequency/Duration	Statistic	Lamivudine (3TC) Weight-Normalized Dose and PK Parameter			
					Dose (mg/kg)	AUC(0-24) (μg·h/mL)	Cmax (μg/mL)	CL/F/kg (L/h/kg)
PENTA 15 (COL104929) Complete	Two-period, single sequence, crossover, open-label, pediatric PK study of once- versus twice-daily 3TC and ABC in HIV-1–infected infants and children aged 3-36 months	17 (10 M/7 F) Median (range) age: 23.2 months ([redacted], [redacted]) HIV-1–infected	Overall 3TC/4 mg per kg/solution (10 mg/mL)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	17 NA NA NA 4.04 [a] (3.87, 4.13) [a]	17 NA NA 39 9.48 (7.89, 11.40)	16 NA NA 34 1.05 (0.88, 1.26)	17 NA NA 40 0.79 (0.65, 0.96)
			Overall 3TC/8 mg per kg/solution (10 mg/mL)/oral/ once daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	17 NA NA NA 8.02 [a] (7.77, 8.13) [a]	17 NA NA 32 8.66 (7.46, 10.06)	16 NA NA 25 1.87 (1.65, 2.13)	17 NA NA 28 0.86 (0.74, 1.01)
			3-12 mo 3TC/4 mg per kg/solution (10 mg/mL)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	4 NA NA NA 4.02 [a] (3.83, 4.05) [a]	4 NA NA 48 9.24 (4.66, 18.32)	4 NA NA 21 1.04 (0.76, 1.41)	4 NA NA 48 0.79 (0.36, 1.73)
			3-12 mo 3TC/8 mg per kg/solution (10 mg/mL)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	4 NA NA NA 7.78 [a] (7.58, 7.92) [a]	4 NA NA 33 10.31 (6.26, 16.96)	4 NA NA 23 2.37 (1.57, 3.57)	4 NA NA 34 0.72 (0.42, 1.26)

Protocol No. Study Status	Study Design and Objectives	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Population Treatment Details Drug/Dose/Form (Strength)/Route/ Frequency/Duration	Statistic	Lamivudine (3TC) Weight-Normalized Dose and PK Parameter			
					Dose (mg/kg)	AUC(0-24) (μg·h/mL)	Cmax (μg/mL)	CL/F/kg (L/h/kg)
			12-24 mo 3TC/4 mg per kg/solution (10 mg/mL)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	6 NA NA NA 4.18 [a] (3.83, 4.32) [a]	6 NA NA 29 9.54 (6.71, 13.57)	6 NA NA 36 1.22 (0.82, 1.80)	6 NA NA 46 0.80 (0.55, 1.18)
			12-24 mo 3TC/8 mg per kg/solution (10 mg/mL)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	6 NA NA NA 8.02 [a] (7.56, 8.84) [a]	6 NA NA 21 7.13 (5.84, 8.71)	6 NA NA 15 1.71 (1.46, 2.02)	6 NA NA 15 1.05 (0.88, 1.25)
			24-36 mo 3TC/4 mg per kg/solution (10 mg/mL)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	7 NA NA NA 3.88 [a] (3.87, 4.13) [a]	7 NA NA 46 9.58 (6.65, 13.78)	6 NA NA 35 0.92 (0.62, 1.35)	7 NA NA 38 0.77 (0.53, 1.12)
			24-36 mo 3TC/8 mg per kg/solution (10 mg/mL)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	7 NA NA NA 8.03 (7.77, 8.13) [a]	7 NA NA 30 9.27 (7.11, 12.09)	6 NA NA 20 1.75 (1.39, 2.20)	7 NA NA 31 0.81 (0.61, 1.07)

Protocol No. Study Status	Study Design and Objectives	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Population Treatment Details Drug/Dose/Form (Strength)/Route/ Frequency/Duration	Statistic	Lamivudine (3TC) Weight-Normalized Dose and PK Parameter			
					Dose (mg/kg)	AUC(0-24) (μg·h/mL)	Cmax (μg/mL)	CL/F/kg (L/h/kg)
PENTA 13 (EPV40002) Complete	Two-period, single sequence crossover, open-label pediatric PK study of once- versus twice-daily 3TC and ABC in HIV-1–infected children, age 2-12 y	19 (9 M/10 F) Median (range): 5.8 y ([redacted], [redacted]) HIV-1–infected	Overall 3TC/4 mg per kg/solution (10 mg/mL) or tablets (150 mg)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (90% CI)	19 NA NA NA 4.1 [a] (4.0, 4.3) [a]	19 NA NA NA 8.88 (7.67, 10.28)	19 NA NA NA 1.11 (0.96, 1.29)	19 NA NA NA 0.90 (0.78, 1.04)
			Overall 3TC/8 mg per kg/solution (10 mg/mL) or tablets (150 mg)/oral/ once daily/4 weeks	N Mean SD %CV Geo Mean (90% CI)	19 NA NA NA 8.2 [a] (7.8, 8.4) [a]	19 NA NA NA 9.80 (8.64, 11.12)	19 NA NA NA 2.09 (1.80, 2.42)	19 NA NA NA 0.80 (0.70, 0.92)
			≥2-6 y 3TC/4 mg per kg/solution (10 mg/mL) or tablets (150 mg)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (90% CI)	10 NA NA NA 4.1[b] (3.6, 4.4)[b]	10 NA NA NA 7.60 (6.12, 9.45)	10 NA NA NA 0.94 (0.78, 1.13)	10 NA NA NA 1.09 (0.89, 1.34)

Protocol No. Study Status	Study Design and Objectives	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Population Treatment Details Drug/Dose/Form (Strength)/Route/ Frequency/Duration	Statistic	Lamivudine (3TC) Weight-Normalized Dose and PK Parameter			
					Dose (mg/kg)	AUC(0-24) (μg·h/mL)	Cmax (μg/mL)	CL/F/kg (L/h/kg)
			≥2-6 y 3TC/8 mg per kg/solution (10 mg/mL) or tablets (150 mg)/oral/ once daily/4 weeks	N Mean SD %CV Geo Mean (90% CI)[c]	10 NA NA NA 8.3[b] (7.4, 8.5)[b]	10 NA NA NA 8.80 (7.43, 10.43)	10 NA NA NA 1.72 (1.48, 1.99)	10 NA NA NA 0.92 (0.78, 1.08)
			>6-<13 y 3TC/4 mg per kg/solution (10 mg/mL) or tablets (150 mg)/oral/ twice daily/4 weeks	N Mean SD %CV Geo Mean (90% CI)[c]	9 NA NA NA 4.0[b] (2.5, 4.9)[b]	9 NA NA NA 10.55 (8.82, 12.63)	9 NA NA NA 1.34 (1.08, 1.67)	9 NA NA NA 0.73 (0.63, 0.85)
			>6-<13 y 3TC/8 mg per kg/solution (10 mg/mL) or tablets (150 mg)/oral/ once daily/4 weeks	N Mean SD %CV Geo Mean (90% CI)[c]	9 NA NA NA 7.9[b] (4.9, 9.3)[b]	9 NA NA NA 11.04 (9.06, 13.45)	9 NA NA NA 2.59 (2.04, 3.28)	9 NA NA NA 0.69 (0.55, 0.87)

Protocol No. Study Status	Study Design and Objectives	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Population Treatment Details Drug/Dose/Form (Strength)/Route/ Frequency/Duration	Statistic	Lamivudine (3TC) Weight-Normalized Dose and PK Parameter			
					Dose (mg/kg)	AUC(0-24) (μg·h/mL)	Cmax (μg/mL)	CL/F/kg (L/h/kg)
ARROW PK Substudy Part 1 (COL105677) Complete	Two-period, crossover, open-label, pediatric PK Substudy Part 1 of once- versus twice-daily 3TC, ABC scored tablets in HIV-1-infected African children aged 3-12 years	35 (14 M/21 F) Mean (±SD): 7.02 y (±2.06) HIV-1–infected	Overall 3TC/WHO weight band-based dosing[c]/scored tablets (150 mg)[d]/oral/ twice daily/36 weeks	N Mean SD %CV Geo Mean (95% CI)	35 NA NA NA 5.0[b] (4, 8)[b]	35 12.65 4.82 33 11.97 (10.70, 13.38)	35 1.93 0.83 38 1.80 (1.59, 2.04)	35 0.83 0.24 32 0.79 (0.71, 0.88)
			Overall 3TC/WHO weight band-based dosing[c]/scored tablets (150 mg)[d]/oral/ once daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	35 NA NA NA 9.6[b] (7, 11)[b]	35 13.98 5.46 41 12.99 (11.35, 14.86)	35 3.43 1.38 42 3.17 (2.76, 3.64)	35 0.76 0.27 36 0.72 (0.64, 0.81)
			3-6 y 3TC/WHO weight band-based dosing[c]/scored tablets (150 mg)[d]/oral/ twice daily/36 weeks	N Mean SD %CV Geo Mean (95% CI)	17 NA NA NA 4.7[b] (4, 7)[b]	17 11.63 3.93 29 11.14 (9.61, 12.91)	17 1.86 1.03 44 1.69 (1.36, 2.09)	17 0.87 0.22 29 0.84 (0.72, 0.97)

Protocol No. Study Status	Study Design and Objectives	No. of Subjects Sex M/F Mean Age (Range) Subject Type	Population Treatment Details Drug/Dose/Form (Strength)/Route/ Frequency/Duration	Statistic	Lamivudine (3TC) Weight-Normalized Dose and PK Parameter			
					Dose (mg/kg)	AUC(0-24) (μg·h/mL)	Cmax (μg/mL)	CL/F/kg (L/h/kg)
			3-6 y 3TC/WHO weight band-based dosing[c]/scored tablets (150 mg)[d]/oral/ once daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	17 NA NA NA 9.4[b] (7, 11)[b]	17 13.03 4.93 36 12.29 (10.29, 14.68)	17 3.19 1.25 35 3.01 (2.52, 3.59)	17 0.79 0.24 33 0.75 (0.64, 0.88)
			7-12 y 3TC/WHO weight band-based dosing[c]/scored tablets (150 mg)[d]/oral/ twice daily/36 weeks	N Mean SD %CV Geo Mean (95% CI)	18 NA NA NA 6.3[b] (4, 8)[b]	18 13.62 5.46 36 12.80 (10.75, 15.24)	18 2.00 0.60 32 1.91 (1.64, 2.23)	18 0.79 0.26 34 0.75 (0.64, 0.88)
			7-12 y 3TC/WHO weight band-based dosing[c]/scored tablets (150 mg)[d]/oral/ once daily/4 weeks	N Mean SD %CV Geo Mean (95% CI)	18 NA NA NA 9.6[b] (7, 11)[b]	18 14.88 5.92 46 13.69 (11.02, 17.00)	18 3.66 1.49 48 3.34 (2.66, 4.19)	18 0.74 0.29 39 0.69 (0.57, 0.83)

3TC = lamivudine; ABC = abacavir; AUC(0-24) = area under the concentration-time curve from time 0 to 24 hours; CI = confidence interval; CL/F/kg = apparent clearance following oral dosing normalized for body weight; Cmax = maximum observed concentration; CV = coefficient of variation; F = females; HIV-1 = human immunodeficiency virus type 1; M = males; NA = not available; PK = pharmacokinetic; SD = standard deviation; WHO = World Health Organization.

a. Median (interquartile range) presented rather than geometric mean (95% confidence interval).

b. Median (range) presented rather than geometric mean (95% confidence interval).

c. WHO dosage regimens for lamivudine:

12-20 kg: 75 mg (one-half tablet) twice daily or 150 mg (1 tablet) once daily

>20-25 kg: 150 mg (1 tablet) in the AM + 75 mg (one-half tablet) in the PM or 225 mg (1 and one-half tablets) once daily

>25 kg: 150 mg (1 tablet) twice daily or 300 mg (2 tablets) once daily

*Subjects >25-30 kg receiving COMBIVIR (lamivudine/zidovudine) were dosed 150/300 mg (1 tablet) in the AM + 75/150 mg (one-half tablet) in the PM or 225/450 mg (1 and one-half tablets) once daily.

d. Lamivudine was administered either as Epivir 150-mg scored tablet or COMBIVIR (lamivudine/zidovudine) 150-/300-mg scored tablet.

e. Pediatric PK data from the original twice daily dosing studies (NUCA2002, NUCA2005, NUCB2020) can be found in Appendix Table 7

Appendix Table 9 Summary of Pharmacokinetic Parameters of Co-administered Drugs with Dolutegravir

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter [a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg/mL)
ING111322	Healthy adult/ 32	MDZ/ Oral Tablet	3 mg/ 10	Single dose	NR	NR	0.0163 (23)[b]	NR	NR
			3 mg (+25 mg DTG)/ 10	Single dose (DTG once daily x 10 days)	NR	NR	0.0154 (41)[b]	NR	NR
ING111405	Healthy adult/ 31	LPV/ Oral Tablet	400 mg (+100 mg RTV + 30 mg DTG)/ 15	BID (RTV BID, DTG once daily) x 14 days (mod. fat meal)	11.5 (22)	NR	95.8 (25)	NR	4.52 (43)
		DRV/ Oral Tablet	600 mg (+100 mg RTV + 30 mg DTG)/ 15	BID (RTV BID, DTG once daily) x 14 days (mod. fat meal)	5.811 (23)	NR	46.5 (29)	NR	2.190 (47)
		RTV/ Oral Tablet	100 mg (+400 mg LPV + 30 mg DTG)/ 15	BID (LPV BID, DTG once daily) x 14 days (mod. fat meal)	0.884 (36)	NR	4.59 (33)	NR	0.115 (50)
		RTV/ Oral Tablet	100 mg (+600 mg DRV + 30 mg DTG)/ 15	BID (DRV BID, DTG (once daily) x 14 days (mod. fat meal)	0.815 (32)	NR	5.42 (25)	NR	0.202 (34)
ING111603	Healthy adult/ 16	ETV/Oral Tablet	200 mg (+50 mg DTG)/ 15	BID (DTG once daily) x 14 days	1.12 (28)	NR	10.3 (24)	NR	0.638 (24)

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter [a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg/mL)
ING111604	Healthy adult/ 16	TDF/Oral Tablet	300 mg/ 15	Once daily x 7 days	0.274 (34)	1.00 (1.00-2.00)	2.45 (41)	NR	0.0472 (49)
			300 mg (+DTG 50 mg)/ 15	Once daily x 5 days	0.300 (34)	1.00 (1.00-4.03)	2.74 (39)	NR	0.0560 (46)
ING111854	Healthy adult/ 24	ATV/Oral Tablet	400 mg (+100 mg RTV + 30 mg DTG)/ 12	Once daily x 14 days (mod. fat meal)	5.39 (26)	NR	53.08 (31)	NR	1.08 (42)
			400 mg (+ 30 mg DTG)/ 12	Once daily x 14 days (mod. fat meal)	4.85 (42)	NR	27.49 (45)	NR	0.19 (84)
ING111855	Healthy adult female/ 16	NGMN (as Ortho-Cyclen)/ Oral Tablet	0.25 mg (+ 0.035 mg EE +50 mg DTG)/ 15 Analyte: NGMN	Once daily (DTG BID) x 10 days	0.00142 (18)	1.50 (1.0-2.5)	0.0138 (16)	22.02 (19)	NR
		NGMN (as Ortho-Cyclen)/ Oral Tablet	0.25 mg (+ 0.035 mg EE)/ 15 Analyte: NGMN	Once daily x 10 days	0.00159 (30)	1.00 (1.0-3.0)	0.0141 (25)	22.29 (32)	NR
		EE (as Ortho-Cyclen)/ Oral Tablet	0.035 mg (+0.25 mg NGMN +50 mg DTG)/ 15	Once daily (DTG BID) x 10 days	0.000100 (22)	1.00 (0.5-2.5)	0.000952 (19)[c]	14.39 (19)[c]	NR
		EE (as Ortho-Cyclen)/ Oral Tablet	0.035 mg (+0.25 mg NGMN)/ 15	Once daily x 10 days	0.000101 (25)	1.00 (0.5-2.0)	0.000916 (27)	13.60 (24)	NR
ING112934	Healthy adult/ 17	ETV/Oral Tablet	200 mg (+400 mg LPV +100 mg RTV + 50 mg DTG)/ 8	BID (LPV, RTV BID; DTG once daily) x 14 days (mod. fat meal)	0.974 (73)	4.00 (2.00-4.00)	8.834 (79)	NR	0.585 (93)

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter [a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg/mL)
			200 mg (+ 600 mg DRV +100 mg RTV + 50 mg DTG)/ 9	BID (DRV, RTV BID; DTG once daily) x 14 days (mod. fat meal)	0.886 (32)	4.00 (3.00-4.00)	7.691 (34)	NR	0.495 (42)
ING113068	Healthy adult/ 12	FPV/Oral Tablet	700 mg (+100 mg RTV +50 mg DTG)/ 12 Analyte: amprenavir	BID (RTV BID, DTG Once daily) x 10 days	6.34 (28.1)	1.00 (0.50-2.00)	40.9 (35.8)	8.35 (45.9)	1.91 (59.4)
ING114005	Healthy adult/ 12	EFV/Oral Tablet	600 mg (+50 mg DTG)/ 12	Once daily x 14 days	6.02 (40)	NR	84.18 (62)	22.17 (54)	2.41 (80)
			600 mg (+50 mg DTG; CYP2B6*6 subjects)/ 3	Once daily x 14 days	9.50 (27)	NR	173.78 (26)	39.09 (34)	5.85 (25)
			600 mg (+50 mg DTG; CYP2B6*1/*6 subjects)/ 6	Once daily x 14 days	4.52 (17)	NR	55.69 (28)	15.61 (24)	1.45 (40)
ING115697	Healthy adult/ 32	TVR/Oral Tablet	750 mg (+50 mg DTG)/ 15 (except n=10 for t1/2)	q8h (DTG once daily) x 10 days (mod. fat meal)	3.21 (17)	3.00 (2.0-4.0)	19.22 (19)	5.14 (27)	1.75 (26)
ING115698	Healthy adult/ 11	Methadone/Oral Tablet	Individualized doses/ 11 Analyte: R-methadone	Once daily x 3 days	0.150 (81.4)	NR	2.51 (77.9)	NR	0.082 (79.9)
			Individualized doses (+50 mg DTG) / 11 Analyte: R-methadone	Once daily (DTG BID) x 5 days	0.145 (78.5)	NR	2.39 (77.7)	NR	0.078 (80.6)

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter [a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg/mL)
			Individualized doses/ 11 Analyte: S-methadone	Once daily x 3 days	0.188 (91.4)	NR	2.79 (90.3)	NR	0.0838 (97.3)
			Individualized doses (+50 mg DTG) / 11 Analyte: S-methadone	Once daily (DTG BID) x 5 days	0.195 (82.3)	NR	2.81 (85.4)	NR	0.0847 (92.7)
			Individualized doses/ 11 Analyte: total methadone	Once daily x 3 days	0.337 (86.5)	NR	5.32 (83.2)	NR	0.166 (86.9)
			Individualized doses (+50 mg DTG) / 11 Analyte: total methadone	Once daily (DTG BID) x 5 days	0.337 (80.1)	NR	5.23 (80.6)	NR	0.164 (84.9)
LAI116181	Healthy adult/ 28	RPV/Oral Tablet	25 mg/ 16 (Cohort 1, Period 2)	Once daily x 11 days (mod. fat meal)	0.148 (29)	4.00 (4.0-6.0)	2.23 (33)	NR	0.0745 (41)
			25 mg (+50 mg DTG)/ 16 (Cohort 1, Period 3)	Once daily x 5 days (mod. fat meal)	0.164 (36)	4.00 (2.0-5.0)	2.37 (34)	NR	0.0905 (48)
201102	Healthy adult/ 12	DCV/Oral Tablet	60 mg/ 12	Once daily x 5 days	1.19 (42.6)	1.01 (1.00, 6.00)	11.4 (47.9)	8.58 (23.2)	0.166 (69.3)
			60 mg (+ DTG 50 mg/ 12	Once daily x 5 days	1.22 (42.2)	1.00 (0.50, 4.00)	11.2 (41.6)	8.42 (29.4)	0.176 (53.8)
201167	Healthy adult/ 15	Metformin/Oral Tablet	500 mg/ 15 (Cohort 1, Period 1)	BID x 5 day (mod. fat meal)s	0.932 (26.2)	4.00 (1.00, 6.00)	6.82 (26.5)	3.97 (18.2)	NR

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter [a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg/mL)
			500 mg/ 14 (+50 mg DTG) (Cohort 1, Period 2)	BID (DTG Once daily) x 7 days (mod. fat meal)	1.55 (22.6)	4.00 (1.00, 6.03)	12.2 (23.1)	4.33 (24.0)	NR
			500 mg/ 14 (Cohort 1, Period 3)	BID x 10 days (mod. fat meal)	0.979 (31.1)	4.00 (1.00, 6.00)	7.55 (28.1)	4.60 (35.8)	NR
			500 mg/ 15 (Cohort 2, Period 1)	BID x 5 days (mod. fat meal)	0.875 (24.3)	4.00 (1.50, 8.00)	6.49 (16.0)[d]	4.27 (26.5)[c]	NR
			500 mg/ 14 (+50 mg DTG) (Cohort 1, Period 2)	BID (DTG Once daily) x 7 days (mod. fat meal)	1.85 (13.1)	4.00 (1.00, 6.00)	15.9 (15.9)	4.89 (19.6)	NR
			500 mg/ 13 (Cohort 1, Period 3)	BID x 10 days (mod. fat meal)	0.872 (14.8)	4.00 (2.00, 8.00)	6.69 (16.4)	4.48 (24.3)[e]	NR

a. Data presented are geometric mean (%CVb) except for tmax where median (range) is presented.
b. Presented as AUC(0-t).
c. N = 14
d. For 1 subject, AUC(0-t) with last observed concentration at 11.93 hr post-dose was used as AUC(0-τ)as there were not enough data points in the terminal phase to estimate AUC(0-τ).
e. PK Parameter could not be calculated for 1 subject

ATV = Atazanavir; BID = Twice daily; DCV = Daclatasvir; DRV = Darunavir; DTG = Dolutegravir; EE = Ethinyl estradiol; EFV = Efavirenz; ETV = Etravirine; FPV=Fosamprenavir; LPV= Lopinavir; NGMN = Norelgestromin/ Norgestimate; MDZ = Midazolam; NR = Not reported; RPV = Rilpivirine; RTV = Ritonavir; TDF = Tenofovir disoproxil fumarate; TVR = Telaprevir

Module 2.7.2.4

Special Studies

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ABBREVIATIONS

3TC	Lamivudine
AAG	α_1-acid glycoprotein
ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
APV	Amprenavir
BID	Twice daily (bis in die)
BVDV	Bovine Viral Diarrhea Virus
C8166	Human T cells
CBMC	Umbilical cord blood mononuclear cells
CCR5	Chemokine receptor 5
CCRF-CEM	Human lymphoblastoid cell line
CD4+	Cluster of differentiation 4
CDC	Centers for Disease and Prevention Control
CI	Confidence Interval
CEM-SS	Human lymphoblastoid cell line
CIP4	Cell line derived from 293T cells
CSR	Clinical study report
CVW	Confirmed Virologic Withdrawal
D4T	Stavudine
DTG	Dolutegravir
DRV/r	Darunavir + ritonavir
EBV	Epstein-Barr virus
EFV	Efavirenz
EVG	Elvitegravir
ETR	Etravirine
FC	Fold Change
FDA	Food and Drug Administration
FPV	Fosamprenavir
FTC	Emtricitabine
g	Gram
GSK	GlaxoSmithKline
GSS	Genotypic susceptibility score
H9	Human T cells
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCMV	Human Cytomegalovirus
HeLa CD4	Human cell line
HEP G2	Human hepatoma cells
HIV-1	Human Immunodeficiency Virus type 1
IC50	50% Inhibitory Concentration
IM9	Human B cell lymphocytic leukemia cell line
IN	Integrase
INI	Integrase Inhibitor
IP	Investigational product

IQR	Interquartile range
ITT-E	Intent to treat exposed
[redacted]	[redacted] Database
LOCFDB	Last observation carried forward, discontinuation=Baseline
LPV	Lopinavir
µg	Microgram
Magi CCR5	Cells obtained through the NIH AIDS Research and Reference Reagent Program
mg	Milligrams
mL	Millilitre
Molt-4	Human T cell lymphocytic leukemia cell line
MT2	Human T cell lymphocytic leukemia cell line
MT4	Human T cell lymphocytic leukemia cell line
M8166	Human T cell lymphocytic leukemia cell line
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
N(t)RTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
OBR	Optimised background regimen
OSS	Overall susceptibility score
PBMC	Peripheral Blood Mononuclear Cells
PDVF	Protocol Defined Virologic Failure
PHIV	Pseudotyped HIV
PI	Protease Inhibitor
PIQ	Phenotypic inhibitory quotient
PSS	Phenotypic susceptibility score
RAP	Reporting and analysis plan
RAL	Raltegravir, Isentress
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
RTV, /r	Ritonavir
SDM	Site Directed Mutant
SPA	Scintillation Proximity Assay
SVW	Suspected Virologic Withdrawal
T-20	Enfuvirtide
TZM-bl	Cells obtained through the NIH AIDS Research and Reference Reagent Program
[redacted]	[redacted] Database
TDF	Tenofovir
TLOVR	Time to Loss of Virological Response
TPV	Tipranavir
U937	Human macrophage cells
UDPS	Ultra-deep pyrosequencing
USA	United States of America
U937	Human monocytic lymphoma cell line
VZV	Varicella Zoster Virus

VO	Virologic Outcomes Population

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1. BACKGROUND AND OVERVIEW OF CLINICAL PHARMACOLOGY

Refer to m2.7.2 as these headings are not relevant to m2.7.2.4.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Refer to m2.7.2 as these headings are not relevant to m2.7.2.4.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

Refer to m2.7.2 as these headings are not relevant to m2.7.2.4.

4. SPECIAL STUDIES

Dolutegravir (DTG) inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle. In vitro data are supportive of DTG's high barrier to resistance. DTG retained activity against a vast majority of 60 RAL resistant site-directed HIV-1 mutants and 6 site directed HIV-2 mutants. Additionally, susceptibilities to DTG and RAL were determined for over 700 RAL resistance clinical isolates with DTG retaining activity <10 FC against >90% of them. DTG was slower to select for resistant mutants during in vitro passage than RAL; the level of DTG fold change in susceptibility in these mutants was less than for RAL. DTG demonstrated slower dissociation from all IN-DNA complexes tested as compared to RAL and elvitegravir, including those with single, double, and up to four residues clinically relevant IN substitutions.

Dolutegravir 50 mg once daily has a higher barrier to resistance in INI-naive patients, as demonstrated in the treatment-experienced (INI-naive) study ING111762 where fewer virologic failures and significantly fewer subjects with treatment emergent INI resistance (in addition to less treatment-emergent resistance to the background regimens) were observed when compared with RAL. Data from three studies (ING113086, ING114467, and ING114915) including over 2000 treatment-naive patients are also supportive of DTG's higher barrier to resistance, given that no subjects on the DTG regimen developed resistance to either the INI or the background NRTIs, whereas resistance to both the third agent and the background NRTIs was observed in both the RAL and EFV-based comparator arms of ING113086 and ING114467, respectively.

4.1. Nonclinical Virology - Dolutegravir

Dolutegravir (DTG) inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle.

Dolutegravir has low nM activity against wild type HIV-1 and HIV-2 in a variety of cells lines, regardless of subtype. DTG has little activity against non-HIV viruses. Human

serum causes approximately 75-fold increase in DTG IC50 against HIV-1. DTG is additive or synergistic when assayed in combination with other antiretroviral agents.

When HIV-1 Strain IIIB was passaged in the presence of DTG for 112 days, viruses with a 4.1-fold maximum increase in IC50 and S153Y or S153F substitutions in the integrase gene were observed. Passage of the wild type HIV-1 NL432 in the presence of 6.4 nM DTG selected for E92Q (FC=3.1) and G193E (FC=3.2) substitutions in the IN region on Day 56. Passage of HIV-1 NL432 with Q148H, Q148K, or Q148R RAL resistant mutations resulted in selection of additional mutations and an increase in DTG FC relative to wild type. Passage of HIV-1 NL432 with E92Q, Y143C, Y143R or N155H RAL resistant mutations did not lead to additional substitutions. Passage of HIV-1 subtypes B, and A/G in TZM-bl cells selected for integrase mutation R263K.

Comparative susceptibilities to DTG and raltegravir (RAL) were obtained from 60 RAL resistant site directed HIV-1 mutants and 6 site directed HIV-2 mutants. DTG retained activity against a vast majority of these mutants, and had similar activity for equivalent mutants for both HIV-1 and HIV-2. Additionally, susceptibilities to DTG and RAL were determined for over 700 RAL resistant clinical isolates, with DTG retaining activity <10 FC against >90% of them.

Evaluation of ~1000 RAL- resistant isolates from [redacted] clinical isolate library collected from [redacted] to [redacted] demonstrated a decreasing proportion of Q148+≥2 pathway isolates over time. The derived mutational group Q148+≥2 included the subset of key RAL-associated resistance mutations of L74I, E138A/K/T, G140A/C/S.

The dissociation of DTG, RAL, and EVG from wild type and mutant IN proteins complexed with DNA was investigated to obtain a better understanding of INI dissociation kinetics. DTG demonstrated slower dissociation from all IN-DNA complexes test, including those with single, double, and up to four residues clinically relevant IN substitutions; these studies provide a mechanism-based explanation for DTG's different in vitro and clinical profile.

Clonal analyses provided information that the INI-associated resistance mutations reside on the same subset of viral genomes and that this accumulation of INI-associated resistance mutations results in the reduction of DTG susceptibility. Polymorphisms at the most variable positions in wild type IN do not reduce susceptibility to DTG.

4.1.1. Listing of in vitro Virology Non-Clinical Studies

A series of in vitro studies have been conducted to investigate the virology of DTG. A listing of these studies is provided in Table 1.

Table 1 List of Virology (Primary Pharmacodynamic) Non-Clinical Studies Performed with DTG

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)
Antiviral mechanistic study using quantitative PCR	MT-4 cells	In vitro	B	No	[redacted]	RH2010/00018/00
Anti-HIV activity in peripheral blood mononuclear cells (PBMCs)	Human PBMCs	In vitro	B	No	GSK and [redacted]	RH2007/00071/00 and RH2007/00116/00
Antiviral activity in tissue culture cells	Human MT-4 and CIP-4 cells	In vitro	B	No	GSK and [redacted]	RH2007/00071/00 and RH2007/00116/00
Integrase inhibition in strand transfer assays	Recombinant HIV integrase	In vitro	B	No	GSK and [redacted]	RH2007/00071/00 and RH2007/00116/00
Anti-HIV activity in the presence of human serum and purified human serum proteins	Human MT-4 and CIP-4 cells	In vitro	B	No	GSK and [redacted]	RH2007/00071/00 and RH2007/00116/00
Anti-HIV activity in combination with other antiviral agents[a]	MT-4 cells	In vitro	A	No	GSK	RH2009/00002/00
Anti-HIV activity in combination with maraviroc	Magi-CCR5 cells	In vitro	A	No	[redacted]	RH2009/00009/00
Evaluation of cytotoxicity in antiviral assays	Human MT-4 and CIP-4 cells	In vitro	B	No	GSK and [redacted]	RH2007/00071/00 and RH2007/00116/00
Evaluation of cytotoxicity in human cell lines and peripheral blood lymphocytes (PBMCs)	Human leukemic B- and T-cells lines and PBMCs	In vitro	B	No	GSK	RH2007/00036/00
Testing of GSK1349572A Against a Range of Viruses		In vitro	A	No	[redacted]	2011N113854_00
Dissociation from integrase-DNA complexes	Wildtype and mutant integrase protein	In vitro	B	No	GSK	2011N114191_00
Integrase inhibitor susceptibility of multiple clinical isolates of HIV-1	293 cells	In vitro	A	No	[redacted]	RH2007/00090/00

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)
Anti-HIV activity against a panel of HIV-1 and HIV-2 isolates	Human PBMC and MDM cells	In vitro	A	No	[redacted]	RH2008/00134/00
Anti-HIV activity against protease inhibitor (PRI)-resistant strains	MT-4 cells	In vitro	A	No	[redacted]	RH2008/00141/00
Anti-HIV activity against reverse transcriptase inhibitor (RTI)-resistant strains	HeLa-CD4 cells	In vitro	A	No	[redacted]	RH2008/00142/00
Anti-HIV activity against integrase inhibitor resistant HIV-1 strains	HeLa-CD4 cells	In vitro	A	No	[redacted]	RH2007/00115/00
Anti-HIV activity of RSC-364735 against integrase inhibitor resistant HIV-1 strains	HeLa-CD4 cells	In vitro	A	No	[redacted]	RH2005/00088/00
Anti-HIV activity against raltegravir-resistant strains	HeLa-CD4 cells	In vitro	A	No	[redacted]	RH2008/00143/00
Anti-HIV activity against raltegravir-resistant HIV-2 strains	M8166	In vitro	A	No	[redacted]	2012N141511_00
Anti-HIV activity against integrase site directed mutant strains and resistant clinical isolates	293 cells	In vitro	A	No	[redacted]	RH2009/00010/00
Isolation of GSK1349572-resistant HIV-1 mutants	MT-2 cells	In vitro	A	No	[redacted]	RH2007/00119/00
Isolation of GSK1349572-resistant mutants from integrase inhibitor resistant HIV-1 strains	MT-2 cells	In vitro	A	No	[redacted]	RH2008/00144/00
Isolation of GSK1349572-resistant mutants	HeLa-CD4 cells	In vitro	A	No	[redacted]	RH2010/00017/00
Activity against 700 raltegravir resistant clinical isolates	293 cells	In vitro	A	No	[redacted]	2012N146158_00
Characterization of DTG resistance in the raltegravir resistance clinical isolation population	293 cells	In vitro	A	No	[redacted]	2012N152930_00

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)
Dissociation from integrase-DNA complexes with various substitutions including combinations observed during Viking	Wildtype and mutant integrase protein	In vitro	B	No	GSK	2012N145179_00
Minority species analysis of samples from antiretroviral experienced, raltegravir resistant subjects in ING112961	Ultradeep pyrosequencing, clonal analysis	In vitro		No	GSK	2012N151522_00
Isolation of GSK1349572 Resistant Mutants from Integrase Inhibitor-Resistant HIV-1 Strains (2)	MT-2 cells	In vitro	A	No	[redacted]	2012N141510_00
Antiviral activity of DTG by Baseline Resistance in ING112574	293 Cells	In vitro	A	No	[redacted]	2012N148111_00
Anti-HIV activity against integrase inhibitor resistant HIV-1 strains of interest	HeLa-CD4 cells	In vitro	A	No	[redacted]	2013N167276_00

Key:
a = Other antiviral agents including anti-HBV and anti-HCV drugs. A = GSK1349572A (sodium salt of dolutegravir). B = GSK1349572B (dolutegravir parent form). HeLa-CD4 = Human epithelial cell line expressing CD4. MDM = Monocyte-derived macrophage cells. MT-4 = Human T-cell lymphotropic virus transformed cell line. PBMC = Peripheral blood mononuclear cells. Magi-CCR5 cells = HeLa CD4 LTR β-gal cells expressing high levels of CD4 and CCR5

Testing Facility:
GSK = GlaxoSmithKline.
[redacted] = [redacted]
[redacted] = [redacted]
[redacted] = [redacted]

4.1.2. Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

The antiviral mechanism of DTG on HIV replication was investigated (GSK Document numbers RH2010/00018/00, RH2007/00119/00, RH2010/00017/00, 2011N114191_00) using quantitative PCR. A dose dependent decrease in integrated HIV-1 DNA (Alu PCR) and an increase of 2 LTR circles was observed with DTG treatment suggesting that the antiviral activity is a direct consequence of its effect on viral integration. Dolutegravir demonstrated equivalent potency against two nonnucleoside inhibitor resistant, three nucleoside inhibitor resistant and two protease inhibitor resistant HIV-1 mutant clones (one with three and one with six mutations) compared with the wild type strain (GSK Document numbers RH2008/00141/00, RH2008/00142/00). In addition, passage studies with DTG selected mutations within the integrase enzyme; some of those mutations recreated as site-direct mutant HIV virus conferred moderate but greater than wild-type levels of DTG resistance. Direct and prolonged DTG binding to integrase protein was demonstrated with purified integrase in cDNA:Mg2+ complexes in bead based assays. These data are also consistent with direct targeting of the HIV-1 integrase in cells.

4.1.3. Cell Based Antiviral Assays

Dolutegravir activity against Ba-L HIV-1 in peripheral blood mononuclear cells (PBMCs), HIV-1 strain IIIB in MT4 cells and pseudotyped HIV-1 in CIP4 cells was examined (GSK Document numbers RH2007/0071/00, RH2007/00116/00).

For PBMC assays, cells were stimulated with phytohemagglutinin and interleukin-2 and infected with HIV-1 strain BaL or HIV-1 strain NL432. Following incubation with DTG for 4 or 7 days, the antiviral activity was assayed by reverse transcriptase (RT) activity resulting in IC50s of 0.51 nM (BaL) and 0.53 nM (NL432). For MT-4 assays, cells were infected with HIV-1 strain IIIB and incubated with DTG for 4 or 5 days followed by cell viability analyses with CellTiter-Glo or MTT resulting in IC50s of 0.71 and 2.1 nM, respectively Table 2). For pseudotyped HIV (PHIV) assays, the infected cells were incubated with DTG for 2 days and when assayed for cell viability by Steady Glo gave an IC50 of 2.2 nM. In vitro strand transfer biochemical assays using purified HIV-1 integrase, which measure the inhibition of the amount of donor DNA covalently attached to target DNA by DTG using either [^{3}H] target DNA or a sandwich ELISA resulted in IC50s of 2.7 nM and 12.6 nM, respectively.

Table 2 Antiviral Activity of DTG in PBMC, MT4, or CIP4 cells

Cell lines	Virus	DTG Geometric mean IC50 (nM)	95% CI	N
PBMC	Ba-L	0.51	0.34-0.77	12
PBMC	NL432	0.53	SD = 0.21	5
MT4	HIV-1^{IIIB}	0.71	0.40-1.3	9
MT4	HIV-1^{IIIB}	2.1	SD = 0.82	3
CIP4	PHIV vector	2.2	0.96-5.2	2

4.1.4. Effect of Human Serum and Serum Proteins

The effect of human serum albumin (HSA)(20 or 40 mg/mL), α_1-acid glycoprotein (AAG) (2 mg/mL) (Table 3) and human serum (extrapolated up to 100%) on the antiviral activity of DTG was evaluated in the PHIV or MT-4 assay systems. HSA was the predominant DTG binding component compared with AAG. Maximum fold shift observed with MT-4 assays performed at GSK (GSK Document number RH2007/00071/00) and [redacted] (GSK Document number RH2007/00116/00) and extrapolated to 100% human serum provided a mean consensus 75-fold shift in the IC_{50} values for DTG and a resulting PA-IC_{50} of 38 nM for PBMCs in 100% serum.

Table 3 The Effect of Serum Proteins on Antiviral Activity of DTG in HIV-1 IIIB-Infected MT4 Cells

Serum Protein	Geometric Mean IC50	95% Confidence Interval	Potency Shift	N
40 mg/mL HSA	18 nM	16 – 21 nM	12-fold	10
2 mg/mL AAG	3 nM	2.6 – 3.5 nM	2-fold	4

4.1.5. Antiviral Activity in Combination with other Antiviral Agents

Dolutegravir was tested for antiviral activity in combination with currently approved antiviral drugs (GSK Document numbers RH2009/00002/00, RH2009/00009/00). The greatest value of the in vitro combination studies is to identify antagonism of antiviral activity indicating that certain drugs should not be used clinically in combination. In this regard, the in vitro combination data support the conclusion that the antiviral activity of DTG is compatible with other approved antiretrovirals.

The in vitro anti-HIV-1 activity of DTG was studied in checkerboard format in combination with representative anti-HIV drugs (stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, and RAL) and anti-HBV (adefovir) and anti-HCV (ribavirin) drugs in MT-4 cells with HIV-1 strain IIIB (Table 4), and in combination with the anti-HIV drug maraviroc in cells obtained through the NIH AIDS Research and Reference Reagent Program (Magi-CCR5 cell line) with HIV-1 strain BaL (Table 5). All drugs with inherent anti-HIV activity were additive or synergistic with DTG, or if without inherent anti-HIV activity (ribavirin) had no apparent effect on DTG activity.

Table 4 Inhibition of HIV-1_{IIIB} by DTG in Combination with Other Marketed Anti-HIV Agents in MT-4 cells

Compound	Deviation from Additivity			Interaction with DTG
	Average	S.E.	p-value	
DTG	0.031	0.151	0.423	Additive
D4T	-0.473	0.083	0.001	Synergy
ABC	-0.605	0.150	0.002	Synergy
EFV	-0.356	0.102	0.005	Synergy
NVP	-0.246	0.087	0.015	Synergy
LPV	-0.310	0.082	0.005	Synergy
APV	-0.332	0.085	0.003	Synergy
T-20	-0.245	0.110	0.034	Synergy
PMEA	-0.179	0.168	0.168	Additive
RAL	-0.05	0.16	0.39	Additive

Table 5 Antiviral Efficacy and Cytotoxicity Results for DTG in Combination with Maraviroc vs HIV-1 BA-L in MAGI-CCR5 Cells

Setup	Antiviral	Cytotoxicity	Interpretation
1	44.6 / -0.08	3.41 / -2.15	Antiviral: Additive (Nonantagonistic) Cytotoxicity: Additive to Slightly Antagonistic
2	38.7 / -0.73	0 / -93.8	
3A	28.4 / 0	0 / -132	
3B	33.4 / -0.08	2.52 / -35.7	
Mean	**36.3 / -0.21**	**0.18 / -64.6**	

4.1.6. Evaluation of Cytotoxicity in Antiviral Assays

Cytotoxicity assays with DTG were conducted in parallel with the antiviral assays (GSK Document numbers RH2007/0071/00, RH2007/00116/00). Overall the cytotoxicities measured in these assays were distinct from the antiviral potencies and provided selectivity ratios from >350-fold to 6800-fold indicating that the observed antiviral activity of DTG was not due to cytotoxicity.

4.1.7. Evaluation of Cytotoxicity in Human Cell Lines and Peripheral Blood Mononuclear Cells

Cytotoxicity assays were conducted in proliferating human leukemic and lymphomic cell lines and PHA stimulated and unstimulated human PBMCs from the same donors, with resulting cell cytotoxicity (CC) IC50s for DTG in proliferating IM-9, U-937, MT-4 and Molt-4 cells of 4.8, 7.0, 14 and 15 µM, respectively and in unstimulated and stimulated PBMCs of 189 µM and 52 µM, respectively (GSK Document number RH2007/00036/00) (Table 6). When compared to the antiviral activity of DTG IC50 of 0.51 nM in PBMCs the selectivity index for antiviral activity was >9400.

Table 6 Cytotoxicity Assay Results in PBMCs and B and T Cells

Cell lines	DTG CC50 (μM)	95% CI	Flavopiridol CC50 (μM)	95% CI
IM-9 (n=4)	4.8	3.0-7.7	0.019	0.012-0.030
U-937 (n=4)	7.0	4.8-10	0.035	0.024-0.050
MT-4 (n=4)	14	7.0-29	0.13	0.062-0.26
Molt-4 (n=4)	15	12-19	0.16	0.13-0.21
Stimulated PBMCs (n=8)	52	36-76	0.36	0.25-0.53
Unstimulated PBMCs (n=8)	189	58-620	0.29	0.15-0.56

4.1.8. Susceptibility of Multiple Subtype B Clinical Isolates of HIV-1

Dolutegravir activity against site directed mutant strains and clinical isolates with integrase resistance mutations was evaluated at [redacted] using the Integrase PhenoSense assay (GSK Document number RH2007/00090/00).

The susceptibility of 13 clinically diverse HIV-1 subtype B isolates to integrase inhibition by DTG was tested with [redacted]'s PhenoSense assay. The mean IC50 for viral replication of the clinical isolate based viruses was 0.52 nM (range 0.41 to 0.60 nM) (Table 7).

Table 7 Activity of DTG against a Panel of HIV-1 Clinical Isolates

Virus	IC_{50} (nM)
ASJM 108	0.54
ASM 34	0.54
ASM 42	0.59
NIH 57	0.60
NIH 660	0.41
NIH 657	0.54
NIH 714	0.54
NIH 727	0.50
CV 110	0.49
CV 154	0.49
CV 163	0.55
CV 243	0.43
CV 281	0.49
HIV-1 IIIB	0.46
HXB2	0.65
NL4-3	0.60
Isolate mean	0.52
Isolate Median	0.54
Isolate standard deviation	0.06
Isolate range	0.41 - 0.60
Laboratory virus mean	0.57
Laboratory virus median	0.60
Laboratory virus standard deviation	0.10
Laboratory virus range	0.46 - 0.65

4.1.9. Susceptibility of a Panel of HIV-1 and HIV-2 Isolates in PBMCs and Monocyte Derived Macrophages

The antiviral activity of DTG was tested against a panel of HIV-1 isolates (3 in each group of M subtypes A, B, C, D, E, F and G, and 3 group O isolates) (Table 8) and 3 HIV-2 isolates, in PBMC assays (GSK Document number RH2008/00134/00) (Table 9). The antiviral activity of DTG against four subtypes B HIV-1 isolates was also evaluated in cell based monocyte-derived macrophage assays (Table 10). DTG was highly active with broad activity against all HIV-1 (geometric mean IC50 of 0.20 nM and range of 0.02 to 2.14 nM) and HIV-2 (geometric mean IC50 of 0.18 nM and range of 0.09 to 0.61 nM) isolates tested. In the monocyte-derived macrophage assays using 4 subtype B isolates, the geometric mean IC50 was 0.87 nM and values ranged from 0.37 to 1.98 nM. Mean IC50s for each of these categories are listed in Table 11.

Table 8 Activity of DTG against HIV-1 in PBMCs

HIV-1 Isolate	Envelope Subtype	IC_{50} (nM)
92RW009	A	0.18
92UG037	A	0.09
92UG029	A	0.50
92BR014	B	2.14
JR-CSF	B	0.05
92TH026	B	0.08
Ba-L	B	<0.10
Ba-L	B	0.20
92BR025	C	0.14
93IN101	C	<0.10
93IN101	C	0.51
93MW959	C	0.05
92UG001	D	0.17
92UG024	D	0.35
92UG046	D	0.16
93TH073	E	0.09
CMU08	E	0.24
CMU06	E	0.32
93BR019	F	0.44
93BR020	F	0.23
93BR029	F	<0.10
93BR029	F	0.07
JV1083	G	0.87
RU132	G	0.20
G3	G	0.02
BCF01	O	0.41
BCF02	O	0.42
BCF03	O	1.79

Table 9 Activity of DTG against HIV-2 Isolates in PBMCs

HIV-2 Isolate	IC_{50} (nM)
CDC 310319	0.61
CDC 310342	<0.10
CEC 310342	0.18
CBL 20	0.09

Table 10 Activity of DTG against Subtype B Isolates in Macrophages

HIV-1 Isolate	IC_{50} (nM)
Ada	1.33
Ba-L	1.98
92BR014	0.58
92TH026	0.37

Table 11 Mean Activity of DTG against Broad Subtypes and HIV-2 in PBMCs, and Subtype B Isolates in Macrophages

Virus	Mean IC_{50} (nM)
Subtype A	0.26
Subtype B	0.62
Subtype C	0.23
Subtype D	0.23
Subtype E	0.22
Subtype F	0.25
Subtype G	0.36
Group O	0.87
HIV-2	0.29
Subtype B in Macrophages	1.07

4.1.10. Activity against non-HIV Viruses

Dolutegravir was evaluated for antiviral activity against a panel of 19 non-HIV viruses. In general, DTG did not exhibit significant antiviral activity in this panel (GSK Document number 2011N113854_00). Some activity was observed against BVDV (IC50 = 66 μM), DENV (IC50 = 69.5 μM), measles (IC50 = 30.3 μM), HCV (IC50 = 11.2 μM), and VZV (IC50 = 88.1μM) (Table 12, Table 13, Table 14). DTG displayed the highest antiviral activity against HCV. DTG caused a mild cytotoxic effect at the high test concentration.

Table 12 Activity of DTG against a Range of Viruses in Cytoprotection Assays

Virus	High Concentration (μM)	IC50 (μM)	TC50 (μM)
Adenovirus	100	>100	>100
Bovine Viral Diarrhea Virus	100	66	>100
Dengue Virus (serotype 2)	100	69.5	>100
Yellow Fever Virus	100	>100	>100
HSV-1	100	>100	>100
HSV-2	100	>100	>100
Influenza A	100	>100	64.9
Influenza B	100	>100	75.7
Human Parainfluenza	100	>100	>100
Measles Virus (Morilli virus)	100	30.3	>100
Respiratory Syncytial Virus	100	>100	>100
Coxsackie A Virus	100	>100	97.6
Coxsackie B Virus	100	>100	>100
Enterovirus	100	>100	>100
Polio Virus	100	>100	>100
Rhinovirus	100	>100	>100

Table 13 Activity of DTG against Hepatitis C Virus (Replicon Assay)

Virus	High Concentration (μM)	IC50 (μM)	TC50 (μM)
HCV	100	11.2	96.7

Table 14 Activity of DTG in a Plaque Reduction Assay

Virus	High Concentration (μM)	IC50 (μM)	TC50 (μM)
HCMV	100	>100	>100
VZV	100	88.1	>100

4.1.11. Isolation of DTG Resistant HIV-1 Mutants

Selection of resistant mutants during in vitro passage of virus in the presence of drug may provide insight into the resistance mutations selected in vivo. Resistant mutants were

isolated during passage of wild type virus, virus with RAL resistant mutants, and during simultaneous passage of HIV-1 subtypes B, A/G, and C.

4.1.11.1. Isolation from Wild type HIV-1 Strain IIIB

Virus cultures were derived by co-culturing MT-2 cells with Molt-4 cells persistently infected with HIV-1 strain IIIB (GSK Document number RH2007/00119/00). This strain has ~40% T124A polymorphism in integrase in viral stocks used for passage (Kobayashi, 2011). The culture media from the co-cultures including resuspended co-cultured cells was used for initiating passage of resistant variants. Every 3 or 4 days the cells were examined for apparent cytopathic effects and supernatants were used to infect new MT-2 cells in the presence of increasing DTG concentrations (up to 5-fold). Infected cell DNA was prepared and HIV proviral DNA sequence was determined.

At selected intervals (14, 28, 42, 56, 70, 84, 98 and 112 days), susceptibility to DTG was measured using the supernatant from passaged cells (briefly expanded in fresh M8166 cells) in assays using HeLa-CD4 cells carrying a reporter β-galactosidase gene. Viruses highly resistant to DTG were not observed during the 112 day passage, with a 4.1-fold maximum fold resistance observed for the passaged resistant virus with substitutions at the conserved IN positions S153Y and S153F. These data are consistent with direct targeting of the HIV-1 integrase in cells and provide a relative fold resistance level for virus with these substitutions (Table 15).

Table 15 Passage with HIV IIIB

Days of Culture	Amino Acid Substitution	DTG Fold Change
14	T124A	1.2-2.5
28	T124A	0.57-1.0
	T124A, S153F	1.9
42	T124A	0.48-1.7
	T124A, S153F	1.7
56	T124A	0.95-2.9
	T124A, S153F	2.7
70	T124A	1.1-3.1
	T124A, S153Y	2.9
	L101I, T124A, S153F	2.4
84	T124A	0.82-3.1
	S153Y	3.7
	T124A, S153Y	3.3
	L101I, T124A, S153F	2.4
98	T124A	1.3-3.1
	T124A, S153Y	4.1
	L101I, T124A, S153F	3.0
112	T124A	1.2-4.1
	S153Y	2.1
	T124A, S153Y	1.8-2.6
	L101I, T124A/, 153F	2.0

4.1.11.2. Isolation from Wild Type and Site Directed Mutant INI Resistant HIV-1 Strain NL432

Wild type HIV-1 NL432 and molecular clones with single amino acid substitutions (E92Q, Q148H, Q148K, Q148R, and N155H) within the IN open reading frame were passaged sequentially under increasing concentration of DTG for up to 56 days (GSK Document number RH2008/00144/00). Passaged virus populations were analyzed for genotypic changes on Days 14, 28, 42 and 56, and for phenotypic fold change (FC) on Day 56 samples (Table 16).

Table 16 Passage of NL-432 and Single Mutants with DTG.

Initial Virus	DTG Initial Conc. / Final Conc (nM)	Days of Culture	Amino Acid Substitution	DTG Fold Change of Passaged Virus Pools
NL-432	6.4 / 6.4	56	E92Q	3.1
			G193E	3.2
Q148K	6.4 / 32	14	E138K, Q148K	-
		28	E138K, Q148K	-
		42	E138K, Q148K	-
		56	E138K, Q148K	47 - 190
Q148R	6.4 / 6.4 or 32	14	Q148R	-
		28	G140S, Q148R	-
		42	G140S, Q148R	-
		56	G140S, Q148R	16 (6.4 final conc.)
			G140S, Q148R, V201I	39 (32 final conc.)
Q148R	6.4 / 6.4	14	E138K, Q148R	-
		28	E138K, Q148R	-
		42	E138K, Q148R	-
		56	E138K, G140S, Q148R	13
Q148H	6.4 / 6.4 or 32	14	G140S, Q148H	-
		28	G140S, Q148H	-
		42	G140S, Q148H	-
		56	G140S, Q148H	4.8 – 8.0 (6.4 final conc.)
			T97A, G140S, Q148H	44 (32 final conc)
			V75I, E138K, G140S, Q148H, M154I	46 (32 final conc)
N155H	6.4 / 32	14	N155H	-
		28	N155H	-
		42	N155H	-
		56	N155H	2.0 – 3.9
E92Q	6.4 / 6.4	14	E92Q	-
		28	E92Q	-
		42	E92Q	-
		56	E92Q	2.9 – 4.1

Passage of the wild type HIV-1 NL432 in the presence of 6.4 nM DTG selected for E92Q (FC=3.1) and G193E (FC=3.2) substitutions in the IN region on Day 56. Passage of the Q148K mutant selected E138K/Q148K (FC=47 to190) on Day 14 and was present throughout the remaining passages up to 32 nM DTG with no additional substitutions selected up to Day 56. Passage of the Q148R mutant selected E138K/Q148R and G140S/Q148R (FR=16) on Days 14 and 28, respectively, in the presence of 6.4 nM DTG. Further passage at ≤32 nM DTG selected E138K/G140S/Q148R (FC=13) and G140S/Q148R/V201I (FC=39) by Day 56. Passage of Q148H selected G140S/Q148H (FC=4.8 to 8) on Day 14 in the presence of 6.4 nM DTG, and selected T97A/G140S/Q148H (FC=44) and V75I/E138K/G140S/Q148H/M154I (FC=46) on Day 56 in the presence of 32 nM DTG. Passage of the E92Q or N155H mutant viruses in the presence of DTG did not lead to additional substitutions. Passage of site directed mutant virus with polymorphic substitutions L101I, L101I/T124A, and RAL resistance mutations Y143C and Y143R in the presence of DTG did not lead to additional substitutions (GSK Document number 2012N141510)

Passage of site direct double mutant virus G140S/Q148R at 6.4 nM selected V113L at Day 56 (FC not determined). Passage of G140S/Q148H at 6.4 nM dolutegravir selected the addition of N155H at Day 28 (FC = 85 to >120) and E92Q (FC >120), and of E92Q/E138K by Day 56 (FC >120). Passage at 32 nM DTG selected for addition of F139S at day 28 (FC not determined), L74M at Day 42 (FC = 15 to 95), or L74M/T112S/V113L (FC >120). All FCs were determined at Day 56 (Table 17).

Table 17 Passage of Double Mutants with DTG

Initial Virus	DTG Initial Conc. (nM)	Days of Culture	Amino Acid Substitution Added	DTG Fold Change of Passaged Virus Pools
G140S, Q148H	6.4	28	N155H	-
		42	N155H	-
		56	N155H	85 - >120
G140S, Q148H	6.4	28	E92Q	-
		42	E92Q	-
		56	E92Q	>120
G140S, Q148H	32	28	F139S	-
		42	F139S	-
		56	F139S	-
G140S, Q148H	32	42	L74M	-
		56	L74M	15 - 95
		56	L74M, T112S, V113L	>120

4.1.11.3. Selection of R263K in Passage Experiments using HIV-1 with Subtype B, C, and A/G

Serial passage experiments were performed with DTG using healthy donor primary human cord blood mononuclear cells (CBMCs) infected with various subtype B, C, and A/G viruses [Quashie, 2012]. After 20 weeks, the R263K mutation was observed in all

five subtype B selections and one of two subtype A/G selections. During the selections, neither L101I nor T124A appeared. However, the S153Y substitution was observed in combination with R263K for one subtype B virus and S153T; was partially detected in one subtype C virus. Importantly, the only subtype B or A/G virus that did not bear the R263K mutation carried the G118R mutation, which was characterized as a resistance mutation to MK-2048, another second generation integrase inhibitor. The same mutation (G118R) was observed in one subtype C virus. The R263K mutation was detected alone or in combination with other substitutions that varied among virus strains. R263K emerged early in culture in both subtype B and A/G viruses (Table 18).

Table 18 Serial Passage Experiments with CBMCs infected with Subtype B, A/G, and C HIV-1 Viruses in the Presence of Increasing Concentrations of DTG

		Week 20		Week 37	
Subtype	**Virus**	**DTG Concentration (μM)**	**Acquired Mutations**	**DTG Concentration (μM)**	**Acquired Mutations**
B	5331	0.05	R263K		
B	BK-132	0.05	R263K, W243G/W	0.05	R263K, E138E/K
B	5326	0.05	R263K/R, S153Y, R166K/R	0.05	S153Y
B	PNL4.3	0.05	R263K, M50I/M, V151I	0.05	R263K, M50I, V151I
B	12197 RAL TI	0.01	R263K, D288E	0.025	R263K, D288E (week 34)
A/G	6399	0.025	G118R, E69E/K	0.05	G118R
A/G	96USSN20	0.1	R263K	0.1	R263K, H51H/Y
C	4742	0.05	G118R	0.05	G118R, H51Y
C	96USNG31	0.01	S153S/T	0.025	H51Y, G193E/G

4.1.12. Assessment of Resistance

Comparative susceptibilities to DTG and RAL were obtained from 60 RAL resistant site directed HIV-1 mutants and 6 site directed HIV-2 mutants.

4.1.12.1. Sixty Integrase Inhibitor Resistant HIV-1 Strains

HIV-1 viruses (28 with single mutations (Table 19), and 32 with two or more mutations, (Table 20) were produced from wildtype virus NL-432 using site directed mutagenesis. DTG and other INI susceptibilities were tested in HeLa-CD4 cell assay carrying a

reporter β-galactosidase gene driven by HIV-1 LTR (GSK Document numbers RH2005/00088/00, RH2007/00115/00, RH2008/00143/00, RH2010/00017/00). DTG showed anti-HIV activity (susceptibility) with fold change (FC) <5 against 27 of 28 INI-resistant mutant viruses with single mutations including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, Q148R, and N155H, while for RAL there were 17/28 mutant viruses with FC <5. EVG (compound 3927 in GSK Document number RH2005/00088/00) FC was obtained for 21 of these 28 viruses; 11 of 21 had FC <5. In addition, of the 32 INI-resistant mutant viruses with two or more mutations, 23 of 32 showed FC <5 to DTG compared with FC < 5 for 4 of 32 for RAL. EVG FC was obtained for 25 of these 32 viruses; 2 of 25 had FC <5.

Overall against the 60 site directed mutant viruses (single and ≥2 mutations), DTG showed a fold change (FC) of <2 for 39 of 60, while RAL showed a FC of <2 for 16 of 60. DTG showed a FC of ≥10 for 3 of 60, while RAL showed a FC of ≥10 for 32 of 60. Of the 46 mutant viruses with data for EVG, 7 of 46 showed a FC of <2, and 30 of 46 showed a FC of ≥10.

The resistance profile for Q148 pathway RAL-resistant HIV-1 is relatively complex due to the large number of potential substitions which may be present in subjects failing RAL therapy. The in vitro data against site directed mutant HIV-1 with lab strain NL432 reflects this: virus with G140S/Q148H, G140S/Q148K, and G140S/Q148R had respective DTG FCs of 2.6, 1.5, and 8.4. The rank order and relative FC ranges shifted however with E138K in combination with Q148, with FCs for E138K/Q148H = 0.89, E138K/Q148K = 19, and E138K/Q148R = 4.0.

Table 19 Fold Change (FC) of DTG and RAL against INI-Resistance Single Mutant Viruses by HeLa-CD4 Assay

Virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
Wild type (NL432)	1.0 (IC50=2.1 nM, SD=0.36)	1.0 (IC50=6.1 nM, SD=0.89)	-
Wild type (NL432)	1.0 (IC50=2.0 nM, SD=0.34)	1.0 (IC50=8.6 nM, SD=1.3)	1.0 (IC50=1.3 nM, SD=0.24)
T66A	0.26 (0.01)	0.61 (0.09)	-
T66I	0.26 (0.09)	0.51 (0.10	8 (1.7)
T66K	2.3 (0.35)	9.6 (1.3)	84 (29)
E92I	1.5 (0.19)	2.1 (0.62)	-
E92Q	1.6 (0.12)	3.5 (1.4)	19 (8.1)
E92V	1.3 (0.20)	1.4 (0.18)	-
G118R	10 (4.7)	7.2 (1.5)	-
G118S	1.1 (0.21)	1.2 (0.30)	-
F121Y	0.81 (0.12)	6.1 (1.3)	36 (23)
T124A	0.95 (0.19)	0.82 (0.08)	1.2 (0.29)
E138K	0.97(0.029)	1.0 (0.30)	0.93 (0.12)
G140S	0.86 (0.30)	1.1 (0.22)	2.7 (0.63)
Y143C	0.95 (0.26	3.2 (0.57)	1.5 (0.46)
Y143R	1.4 (0.29)	16 (3.9)	1.8 (0.16)
Y143H	0.89 (0.11)	1.8 (0.38)	1.5 (0.047)
P145S	0.49 (0.08)	0.87 (0.20)	>345
Q146R	1.6 (0.17)	1.2 (0.26)	2.8 (0.72)
Q148H	0.97 (0.67)	13 (5.0)	7.3 (2.3)
Q148K	1.1 (0.19)	83 (6.6)	>1726
Q148R	1.2 (0.21)	47 (9.3)	244 (91)
+I151L	3.6 (3.6)	8.4 (4.7)	-
S153F	1.6 (0.20)	1.3 (0.14)	2.8 (0.93)
S153Y	2.5 (1.1)	1.3 (0.19)	2.3 (0.49)
M154I	0.93 (0.27)	0.82 (0.18)	1.1 (0.18)
N155H	0.99 (0.094)	8.4 (1.8)	25 (7.8)

Virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
N155S	1.4 (0.36)	6.2 (1.9)	68 (2.6)
N155T	1.9 (0.32)	5.2 (2.0)	-
G193E	1.3 (0.25)	1.3 (0.35)	1.3 (0.40)

Table 20 Fold Change (FC) of DTG and RAL against INI-Resistance Multiple Mutant Viruses by HeLa-CD4 Assay

virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
Wild type (NL432)	1.0 (IC50=2.1 nM, SD=0.36)	1.0 (IC50=6.1 nM, SD=0.89)	-
Wild type (NL432)	1.0 (IC50=2.0 nM, SD=0.34)	1.0 (IC50=8.6 nM, SD=1.3	1.0 (IC50=1.3 nM, SD=0.24)
T66I, I74M	0.35 (0.08)	2.0 (0.81)	-
T66I, E92Q	1.2 (0.19)	18 (3.6)	185 (103)
T66K, L74M	3.5 (0.94)	40 (13)	117 (33)
V72I, F121Y, T125K	1.3 (0.54)	13 (7.1)	-
V72I, F121Y, T125K, I151V	1.2 (0.32)	7.0 (2.8)	-
L74M, N155H	0.91 (0.17)	28 (12)	42 (8.6)
V75I, E138K, G140S, Q148H, M154I	21 (6.6)	>660	2600 (450)
E92Q, N155H	2.5 (1.2)	>130	320 (39)
T97A, N155H	1.1 (0.46)	26 (7.9)	37 (6.9)
T97A, G140S, Q148H	13 (2.1)	>660	3900 (630)
L101I, S153F	2.0 (0.11)	1.3 (0.54)	2.6 (0.23)
L101I, T124A, S153F	1.9 (0.24)	1.4 (0.14)	2.0 (0.40)
F121Y, T125K	0.98 (0.35)	11 (0.49)	-
E138K, Q148H	0.89 (0.24)	17 (5.9)	6.7 (1.5)
E138K, Q148K	19 (8.0)	330 (75)	-
E138K, Q148R	4.0 (1.1)	110 (37)	461 (229)
E138A, Q148R	2.6 (0.47)	110	260 (12)
E138K, G140S, Q148H	4.5 (1.1)	500 (210)	1600 (370)
E138K, G140S, Q148R	8.3 (1.1)	>660	190 (43)
E138K, G140S, Q148H, M154I	8.4 (1.5)	>660	2400 (670)
E138A, S147G, Q148R	1.9 (0.89)	27 (3.7)	130 (8.8)
G140C, Q148R	4.9 (1.8)	200 (42)	-
G140S, Q148H	2.6 (1.4)	>130	>890
G140S, Q148K	1.5 (0.10	3.7 (1.3)	94 (53)

virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
G140S, Q148R	8.4 (4.0)	200 (5.3)	-
G140S, Q148H, M154I	7.0 (0.98)	>660	3000 (780)
G140S, Q148R, V201I	10 (3.0)	>660	420 (80)
Y143H, N155H	1.7 (0.27)	38	16 (4.6)
Q148R, N155H	10 (1.4)	>140	390
N155H, G163R	1.1 (0.18)	17 (5.9)	35 (12)
N155H, G163K	1.4 (0.40)	23 (7.2)	35 (4.4)
N155H, D232N	1.4 (0.25	20 (3.9)	36 (7.1)

4.1.12.2. Additional HIV-1 Strains with Integrase Mutations of Interest

HIV-1 viruses of special interest, 3 with single mutations and 6 with two or more mutations, (Table 21) were produced from wildtype virus NL-432 using site directed mutagenesis. DTG , RAL, EVG and efavirenz (as a positive control) susceptibilities were tested in HeLa-CD4 cell assay carrying a reporter β-galactosidase gene driven by HIV-1 LTR (GSK Document number 2013N167276_00).

The positive control compound efavirenz had a reasonably small FC range (0.70 to 2.5) through the mutants tested. The polymorphism E157Q/P was detected in the clinical study ING114467. The replication capacity of the E157P mutant was too low to evaluate. The E157Q subtitution did not alter susceptibility to integrase inhibitors, giving a FC of 0.85, 0.92 and 1.1 for DTG, RAL and EVG, respectively.

The R263K variant was observed in in vitro passage and in the clinical study ING111762 . The single R263K substitution did not alter susceptibility to integrase inhibitors, giving a FC of 1.5, 0.81 and 1.3 for DTG, RAL and EVG, respectively.

Table 21 Fold change (FC) of DTG against IN mutant viruses by HeLa-CD4 Assay

Compound	DTG	RAL	EVG	Efavirenz
Virus	Mean FC ± (SD)[a]			
Wild type (NL432)	1.0	1.0	1.0	1.0
Q148N	0.79 (0.33)	0.81 (0.10)	3.8 (0.11)	1.1 (0.065)
E138A, G140S, Q148H	4.5 (0.94)	460 (26)	2300 (1100)	0.97 (0.15)
G140S, Q148H, N155H	69 (16)	>630	>2700	1.5 (0.20)
E92Q, E138T, G140S, Q148H	120 (21)	>630	>2700	1.0 (0.14)
T97A, E138T, G140S, Q148H	92 (40)	>630	3500 (1600)	1.2 (0.24)
E138K, G140S, Q148H, N155H	120 (30)	>630	>2700	0.70 (0.13)
E157Q	0.85 (0.21)	0.92 (0.34)	1.1 (0.62)	0.94 (0.17)
R263K	1.5 (0.39)	0.81 (0.18)	1.3 (0.76)	1.1 (0.17)
N155H, R263K	3.6 (0.74) [b]	5.1 (0.76)[b]	89 (48)	1.5 (0.31)
E92Q, N155H, R263K	39 (16) [b]	76 (36)	1700 (1200)	2.5 (0.26)

a. FC values were calculated as relative IC50 to wild type NL432. Each value represents the mean and SD for 3 independent experiments, which were performed in duplicate
b. FC values reprent the mean and SD for 4 independent experiments, which were performed in duplicate

4.1.12.3. Integrase Inhibitor Resistant HIV-2 Strains

Site directed mutant HIV-2 viruses were constructed based on subjects infected with HIV-2 and treated with RAL who showed virologic failure (GSK Document number 2012N141511). DTG FC resistance was <5 against 4 HIV-2 virus; S163D, G140A/Q148R, A153G/N155H/S163G and E92Q/T97A/N155H/S163D; for E92Q/N155H DTG FC = 8.5, and for G140S/Q148R DTG FC = 17. DTG, RAL and EVG all had the same activity against site directed mutant HIV-2 with S163D as wild

type, and for the remaining mutant HIV-2 virus RAL and EVG FC ranges were respectively 6.4 to 420 and 22 to 640 (Table 22).

Table 22 Fold Change (FC) of DTG against RAL Resistant HIV-2 Viruses

Compound	DTG	RAL	EVG	AZT
Viruses	**Mean FC (SD)**			
Wild type (ROD)	1.0	1.0	1.0	1.0
S163D	0.87 (0.070)	0.86 (0.093)	1.1 (0.40)	1.2 (0.26)
E92Q, N155H	8.5 (0.57)	110 (24)	340 (49)	2.8 (0.67)
G140A, Q148R	0.60 (0.35)	6.4 (0.38)	110 (5.7)	0.21 (0.087)
G140S, Q148R	17 (1.5)	420 (100)	640 (190)	0.43 (0.11)
A153G, N155H, S163G	3.8 (0.12)	16 (2.6)	22 (3.2)	4.5 (0.99)
E92Q, T97A, N155H, S163D	3.9 (0.35)	57 (8.0)	200 (82)	0.43 (0.049)

4.1.12.4. Clinical Isolates from RAL Therapy Virologic Failure Subjects

Susceptibility to DTG and RAL was obtained with over 700 RAL resistant clinical isolates from subjects not enrolled in ViiV Healthcare sponsored studies. DTG retained activity against a vast majority of these viruses.

4.1.12.4.1. Activity against Thirty-nine Clinical Isolates

Thirty-nine clinical isolate samples, 30 with genotypic and phenotypic resistance to RAL (median FC >81), were examined for susceptibility to DTG (median FC 1.5) using [redacted] PhenoSense assay Integrase (GSK Document number RH2009/00010/00) *(*Table 23). The median FC to DTG for isolates containing changes at G140S + Q148H; G140S + Q148R, T97A + Y143R and N155H were 3.75, 13.3, 1.05 and 1.37, respectively (Table 24).

Table 23 Genotypes and FCs to DTG and RAL for Clinical Isolates in Subjects Failing RAL Therapy

Sample Number	Genotype	DTG FC	RAL FC	Months on RAL
3242	N155H	1.37	34	5.7
3242	N155H	1.22	36	7.5
3251	N155H	1.45	14	6.7
3246	T97A, Y143R	1.04	>81	6.4
3246	T97A, Y143R	1.06	>81	11.6
3249	T97A, Y143Y/C	1.09	49	5.6
3249	T97T/A, Y143Y/C	1.05	7.08	9.6
3249	T97T/A, Y143Y/C	0.91	>81	14.4
3261	T97T/A, N155N/H	1.11	3.74	13.7
3508	E92E/Q, T97T/A, Y143R	0.87	59	6.6
3501	G140G/S, Q148Q/H	1.38	3.9	5.6
3180	G140S, Q148H	4.96	>87	5.9
3180	G140S, Q148H	3.75	>87	7.8
3223	G140S, Q148H	3.16	>87	10.5
3240	G140S, Q148H	15.0	>87	3.3
3501	G140S, Q148H	2.05	58	1.8
3501	E138E/A, G140G/S, Q148Q/H	2.96	>81	7.5
3501	E138E/A, G140G/S, Q148Q/H	1.94	19	8.9
3501	E138E/A, G140G/S, Q148Q/H	2.64	>81	11.3
3501	E138E/A, G140G/S, Q148Q/H	1.58	12	3.8
3508	E92Q, N155N/H, G140G/S, Q148Q/R	4.07	>81	2.8
3501	E138E/K, G140G/S, Q148Q/H, N155N/D	2.16	25	6.3
3180	Wild type	1.11	1.18	-0.7
3223	Wild type	0.69	0.9	-2.2
3223	Wild type	0.65	0.85	6.2
3240	Wild type	0.64	1.02	0
3242	Wild type	0.59	0.45	0
3242	Wild type	0.54	0.45	8.7
3261	Wild type	0.84	0.79	6.7
3501	Wild type	0.79	0.58	0
3508	Wild type	0.63	0.83	-0.2
Library 44	N155H	1.45	18	NA
Library 45	G140S, Q148R	7.57	>87	NA
Library 46	G140S, Q148R	19	>87	NA
Library 47	N155H	1.33	19	NA
Library 48	T97A, E138E/K, Y143R	1.32	>87	NA

Sample Number	Genotype	DTG FC	RAL FC	Months on RAL
Library 49	G140S, Q148H	7.32	>87	NA
Lib 50	T97A, Y143C	1.21	>87	NA
Lib 51	G140S, Q148H	3	>87	NA

Table 24 Representative Isolate Susceptibilities to DTG and RAL

Genotype	n	DTG FC		RAL FC	
		Median	Range	Median	Range
N155H	5	1.37	1.22 to 1.45	19.0	14.0 to 36.0
G140S, Q148H	7	3.75	2.05 to 15.0	>87	58.0 to >87
G140s, Q148R	2	13.3	7.57 to 19.0	>87	>87 to >87
T97A, Y143R	2	1.05	1.04 to 1.06	>81	>81 to >81

4.1.12.4.2. Activity against 705 RAL Resistant Clinical Isolates

Seven hundred and five clinical isolates from RAL-experienced patients in [redacted]'s isolate library [redacted] through [redacted] were analyzed for susceptibility to DTG using the [redacted] PhenoSense assay (GSK Document number 2012N146158_00). The 705 isolates were selected based upon a RAL FC >1.5, and had diverse RAL-associated IN resistance patterns and proportions (Table 25) which were consistent with what has been observed previously (https://www.intmedpress.com/serveFile.cfm?sUID=c10a93ca-a12a-4ff9-980d-07561299189b, 2010). Overall 662 (93.9%) of the 705 RAL resistant isolates had a DTG FC of ≤10, and 13 (1.8%) had a DTG FC of >25 (Table 26). The two Q148 categories Q148+1 and Q148+≥2 IN mutation consisted of 92 and 184 isolates respectively, and contain the majority (41 of 43) of the isolates which had a DTG FC>10. Of the 705 isolates 332 (47.1%) had RAL FC > max measurable and were found within all categories, while only three of 705 isolates (which were within the Q148+≥2 category) had DTG FC > max measurable (Table 26).

A broad range of DTG FC with virus harboring the same mutation profile (eg G140S/ Q148H) has also been shown in this large datatset of INI resistant clinical isolates. This diversity in DTG susceptibility could be the result of mixtures of wildtype and mutant at both or either positions Q148 or G140 or the presence of additional minor variants of mutations below the population detection level.

Table 25 Proportion of Samples for IN Mutation Categories

Mutation Category[a]	Percent (N=705)
Q148+≥2	13.0
Q148+1	26.1
Y143	13.9
N155	28.9
≥2 Primary	6.0
Primary not detected	12.1

a. INI mutations list, primary mutations are bolded: **Q148H, Q148K, Q148R, Y143C, Y143H, Y143R, N155H**, H51Y, G118R, S147G, S153F, S153Y, G193E, R263K, L74I, L74M, T97A, E92Q, E92V, E138A, E138K, E138T, G140A, G140C, G140S, V151I, G163K, G163R

Table 26 DTG and RAL Susceptibility by Fold Change Range and IN Mutation Category

FC Range	Number of viruses with FC to DTG (%) or RAL (%) in each Mutation Category[a]													
	All		Q148+≥2		Q148+1		Y143		N155		≥2 Primary		Primary not detected	
	DTG	RAL	DTG	RAL	DTG	RAL	DTG	RAL	DTG	RAL	DTG	RAL	DTG	RAL
0 to 1.5	282 (40.0)	15 (2.1)	1 (1.1)	0	13 (7.1)	0	72 (73.5)	0	102 (50.0)	2 (1.0)	18 (42.9)	0	76 (89.4)	13 (15.3)
>1.5 to 2.5	147 (20.9)	23 (3.3)	4 (4.3)	0	12 (6.5)	2 (1.1)	26 (26.5)	0	86 (42.2)	3 (1.5)	13 (31.0)	0	6 (7.1)	18 (21.2)
>2.5 to 4	77 (10.9)	23 (3.3)	19 (20.7)	0	37 (20.1)	3 (1.6)	0	0	13 (6.4)	5 (2.5)	6 (14.3)	2 (4.8)	2 (2.4)	13 (15.3)
>4 to 8	137 (19.4)	21 (3.0)	34 (37.0)	0	96 (52.2)	3 (1.6)	0	3 (3.1)	3 (1.5)	11 (5.4)	3 (7.1)	0	1 (1.2)	4 (4.7)
>8 to 10	19 (2.7)	20 (2.8)	9 (9.8)	0	10 (5.4)	1 (0.5)	0	1 (1.0)	0	12 (5.9)	0	3 (7.1)	0	3 (3.5)
>10 to 15	20 (2.8)	40 (5.7)	13 (14.1)	1 (1.1)	7 (3.8)	3 (1.6)	0	5 (5.1)	0	23 (11.3)	0	1 (2.4)	0	7 (8.2)
>15 to 20	7 (1.0)	36 (5.1)	4 (4.3)	1 (1.1)	3 (1.6)	1 (0.5)	0	4 (4.1)	0	26 (12.7)	0	4 (9.5)	0	0
>20 to 25	3 (0.4)	35 (5.0)	0	0	3 (1.6)	3 (1.6)	0	7 (7.1)	0	22 (10.8)	0	1 (2.4)	0	2 (2.4)
>25	13 (1.8)	492 (69.8)	8 (8.7)	90 (97.8)	3 (1.6)	168 (91.3)	0	78 (79.6)	0	100 (49.0)	2 (4.8)	31 (73.8)	0	25 (29.4)
N	705	705	92	92	184	184	98	98	204	204	42	42	85	85
Median	1.76	89	5.98	115.92	4.84	115.92	1.24	100.24	1.5	25	1.81	79	0.88	3.98
Range	0.19-58	0.81->max	1.46-58	11->max	0.49-44	2.24->max	0.45-2.16	4.24->max	0.75-6.78	0.9-137.3	0.91-37	2.61-135.9	0.19-4.34	0.81->max
>max N (%)[b]	3 (0.43)	332 (47.1)	3 (3.26)	84 (91.3)	0	153 (83.2)	0	47 (48.0)	0	17 (8.3)	0	19 (45.2)	0	12 (14.1)

a. INI mutations list, primary mutations are bolded: **Q148H**, **Q148K**, **Q148R**, **Y143C**, **Y143H**, **Y143R**, **N155H**, H51Y, G118R, S147G, S153F, S153Y, G193E, R263K, L74I, L74M, T97A, E92Q, E92V, E138A, E138K, E138T, G140A, G140C, G140S, V151I, G163K, G163R

b. >max is the maximum measureable FC within assay and ranged from >42.8 to >49.8 FC DTG and from >100.24 to >170.6 FC RAL

4.1.12.4.3. Characterization of DTG resistance in the Raltegravir Resistant Clinical Isolate Population

To better understand the extent and evolving characteristics of DTG resistance in broad clinical practice for subjects experiencing virologic failure on RAL, queries into RAL resistant pathway frequencies was carried out on 1079 patient samples with an aim to detecting genotypic changes over time, and the proportion of isolates with potential increased DTG fold change resistance (GSK Document number 2012N152930_00).

Query analysis

The query was in two parts and compared samples received and tested at [redacted] over two time periods encompassing collection dates between [redacted] through [redacted] inclusive (N=273) compared with [redacted] through [redacted] inclusive (N=806). [redacted] carried out the Queries into their dataset and provided proportions within the defined groups.

Query One compared proportions of specific primary and secondary mutations and also samples without the defined mutations:

- Primary mutations: Y143C; Y143H; Y143R; Q148H; Q148K; Q148R; N155H. Secondary mutations: L74I,M; T97A; E92Q,V; E138A,K,T; G140A,C,S; V151I; G163K,R; None of above mutations.

- Query parameters: Mixtures at a specific position will be counted as one mutation (example: both E92Q/V and E92Q will be counted as one E92Q mutation).

Query Two compared Q148H/K/R in combination with increasing number of other RAL associated secondary resistance mutations, or with other primary resistance mutations:

- Primary RAL Resistance Associated Mutations: Y143C, Y143H, Y143R, N155H. Secondary RAL Resistance Associated Mutations: L74I, L74M, T97A, E92Q, E92V, E138A, E138K, E138T, G140A, G140C, G140S, V151I, G163K, G163R

- Parameters: Proportions of five groups were determined: Q148H or Q148K or Q148R + 1 secondary; Q148H or Q148K or Q148R + 2 secondary; Q148H or Q148K or Q148R + 3 secondary; Q148H or Q148K or Q148R + 4 secondary; or Q148H or Q148K or Q148R + other primaries. Mixtures at a specific position were counted as one mutation (example: both E92Q/V and E92Q be counted as one E92Q mutation). Prevalence for categories 1, 2, 3, and 4 were calculated within samples with no other primary RAL resistance associated mutations.

Enumeration of key RAL associated resistance mutations in virus samples with Q148+≥2

Data for the frequencies of RAL primary and secondary mutations (and associated DTG susceptibilities) for a set of 705 isolates randomly selected from the 806 isolates in the [redacted] through [redacted] window is found in GSK Document number

2012N146158_00. The different IN mutation categories evaluated within that report were Q148 + ≥2 mutation category, Q148+1 mutation category, Y143 mutation category, N155 mutation category, ≥2 Primary IN mutations category, and Primary not detected category.

Isolates from the ≥2 Primary IN mutations category with genotypes demonstrating presence of Q148 + at least two secondary mutations were included within the Q148 + ≥2 mutation category for this enumeration. This supergroup category called Q148 + ≥2 +P allows for evaluating proportions of key resistance mutations (L74I, E138A/K/T, and G140A/C/S) in all available virus possessing Q148 + ≥2 RAL associated resistance mutations.

Phenotypic data was provided with listed defined INI-associated resistance mutations within the integrase open reading frame. The defined list of mutations is provided, primary mutations are in bold: **Q148H, Q148K, Q148R, Y143C, Y143H, Y143R, N155H**, H51Y, G118R, S147G, S153F, S153Y, G193E, R263K, L74I, L74M, T97A, E92Q, E92V, E138A, E138K, E138T, G140A, G140C, G140S, V151I, G163K, G163R.

Table 27 provides the proportions of isolate samples for IN single mutation categories. There were decreases in the proportion of Q148 pathway virus, including the tightly associated G140 secondary mutation, from the early to late window. N155H increased during this time.

Table 27 Proportion of samples for IN single mutation categories

Mutation[a]	[redacted] N=273 Prevalence (%)	[redacted] N=806 Prevalence (%)	Change in Prevalence (%)
Primary[b]			
Y143C	9.52	9.18	-0.34
Y143H	2.93	3.23	0.3
Y143R	7.69	11.04	3.35
Q148H	41.76	31.39	-10.37
Q148K	2.20	0.50	-1.7
Q148R	10.99	9.68	-1.31
N155H	31.50	34.49	2.99
Secondary[c]			
L74I,M	14.65	15.76	1.11
T97A	19.78	24.07	4.29
E92Q,V	3.66	4.47	0.81
E138A,K,T	10.62	10.17	-0.45
G140A,C,S	50.55	37.47	-13.08
V151I	19.05	21.22	2.17
G163K,R	11.72	12.41	0.69
None of above	0.73	2.11	1.38

a. Mixtures at a specific position are counted as one mutation
b. Primary RAL Resistance Associated Mutations: Y143C, Y143H, Y143R, N155H.
c. Secondary RAL Resistance Associated Mutations: L74I, L74M, T97A, E92Q, E92V, E138A, E138K, E138T, G140A, G140C, G140S, V151I, G163K, G163R.

Table 28 provides the proportions of isolate samples for IN Q148 plus multiple mutation categories. Similar to Table 27, there was a decrease in the number of Q148 isolate samples from the early to late window, including those which had Q148 plus additional primary mutations present at Y143 and N155.

Table 28 Proportion of samples for IN Q148 plus multiple mutation categories

Mutation Profile	[redacted] - [redacted] N=273 Prevalence (%)	[redacted] - [redacted] N=806 Prevalence (%)	Difference in Prevalence (%)
Q148H/K/R + 1[a]	33.33	26.67	-6.66
Q148H/K/R + ≥2	15.75	10.3	-5.45
Q148H/K/R + 2	13.55	9.06	-4.49
Q148H/K/R + 3	2.2	1.24	-0.96
Q148H/K/R + other primary(s)[b]	4.4	3.23	-1.17

a. Q148H or Q148K or Q148R + 1, 2, 3, or 4 secondaries were evaluated. Secondaries: H51Y, G118R, S147G, S153F, S153Y, G193E, R263K, L74I, L74M, T97A, E92Q, E92V, E138A, E138K, E138T, G140A, G140C, G140S, V151I, G163K, G163R. Mixtures at a specific position were counted as one mutation.

b. Primaries: Q148H, Q148K, Q148R, Y143C, Y143H, Y143R, N155H

Table 29 describes 115 isolates of a total of 705 random isolates from the [redacted] through [redacted] time frame (GSK Document number 2012N146158_00). The 115 isolate samples include 92 isolates from the Q148 + ≥2 mutations category + 23 isolates from the ≥2 Primary IN mutations category with (in addition to a second primary mutation at Y143 or N155) a Q148 signature mutation plus at least two RAL-associated secondary mutations. There were overall 62 subjects with at least two derived key mutations within the 115 subjects. The majority of those 62 subjects with the derived mutations were in the set Q148 + G140 + E138 (n=46) followed by Q148 + G140 + L74 (n=14) and then all 3 Q148 + G140 + E138 + L74 (n=2).

Table 29 Proportion of Samples with Key Mutations in the Q148+>=2 + P Group

Mutations[a] from Q148 derived mutation group present	Total number per Group
All three mutations:	
Q148 + G140 + E138 + L74	2
Two of three Mutations:	
Q148 + G140 + E138	46
Q148 + G140 + L74	14
Q148 + L74 + E138	0
One of three mutations:	
Q148 + L74	0
Q148 + E138	9
Q148 + G140	41
Zero of three mutations:	
Not L74 or E138 or G140	3
Total	115

a. Key mutations L74I, E138A/K/T, G140A/C/S.

4.1.13. Evaluation of DTG Dissociation from Wild Type and Integrase Inhibitor Resistant Integrase-DNA Complexes

The dissociation of DTG, RAL, and EVG from wild type and mutant IN proteins complexed with DNA was investigated to obtain a better understanding of INI dissociation kinetics. DTG demonstrated slower dissociation from all IN-DNA complexes tested, including those with single and double residue IN substitutions, compared to RAL and EVG.

The dissociation rate of [^{3}H]-labeled INIs, including DTG was determined at 37°C against a panel of integrase proteins, including wild type and signature RAL and EVG resistant mutations (WT, E92Q, G140S, Y143C, Y143H, Y143R, Q148H, Q148K, Q148R, N155H, E92Q/N155H, E138K/Q148R, G140S/Q148H) (GSK Document number, 2011N114191_00). Integrase:DNA duplexes attached to Scintillation Proximity Assay (SPA) imaging beads were incubated with [^{3}H]-labeled DTG, RAL, or EVG overnight to achieve maximum binding. Excess unlabeled INI was added to block re-binding of the released ^{3}H-INI which results in a decrease in signal measured via a ViewLux™ CCD imager for up to 2.5 weeks.

For wild type integrase, the half-life of dissociation for DTG was approximately 71 hours at 37°C, substantially longer than the half-life for RAL (8.8 hours) or EVG (2.7 hours). Prolonged binding ($t_{1/2}$ of at least 7 hours) was observed for DTG with E92, Y143, Q148,

and N155 integrase mutants. For all of the integrase mutants tested, the off-rate of DTG was significantly slower (from 6 to 60 times slower) than the off-rate of RAL or EVG. The addition of a second mutant to either a Q148 or N155 mutant resulted in an increase in the dissociation rate compared to the single mutant but DTG retained significant binding (Table 30).

Table 30 Dissociation of INIs from IN-DNA Complexes at 37°C

IN	$K_{off}(s^{-1})^a$ (10^{-6})			$t_{1/2}$(h)		
	DTG	RAL	EVG	DTG	RAL	EVG
Wild type	2.7 ± 0.4	22 ± 2	71 ± 4	71	8.8	2.7
E92Q	11.4 ± 0.3	59 ± 9	430 ± 20	17	3.3	0.4
E138K	2.3 ± 0.2	17 ± 0.3	52 ± 1	84	11	3.7
G140S	9.6 ± 0.8	44 ± 3	180 ± 20	20	4.4	1.1
Y143C	3.2 ± 0.1	96± 4	91 ± 2	60	2.0	2.1
Y143H	4.4 ± 0.2	78± 2	120 ± 6	44	2.5	1.6
Y143R	4.6 ± 0.3	176 ± 4	116 ± 5	42	1.1	1.7
Q148H	37 ± 3	1160 ± 120	1130± 140	5.2	0.2	0.2
Q148K	18 ± 5	730 ± 130	ND	11	0.3	ND
Q148R	21 ± 2	480 ± 80	ND	9.2	0.4	ND
N155H	20 ± 2	300 ± 80	500 ± 140	9.6	0.6	0.4
E92Q/N155H	49 ± 3	770 ± 70	ND	3.9	0.3	ND
E138K/Q148H	53 ± 10	900 ± 340	ND	3.6	0.2	ND
G140S/Q148H	58 ± 8	1130 ± 210	ND	3.3	0.2	ND

a. k_{off} values represent mean and SD for 3 to 8 independent experiments. ND denotes not determined due to low signal with [^{3}H]EVG.

In addition to specific RAL and EVG resistance-based mutant integrase proteins, the binding of DTG, RAL, and EVG was determined for integrase proteins based on treatment emergent resistance mutations observed with RAL resistant viruses in the clinical study ING112961 and for substitutions and combinations of substitutions identified during passage studies and their related control proteins (GSK Document number 2012N145179_00). G118R and G118R/E138K were observed during passage with MK-2048, P145S was observed during passage with EVG, R263K was observed during passage with DTG, and the V75I/E138K/G140S/Q148H/M154I combination was observed during passage of Q148H virus with DTG. Under the conditions used in these experiments the signal with [^{3}H]RAL and [^{3}H]EVG was not sufficient to determine k_{off} for some of the IN substitutions.

Prolonged binding ($t_{1/2}$>1 h) was observed for DTG with all of the combinations of IN substitutions derived from the ING112961 study genotypes (Table 31), except for proteins with the combinations of E92Q/G140S/Q148H ($t_{1/2}$ = 0.4 – 0.6 h) and G140S/Q148H/N155H ($t_{1/2}$ = 0.3 – 0.5 h).

Table 31 Dissociation of INIs from IN-DNA Complexes at 37°C: IN Substitutions Observed during VIKING

IN	k_{off} (s^{-1})[a] ($x10^{-6}$)			$t_{1/2}$ (h)[b]		
	DTG	RAL	EVG	DTG	RAL	EVG
T97A/Y143R/N155H	84 ± 10	ND	ND	2.3	0.1	ND
L74M/T97A/Y143R	20 ± 2	760 ± 50	280 ± 40	9.6	0.3	0.7
L74M/T97A/Y143R/N155H	80 ± 11	ND	ND	2.4	ND	ND
L74M/T97A/E138A/Y143R/N155H	89 ± 16	2619	2550 ± 620	2.2	0.1	0.1
L74M/G140S/Q148H	58 ± 6	1430 ± 350	ND	3.3	0.1	ND
L74M/E138A/G140S/Q148H	81 ± 15	2482	ND	2.4	0.1	ND
L74M/T97A/G140S/Q148H	170 ± 50	2275	ND	1.1	0.1	ND
G140S/Y143H/Q148H	50 ± 9	ND	ND	3.9	ND	ND
E92Q/G140S/Q148H	300 ± 40	ND	ND	0.6	ND	ND
E92Q/E138T/G140S/Q148H	450 ± 50	ND	ND	0.4	ND	ND
E138K/G140S/Q148H	64 ± 11	1140 ± 300	ND	3.0	0.2	ND
G140S/Q148H/N155H	380 ± 8	ND	ND	0.5	ND	ND
E138K/G140S/Q148H/N155H	560 ± 20	ND	ND	0.3	ND	ND

a. k_{off} values represent mean and SD for 3 to 7 independent experiments except where noted with * ("n = 1 or 2). ND denotes not determined due to low signal with [^{3}H]EVG

b. For reference, $t_{1/2}$ values for DTG, RAL, and EVG with a wild type IN-DNA complex with IN protein from BH10 virus are 71 h, 8.8 h, and 2.7 h, respectively..

The addition of multiple RAL secondary substitutions to IN with Q148H generally resulted in faster DTG dissociation. Dissociative half-lives of 2.1 h and 1.0 h were obtained for DTG with IN-DNA complexes containing the E138K/G140S/Q148H/M154I and V75I/E138K/G140S/Q148H/M154I substitution, respectively. The dissociative half-life for DTG was greater than 10 h (10.3 to 15.5 h) for IN-DNA complexes containing the IN substitutions from DTG passage studies G118R, G118R/E138K, P145S, or R263K Table 32).

Table 32 Dissociation of INIs from IN-DNA Complexes at 37°C: IN Substitutions Observed during Passage Studies

IN	k_{off} (s^{-1})[a] ($x10^{-6}$)			$t_{1/2}$ (h)[b]		
	DTG	RAL	EVG	DTG	RAL	EVG
E138K/G140S/Q148H/M154I	90 ± 17	1630 ± 60	ND	2.1	0.1	ND
V75I/E138K/G140S/Q148H/ M154I	200 ± 40	ND	ND	1.0	ND	ND
G118R	18 ± 1	71 ± 12	215 ± 11	10.7	2.7	0.9
G118R/E138K	19 ± 1	61 ± 3	168 ± 6	10.1	3.2	1.1
P145S	11.1 ± 0.5	57 ± 4	ND	17.3	3.4	ND
WT (B)	7.5 ± 0.4	40 ± 1	88 ± 3	25.7	4.8	2.2
WT(C)	5 ± 0.1	23 ± 1	73 ± 3	38.5	8.4	2.6
R263K(B)	12.4 ± 0.4	52 ± 2	164 ± 8	15.5	3.7	1.2
R263K(C)	8.6 ± 1.1	31 ± 1	ND	22.4	6.2	ND

a. k_{off} values represent mean and SD for 3 to 7 independent experiments except where noted with * (“n = 1 or 2). ND denotes not determined due to low signal with [^{3}H]EVG

b. For reference, t1/2 values for DTG, RAL, and EVG with a wild type IN-DNA complex with IN protein from BH10 virus are 71 h, 8.8 h, and 2.7 h, respectively.

4.1.14. Integrase Polymorphism Effects on DTG Resistance and Clinical Response

A total of 2997 IN sequences were identified and aligned from integrase inhibitor naive sequences obtained from [redacted] and [redacted]. The major genomic subtypes represented in this data set included B (55%), CRF02_AG (13%), C (13%), and CRF01_AE (6%). The analysis revealed a high degree of conservation across the 288 amino acid residues. The majority of positions (59% were found to vary by <1 % at the amino acid level (ie. >99% conservation). These highly conserved positions spanned long regions across the IN protein. However, a total of 34 positions met the criteria for a polymorphic site (>10% amino acid diversity) and were found to be distributed across IN (Vavro, 2013).

To characterize any impact on DTG susceptibility of polymorphisms seen in the integrase enzyme, a panel of site-directed molecular clones (SDMs) was constructed from pNL-432 with single, double, and triple mutants (Vavro, 2013). This panel comprised IN substitutions identified during in vitro passage with DTG as well as IN polymorphic sites. Baseline viruses from a study in INI naive, HIV-infected patients were evaluated for DTG and RAL susceptibility and differences in HIV-1 RNA decline with DTG monotherapy were evaluated. Fold change susceptibility to DTG and RAL was measured using HeLa CD4 cells.

The SDMs with polymorphic amino acid changes T124A and L101I had DTG FC values below the assay cutoff for reduced susceptibility. Fold change for SDMs ranged from 0.91 for the L101I/T124A double substitution to 2.5 for the non-polymorphic substitution S153Y, which arose during in vitro passage of DTG (Table 33). The mean FC for L101I was 1.4 for DTG and 1.2 for RAL, each of which is within the assay’s variability. The

addition of polymorphisms L101I and T124A to the S153F mutation had FC within the assay's variability of 2. DTG trough concentrations are 19-fold above the protein-adjusted inhibitory concentration at 90% (IC90) of 152 nM that was observed at the once-daily, 50 mg dose; this is well above the maximum FC for all SDMs tested in this study.

Table 33 In vitro drug susceptibility[a] for site-directed mutants with polymorphisms and substitutions observed during DTG passage

Amino acid substitution in NL-432	Where observed	DTG FC, mean	RAL FC, mean
L101I	Polymorphism/Passage	1.40	1.20
T124A	Polymorphism/Passage	0.95	0.82
L101I/T124A	Polymorphism	0.91	0.77
S153F	Passage	1.60	1.30
S153Y	Passage	2.50	1.30
L101I/S153F	Polymorphism/Passage	2.00	1.30
L101I/T124A/S153F	Polymorphism/Passage	1.90	1.40
E92Q	Passage	1.60	3.50
G193E	Passage	1.30	1.30

a. Assay variability of 2-fold changes

In the phase IIa dose-ranging study of DTG monotherapy, HIV-infected subjects were randomized to receive DTG (2, 10, or 15 mg) as a monotherapy or placebo every 24 hours for 10 days (Min, 2011). IN genotypes and phenotypes were determined at Day 1 by [redacted]. Differences in the group median FC were calculated for DTG and RAL at sites 101 and 124 (Table 34). All 101 and 124 genotypes had similar IC_{50} values and overlapping variance ranges for DTG and RAL. The average FC to DTG was 0.79, and the average FC to RAL was 0.89. No polymorphism showed an average shift in susceptibility >2-fold to either DTG or RAL, and no median FC observed was greater than the FC assay variability.

Table 34 Fold Change Response to DTG and RAL for Day 1 Isolate Samples (N = 35) with variation at amino acids 101 and 124

Site			DTG FC	RAL FC
101	124	Subjects, n	Median (range)	Median (range)
L101L	T124T	6	0.64 (0.47 – 0.89)	0.72 (0.5 – 0.95)
L101L	T124A	5	0.97 (0.63 – 1.17)	0.91 (0.58 – 1.05)
L101L	T124N	7	0.78 (0.66 – 0.82)	0.92 (0.83 – 1.41)
L101L	T124S	2	0.825 (0.79 – 0.86)	0.965 (0.96 – 0.97)
L101L	T124T/N	1	0.89	0.82
L101L	T124T/N/D/A	1	0.89	1.15
L101I	T124T	5	0.79 (0.72 – 0.88)	0.86 (0.84 – 1.16)
L101I	T124A	3	0.81 (0.78 – 0.89)	0.79 (0.76 – 0.97)
L101I	T124N	3	0.85 (0.46 – 0.86)	0.97 (0.89 – 0.98)
L101I	T124S	1	0.74	0.64
L101I	T124T/N	1	0.8	1.16

Two additional analyses for the phase IIa dose-ranging study evaluated polymorphism effects. Dose-adjusted differences in viral load response at Day 11 were compared across the 34 polymorphic positions. The residuals (ie, differences in change from baseline in $\log_{10}$ HIV-1 RNA at day 11 after adjusting for the effect of dose in a linear model) at positions of polymorphic substitutions were consistent with random variation about a mean of zero and a small variance (<0.3 $\log_{10}$ c/mL). This indicated no apparent difference in viral load decline with any polymorphism. In addition, the effect of substitutions at each position was tested using a multivariate linear model that adjusted for dose and the presence or absence of substitutions at each position. The distribution of P values ranged from 0.035 to 0.99, a pattern consistent with no position examined having an effect on day 11 response to DTG.

Baseline clinical samples taken from participants in the phase IIa study showed no differences in HIV-1 RNA decline with any polymorphism, including those involving sites 101 and 124.

4.2. Nonclinical Virology – Lamivudine

Lamivudine (3TC) is a potent and selective inhibitor of HIV-1 and HIV-2 replication in vitro and appears to show synergistic antiviral activity in vitro in combination with AZT or other inhibitors such as the protease inhibitor Ro 31-8959. 3TC shows good activity against AZT-resistant isolates of HIV from clinical studies and may delay the development of AZT resistance when given in combination with AZT. 3TC -resistant HIV has been selected in vitro; resistance being conferred by a change from methionine to either isoleucine or valine at the 184 position in RT.

4.2.1. Listing of in vitro Virology Non-Clinical Studies

A range of studies has been performed to investigate the antiviral activity of 3TC. A list of these studies, together with their report location within this submission is presented in Table 35.

Table 35 List of Studies Investigating the Effects of 3TC

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)
Activity against HIV-1 and HIV-2 in established lymphocyte and monocyte/macrophage cell lines	MT4, JM, C8166, H9, U927, CEM cells	In vitro		No	GSK	GVR/91/011
Activity against HIV-1 and HIV-2 in peripheral blood lymphocytes	PBMCs	In vitro		No	GSK	GVR/91/012
Activity against HIV-1 in activated human lymphocytes and human macrophages	PBMCs	In vitro		No	[redacted]	GVR/91/016
Combination studies with other anti-HIV compounds	MT-4 cells	In vitro		No	GSK	GVR/91/015
Further combination studies with other anti-HIV compounds	MT-4 cells	In vitro		No	GSK	GVR/91/031
Combination studies with AZT using HIV-1 clinical isolates	PBMCs	In vitro		No	GSK	GVR/93/020
Combination studies in vitro with one or two other HIV reverse transcriptase inhibitors	C8166 cells	In vitro		No	GSK	GVR/94/008
Activity against a series of AZT-resistant mutants of HIV-1	MT-4 cells	In vitro		No	GSK	GVR/91/014
Activity of other anti-retroviral compounds against 3TC resistant HIV-1 generated in vitro	C8166 cells	In vitro		No	GSK	GVR/92/077
Effects of culturing AZT-resistant HIV-1 in 3TC with or without AZT	C8166 cells	In vitro		No	GSK	GVR/94/009
Effect of culturing 3TC-resistant HIV-1 in nevirapine and 3TC.	C8166 cells	In vitro		No	GSK	GVR/94/009

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)
High level resistance in vitro is due to one amino acid substitution in the catalytic site of HIV-1 reverse transcriptase	C8166 cells	In vitro		No	GSK, [redacted]	GVR/93/039
Effect of multiplicity of infection on anti-HIV activity	C8166 cells	In vitro		No	GSK	GVR/91/001
Effect of time of addition on anti-HIV activity	C8166 cells	In vitro		No	GSK	GVR/90/007
Activity against HIV-1 and HIV-2 in chronically infected cell lines	H9 cells	In vitro		No	GSK	GVR/91/004
Effect of a series of anti-infective agents on anti-HIV activity	MT-4 cells	In vitro		No	GSK	GVR/91/002
Effect of ganciclovir on the activity of GR3TC against HIV-1 in vitro	MT-4 cells	In vitro		No	GSK	GVR/92/091
Activity against a series of RNA and DNA viruses	Vero cells	In vitro		No	GSK	GVR/91/013
Activity against duck hepatitis B in vitro	Primary cultures of hepatocytes	In vitro		No	GSK	GVR/92/007
Activity against hepatitis B in vitro	2.2.15 cells	In vitro		No	GSK	GVR/93/034
Activity against bacteria	-	In vitro		No	GSK	GVR/91/021
Activity against mycobacteria	-	In vitro		No	[redacted]	GVR/91/018
Activity against fungi	-	In vitro		No	GSK	GVR/91/022
Activity against Pneumocystis carinii	Pneumocystis carinii	In vitro		No	GSK	GVR/91/023
Activity against Entamoeba histolytica	E. histolytica	In vitro		No	[redacted]	GVR/91/025
Activity in the SCID-hu mouse model	Moose (SCID-hu)	In Vivo		No	[redacted]	GVR/91/020

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)
Cytotoxicity in primary and established lymphocytes and monocyte/macrophages	CEM cells	In vitro		No	GSK	GVR/91/006
Cytotoxicity and therapeutic indices in primary lymphocytes	PBMCs	In vitro		No	GSK	GVR/94/017
Effect of 3TC on human T-cell activation in vitro	T-cells.	In vitro		No	GSK	GVR/93/032
Myelotoxicity in human bone marrow progenitor cells	-	In vitro		No	[redacted]	GVR/91/030
Metabolism in peripheral blood lymphocytes	PBMCs	In vitro		No	GSK	GVR/91/005
Concentration dependence of 3TC and the effect of AZT on the phosphorylation of 3TC in human peripheral blood lymphocytes in vitro	PBMCs	In vitro		No	GSK	GVR/93/013
Studies with human platelet phosphorylase	-	In vitro		No	GSK	GVR/91/003
Effect of 3TC 5'-triphosphate on the RNA-dependent DNA polymerase activity of HIV-1 reverse transcriptase	HIV-1 strain BH10	In vitro		No	GSK	GVR/91/008
Effect of 3TC triphosphate on the DNA-dependent DNA polymerase activity of HIV-1 reverse transcriptase	HIV-1 RT	In vitro		No	GSK	GVR/91/026
Chain termination studies with 3TC - triphosphate	HIV-1 RT	In vitro		No	GSK	GVR/91/009

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)
Steady state kinetic studies confirm that 3TC -triphosphate exerts its anti-HIV activity primarily by chain termination	HIV-1 RT	In vitro		No	GSK	GVR/92/013
The incorporation of 3TC -monophosphate into DNA by HIV-1 reverse transcriptase and human DNA polymerase γ	HIV-1 RT	In vitro		No	GSK	GVR/94/007
Effect of 3TC on deoxynucleotide pools in cultured U937 cells	U937 cells	In vitro		No	GSK	GVR/91/027
Effect of 3TC on mitochondrial DNA content	CEM cells	In vitro		No	GSK	GVR/91/017
Effect of 3TC 5'-triphosphate on mammalian DNA polymerases	-	In vitro		No	GSK	GVR/91/010
Evaluation against a panel of HIV-1 and HIV-2 isolates in fresh hujan PBMCs	PBMCs	In vitro		No	[redacted]	RH2004/00089/00
Antiviral Effects of the combination of TNF, 3TC, and ABC in MT4 cells and PBMCs	MT4 cells and PBMCs	In vitro		No	GSK	RH2004/00012/00
Antiviral effects of ABC, 3TC, or FTC in combination with ribavirin	MT4 cells	In vitro		No	GSK	RH2004/00092/00
Antiviral effects of ABC, 3TC, or FTC in combination with ribavirin	CEM-SS cells	In vitro		No	GSK	RH2004/00097/00
Antiviral effects of ABC/3TC in combination with other antiviral agents	MT4 and Hela Cells	In vitro		No	GSK	RH2004/00060/00
Effects on dNTPs after treatment with ABC, 3TC, or TNF	PBMCs	In vitro		No	GSK	RH2005/00091/00

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)
Effects on a human lymphoblastic cell line	CCRF-CEM	In vitro		No	GSK	WD2008/00107/01
Effects on a human lymphoblastic cell line	CCRF-CEM	In vitro		No	GSK	WD2008/00347/00
Effects on a human hepatoma cell line	HEP G-2	In vitro		No	GSK	WD2005/00979/00
Phosphorylation of 3TC in infected and uninfected PBMCs	PBMCss	In vitro		No	GSK	RD2001/00046/00
In vitro combination with ABC	MT4	In vitro		No	GSK	2013N168472
Susceptibility profile of 943 clinical HIV-1 isolates to ABC	Antivirogram	In vitro		No	[redacted]	RR1998/00082/00

Key:
PBMCs = peripheral blood lymphocytes
.

Testing Facility:
[redacted] = [redacted], France.
[redacted] = In collaboration with: [redacted], The Netherlands; [redacted], Canada.
[redacted] = [redacted], [redacted], UK
[redacted] = [redacted], UK.
[redacted] = [redacted], USA.
[redacted] = [redacted], UK.

4.2.2. Anti-HIV Activity in Established Cell Lines

The anti-HIV activity of nucleoside analogues can be dependent on the virus strain, host cell type and assay used to measure such activity. Consequently, to assess the activity of 3TC accurately, a range of virus-cell combinations were employed and inhibitory activity measured in a variety of assays.

The anti-HIV activity of 3TC has been evaluated in a number of established lymphocyte and monocyte/macrophage cell lines infected with HIV strains isolated from a number of geographical locations (GSK Document number GVR/91/011).

MT-4 cells are human $CD4^+$ cells, with integrated HTLV-1 sequences. These cells were infected with HIV-1 strain RF. Antiviral activity assayed by measuring inhibition of virus-induced cell death and inhibition of reverse transcriptase (RT) synthesis.

JM cells (a semi-mature human T-cell line from lymphoblastoid leukaemia) were infected with HIV-1 strain GB8, a lymphotrophic strain isolated from the UK. The antiviral activity of 3TC was determined by counting the number of virus-induced multinucleate giant cells or syncytia formed and by assaying for extracellular viral core protein, p24, using enzyme-linked immunosorbent assay (ELISA).

HIV-1 strain RF was also used to infect C8166 cells (a human T-lymphoblastoid cell line reported to carry but not express HTLV-1). Following incubation with 3TC the anitviral activity was assessed using the syncytial assay and by measuring p24 and RT. The antiviral activity of 3TC was also determined by syncytial assay and inhibition of p24 levels following incubation for 4 days at 37°C with H9 cells (a human cutaneous T-cell lymphoma) infected with HIV-1 strain III_B (USA) and U937 cells (a human monocyte-like cell line from histiocytic lymphoma) infected with HIV-1 strain U455 (Uganda). In addition, the activity of 3TC against HIV-2 was determined. CEM cells (a human T-lymphoblastoid cell line) were infected with HIV-2 strain ROD (Senegal). The infected cells were incubated with 3TC for 4 days at 37°C and antiviral activity determined by syncytial assay. In each virus-cell combination, a multiplicity of infection (MOI) of 1 times 10^{-3} infectious doses/cell was employed.

The concentrations of compound required to reduce each respective virus-induced effect (e.g., number of syncytia) by 50% (IC50) and 90% (IC90) were determined graphically and these are presented in Table 36. 3TC was found to have antiviral activity in all of the virus-cell combinations studied, including activity against HIV-2.

Table 36 Antiviral Activity (μM) of 3TC

Cell Line	MT-4				JM				C8166					
Virus	HIV-1 RF				HIV-1 GB8				HIV-1 RF					
Assay	Viability		RT		Syncytial		p24		Syncytial		p24		RT	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}
3TC	0.48	1.7	0.004	0.032	0.22	1.3	0.09	1.1	0.09	1.3	0.74	1.8	0.008	0.13
3TC	0.19	1.5			0.13	1.3	0.03	0.17	0.13	2.0	0.70	1.8	0.024	0.19
3TC	0.87	2.4			0.09	2.2	0.1	0.9	0.08	1.3	0.39	1.7	0.014	0.14
3TC	1.14	3.5												
3TC														

Cell Line	H9				U937				CEM	
Virus	HIV-1 $HTLV\text{-}III_B$				HIV-1 U455				HIV-2 ROD	
Assay	Syncytial		p24		Syncytial		p24		Syncytial	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}
3TC	0.024	1.3	0.007	0.096	0.22	1.4	0.11	1.0	0.03	0.15
3TC	0.011	0.44	0.015	0.17	0.09	1.3	0.13	1.2	0.05	0.11
3TC	0.017	0.22	0.003	0.13	0.13	1.5	0.11	1.1		

4.2.3. Anti-HIV Activity in Primary Cells

The anti-HIV activity of 3TC has also been evaluated in human peripheral blood mononuclear cells (PBMCs) (GSK Document number GVR/91/012). PBMCs were isolated from human volunteer whole blood and infected with HIV-1 strains RF, LAV, MN, U455 and IIIB at a MOI of 6.4 times 10^{-2} infectious doses/cell (determined by titration in appropriate cell lines). After incubation for seven days, cell free supernatant was assayed for p24 antigen (Table 37).

Table 37 Antiviral Activity of 3TC in Human Peripheral Blood Mononucleur Cells

Virus Strain	IC50 (μM)	IC90 (μM)
HIV-1 Strain IIIB	0.003	0.002
	0.002	0.08
	<0.002	0.012
HIV-1 Strain LAV	0.17	>2.18
	0.085	0.66
	0.013	0.15
HIV-1 Strain MN	0.008	0.17
	0.035	2.18
	0.014	0.18
HIV-1 Stain RF	0.007	0.12
	0.006	0.10
	0.007	0.12
HIV-1 Strain U455	0.028	0.31
	0.028	0.21
	0.04	0.20

A further study investigated the activity of 3TC on the replication of HIV-1 in activated human lymphocytes and human macrophages (GSK Document number GVR/91/016). Virus production was evaluated in activated lymphocytes by measuring RT activity and in infected macrophages by back-titration of the lysed macrophages on activated lymphocytes. At all concentrations tested (0.1 to 3 μg/mL) 3TC inhibited virus production.

3TC was potent against a variety of HIV-1 (subtypes A, B, C, D, E, FG, and O) and HIV-2 isolates when tested in PBMCs, whether assayed with RT (Table 38, Table 39) or p24 (Table 40) (GSK Document number RH2004/00089/00).

Table 38 Antiviral Activity of 3TC and AZT against HIV-1 Subtype Isolates in PBMCs

Compound	HIV-1 Isolate	Subtype	RT IC50 (nM)	p24 IC50 (nM)
3TC	RW/92/009	A	60.0	70.0
AZT	RW/92/009	A	5.83	21.7
3TC	UG/92/029	A	20.0	20.0
AZT	UG/92/029	A	6.65	13.7
3TC	UG/92/037	A	70.0	150.0
AZT	UG/92/037	A	14.6	57.3
3TC	JR-CSF	B	30.0	70.0
AZT	JR-CSF	B	0.80	3.07
3TC	TH/92/026	B	40.0	60.0
AZT	TH/92/026	B	0.18	16.6
3TC	BR/92/025	C	90.0	150.0
AZT	BR/92/025	C	5.04	27.6
3TC	IN/93/101	C	20.0	50.0
AZT	IN/93/101	C	3.95	26.1
3TC	MW/93/959	C	30.0	40.0
AZT	MW/93/959	C	4.83	25.6
3TC	UG/92/001	D	20.0	50.0
AZT	UG/92/001	D	3.04	70.6
3TC	UG/92/024	D	40.0	40.0
AZT	UG/92/024	D	3.90	19.4
3TC	UG/92/046	D	3.00	6.00
AZT	UG/92/046	D	11.0	35.5
3TC	CMU 06	E	1.00	10.0
AZT	CMU 06	E	23.3	15.8
3TC	CMU 08	E	30.0	70.0
AZT	CMU 08	E	19.9	106.6
3TC	TH/93/073	E	60.0	150.0
AZT	TH/93/073	E	0.69	2.45
3TC	BR/93/029	F	30.0	90.0
AZT	BR/93/029	F	0.45	16.0
3TC	BR/93/019	F	70.0	70.0
AZT	BR/93/019	F	3.47	48.5
3TC	BR/93/020	F	20.0	10.0
AZT	BR/93/020	F	16.0	43.1
3TC	G3	G	70.0	100.0
AZT	G3	G	6.23	29.5
3TC	JV1083	G	30.0	50.0
AZT	JV1083	G	1.24	18.8
3TC	RU132	G	3.0	30.0
AZT	RU132	G	8.16	27.8
3TC	BCF01	O	20.0	150.0
AZT	BCF01	O	2.81	28.6
3TC	BCF02	O	90.0	160.0

Compound	HIV-1 Isolate	Subtype	RT IC50 (nM)	p24 IC50 (nM)
AZT	BCF02	O	0.57	6.99
3TC	BCF03	O	30.0	30.0
AZT	BCF03	O	4.68	34.8

Table 39 Average Activity of 3TC against HIV-1 Isolates

Compound	RT Average IC50 (nM)	RT IC50 Range (nM)	RT IC50 Geometric Mean (nM)	p24 Average IC50 (nM)	p24 IC50 Range (nM)	p24 IC50 Geometric Mean (nM)
3TC	40.2 ±30.8	1.00-120.0	26.3	73.8±51.1	6.00-170.0	53.9
AZT	5.71 ±5.29	0.18-23.3	3.30	44.6±142.6	0.91-1000.0	17.6

Table 40 Average Activity of 3TC against HIV-2 Isolates

Compound	RT Average IC50 (nM)	RT IC50 Range (nM)	RT IC50 Geometric Mean (nM)	p24 Average IC50 (nM)	p24 IC50 Range (nM)	p24 IC50 Geometric Mean (nM)
3TC	41.7 ±67.8	2.00-120.0	8.96	NR	NR	NR
AZT	1.51 ±1.38	0.49-4.25	1.16	NR	NR	NR
NR = Not reactive with RETRO-TEK SIV p27 ELISA antibody						

4.2.4. Antiviral Activity in Combination with other Anti-HIV Compounds

A number of studies have been performed to investigate the antiviral activity of 3TC in combination with one or more other anti-HIV compounds.

The first study investigated the antiviral activities of combinations of 3TC with AZT, ddC or ddI (GSK Document number GVR/91/015). MT-4 cells, infected with HIV-1 strain RF at a MOI of 2 times 10^{-3} infectious doses/cell, were incubated with individual or a combination of compounds for 7 days at 37°C. Antiviral activity was evaluated using the MTT formazan assay. Combination index (CI) values were calculated using the median effect principle, in order to indicate whether each combination was synergistic (CI<1), antagonistic (CI>1) or additive (CI=1).

The IC50 value for each compound, correlated well with previous results; 3TC and AZT had IC50 values of 0.16 and 0.019 μg/mL respectively (Table 41). However, when a combination of 3TC and AZT was tested at a weight ratio of 1:1, the IC_{50} value was lower at 0.014 μg/mL. CI values at IC50 and IC90 doses were between 0.21 and 0.38 confirming that the combination of these two compounds produced a synergistic response. Antiviral CI values for combinations of 3TC with ddC or ddI were near to unity (0.73 to 0.98) and probably reflect an additive response to these combinations.

Table 41 IC50 Values[a] for the Antiviral Activities of 3TC in 1:1 Combinations with AZT, ddC, or ddI

Experiment	Compound	IC50 (μg/mL)
1	3TC	0.16
	AZT	0.019
	3TC:AZT	0.014
2	3TC	0.14
	ddC	0.009
	3TC:ddC	0.019
3	3TC	0.15
	ddI	17
	3TC:ddI	0.28

a. IC50 values for combinations of 3TC with AZT, ddC, or ddI are expressed as the total concentration (μg/mL) of a 1:1 mixture.

Studies were subsequently performed in order to investigate further the antiviral activities of combinations of 3TC with AZT, ddC or ddI (GSK Document number GVR/91/031). In addition, combinations of 3TC with the TIBO derivative, R82150 (Janssen), or the protease inhibitor, Ro 31-8959 (Roche), were also studied.

MT-4 cells were infected with HIV-1 strain RF at a MOI of 2 times10^{-3} infectious doses/cell. Infected cells were incubated for 7 days at 37°C with individual or a combination of compounds, titrated using a checkerboard (variable ratio) experimental design. This method allows the determination of the combined compound concentrations at which antiviral effects are most pronounced. All experiments were performed at compound concentrations well below those required to inhibit MT-4 cell metabolic processes. Antiviral activity was evaluated by the MTT formazan assay. CI values were calculated and isobolograms plotted in order to indicate whether each combination was synergistic, antagonistic or additive.

The IC50 value for each compound when tested alone, correlated well with previous results (GSK Document number GVR/91/011). CI values and isobologram plots demonstrated that a combination of 3TC and AZT had a synergistic antiviral effect whilst combinations of 3TC and ddC or ddI had only additive effects on HIV-1 activity (Figure 1, Figure 2, Figure 3). These results are consistent with those reported above (GSK Document number GVR/91/015).

Figure 1 Isobologram Plot of Inhibition of Virus Activity by Combinations of 3TC and AZT

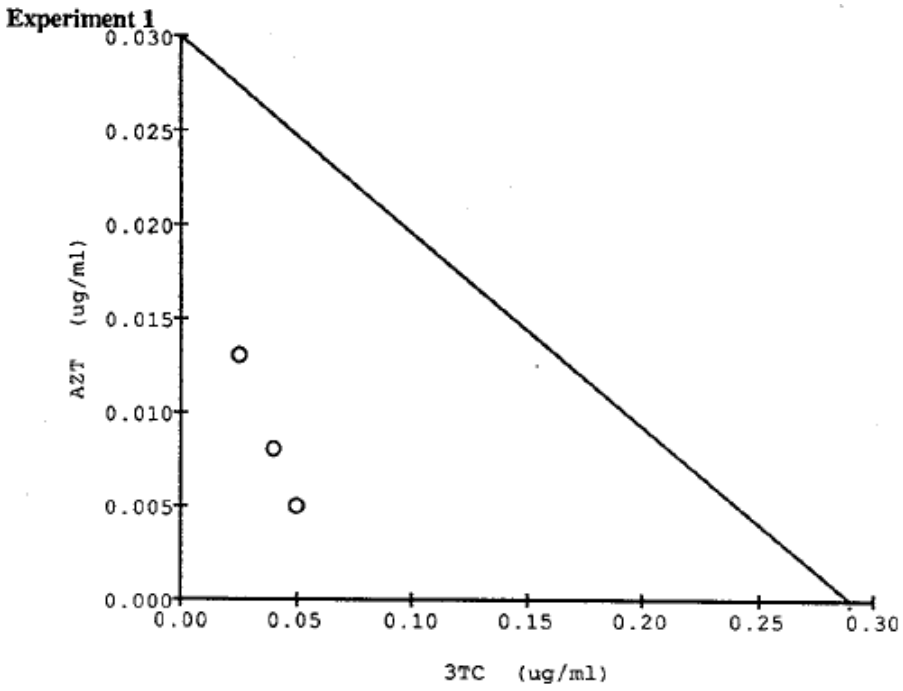


Figure 2 Isobologram Plot of Inhibition of Virus Activity by Combinations of 3TC and ddC

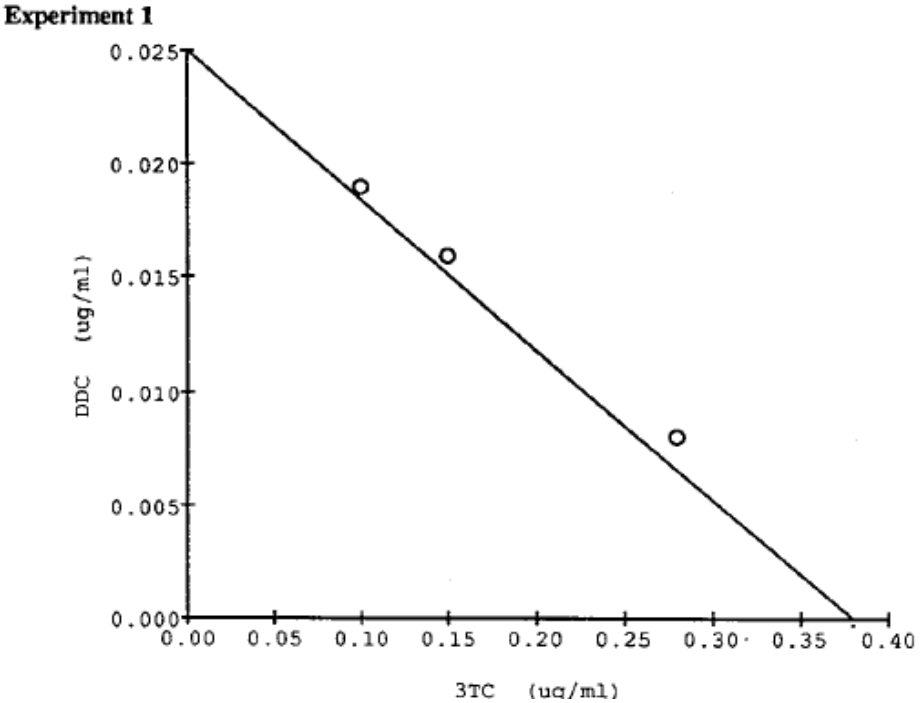
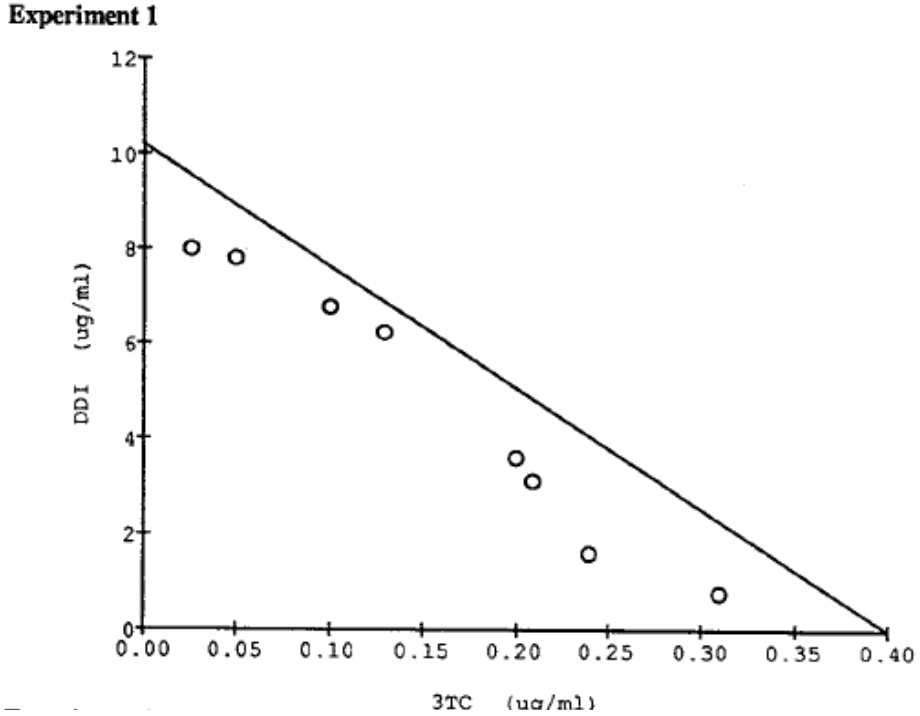


Figure 3 Isobologram Plot of Inhibition of Virus Activity by Combinations of 3TC and ddI



Combinations of 3TC with R82150 or Ro 31-8959 over a range of concentrations showed significant synergistic antiviral activity, since CI values were all less than unity.

As a more direct representation of the clinical situation, a study was subsequently performed which investigated the antiviral activity of 3TC in combination with AZT against a range of HIV-1 clinical isolates in human peripheral blood lymphocytes (PBMCs) (GSK Document number GVR/93/020). The clinical isolates included three of European origin (C0008, C0019 and WP34/29) and a fourth isolate of North American origin [MCK (E174)]. All were isolated from drug-naive patients, and only cultured in human PBMCs.

PBMCs from HIV seronegative donors were infected with each isolate of HIV-1 at a MOI of between 0.002 and 0.05 infectious doses/cell. Infected cells were incubated for 7 days at 37°C with individual or a combination of compounds, titrated using a checkerboard (variable ratio) experimental design. All experiments were performed at compound concentrations which were not cytotoxic. Antiviral activity was evaluated by assaying for p24 antigen in supernatants using ELISA. CI values were calculated and isobolograms plotted in order to indicate whether each combination was synergistic, antagonistic or additive.

The IC50 value for each compound, when tested alone, correlated well with previous results (GSK Document number GVR/91/012). The combined antiviral activities of 3TC and AZT depended on the virus isolate, the dose combination and the batch of PBMCs.

CI values showed that many combinations exhibited synergistic or additive anti-HIV activity whilst there was no evidence of gross antagonistic antiviral activity. Isobolograms indicated that the overall antiviral activity of the combined concentrations of the two compounds was synergistic for isolate C0019, synergistic to additive for isolates WP34/29 and MCK (E174), and additive for isolate C0008.

In a subsequent study the in vitro antiviral activity of 3TC in combination with one or two other HIV RT inhibitors was examined (GSK Document number GVR/94/008). The triple combinations studied were 3TC with:

i) 3'-deoxy-2',3'-didehydrothymidine (d4T) and AZT
ii) d4T and nevirapine (BI-RG-587; Boehringer Ingelheim)
iii) AZT and nevirapine
iv) ddI and nevirapine
v) AZT and ddI

In each case, each inhibitor was also studied in isolation and in double combination with each of the other inhibitors. In addition, combinations of ribavirin and AZT, and ribavirin and ddI were tested in an attempt to validate the studies.

Due to the complexity of the experimental design and data analysis, conclusions from such studies need to be treated with caution. Therefore, the main objectives of the study were to look for antagonism of antiviral activity (and increased cytoxicity).

MT-4 cells were infected with HIV-1 strain RF at a MOI of 2 times 10^{-3} infectious doses/cell. Infected cells were incubated for 7 days with individual or a combination of inhibitors and antiviral activity evaluated using the MTT formazan assay.

In the fixed ratio studies, there was no evidence for substantial antagonism of antiviral activity with any double or triple combination (see Table 42 for an exampleof the data produced).

Table 42 Antiviral Activity of 3TC, AZT, and Nevirapine, Alone or in Combination (Fixed Ratio) in HIV-1 RF Infected MT4 Cells

	Experiment 1		Experiment 2		Experiment 3	
	IC50 (μM)	IC90 (μM)	IC50 (μM)	IC90 (μM)	IC50 (μM)	IC90 (μM)
3TC	0.27	0.78	0.42	3.6	0.21	0.75
AZT	0.032	0.08	0.048	5	0.03	0.088
Nevirapine	0.18	0.7	0.032	0.2	0.032	0.09
3TC + AZT	0.034	0.09	0.029	0.083	0.027	0.078
3TC + Nevirapine	0.033	0.085	0.031	0.078	0.009	0.063
AZT + Nevirapine	0.029	0.076	0.034	≥1	0.005	0.05
3TC + AZT + Nevirapine	0.03	0.076	0.008	1	0.012	0.075

In vitro studies were carried out in human PBMCs, MT-4 or CEM-SS cells (GSK Document numbers RH2004/00012/00 and RH2004/00092/00). No evidence of

antagonism between lamivudine and other NRTIs was seen when cells were treated with various combinations. When fixed dose combinations of abacavir and lamivudine (1:1 or 40:1) were tested in CEM-SS cells, there was no evidence of antagonism with either ribavirin or T-20, but potency was decreased by co-administration of ribavirin (RH2004/00097/00). In combination with protease inhibitors, the mixture was found to be synergistic with the effects of indinavir, lopinavir, amprenavir or nelfinavir, and additive to the effects of saquinavir (GSK Document number RH2004/00060/00).

4.2.5. Activity of 3TC against AZT-Resistant Variants of HIV

A study has been performed to investigate the antiviral activity of 3TC against a series of AZT-resistant HIV-1 variants isolated from HIV seropositive individuals with ongoing AZT therapy of least six months (GSK Document number GVR/91/014). The isolates were propagated in MT-4 cells in the presence of 1 μM AZT to maintain their AZT-resistant phenotype. Infected cells were incubated without treatment, or with 3TC, AZT, ddC or ddI at or above their respective IC90 values, for 7 days at 37°C and the supernatants assayed for p24 core antigen by ELISA. The results are presented in Table 43 and show that all three AZT-resistant isolates were sensitive to 3TC (2 μM); p24 core antigen levels were reduced to 20 to 34% of virus controls. A similar sensitivity was seen to ddC (2 μM) with p24 core antigen levels reduced to 19 to 31%. However, only one of the three isolates was sensitive to ddI (10 μM). None of the isolates showed absolute resistance to AZT or absolute sensitivity to the other dideoxynucleosides which suggests that these isolates were not clonal populations.

Table 43 Sensitivity of AZT-Resistant Isolates of HIV-1 to Other Dideoxynucleosides

Isolate	Phenotype of Isolate	Mean p24 Antigen pg/mL (% virus control)				
		AZT (2 μM)	ddC (2 μM)	ddI (10 μM)	3TC (2 μM)	No Drug
1	AZT-resistant	3190 (67)	1000 (21)	4580 (97)	1210 (26)	4740
2	AZT-resistant	4210 (94)	840 (19)	4400 (98)	890 (20)	4480
3	AZT-resistant	3420 (83)	1260 (31)	1580 (38)	1430 (34)	4140

4.2.6. Activity of other Antiretroviral Compounds against 3TC -Resistant HIV-1 Generated in vitro

In order to investigate the emergence of HIV-1 resistant to 3TC in vitro and the phenotype of resistant viruses, the technique of selection by increasing the drug concentration, reported by Larder, 1991) for AZT, has been followed (GSK Document number GVR/92/077). HIV-1 strain RF was passaged in C8166 cells with increasing amounts of 3TC (up to 457 μM) using the formation of multinucleated giant cells or syncytia as a marker of virus replication. Cell free virus was harvested at 4 days post-infection and used to initiate a new cycle of infection. Resistant virus was titrated by a limiting dilution method after each cycle of infection, and that which grew in the highest dilution was harvested in order to obtain a homogeneous population.

Sensitivity of the 3TC -resistant HIV-1 variant to AZT, ddC, ddI, the non-nucleoside reverse transcriptase inhibitors L-697,639 (Merck, Sharp and Dohme), R-82150 and

nevirapine, and the protease inhibitor Ro 31-8959 (saquinavir) was examined in MT-4 cells by analysis of antiviral activity in the MTT formazan assay. In addition, cross-resistance was also investigated against the (+) enantiomer, gsk002* (the (+) enantiomer of gsk001* ; 3TC is the (-) enantiomer of gsk001*), and against the (+) and (-) enantiomers of the structurally-related analogue, FTC.

In three independent experiments, the IC50 values of 3TC against wild-type HIV-1 RF ranged from 0.16 to 0.4 μM whereas the IC50 values against the 3TC -resistant virus ranged from >4.57 - >457 μM. The data from one of the experiments is presented in Table 44. These data, which are similar to those found in the other two experiments, demonstrate that the 3TC -resistant virus remained sensitive to all compounds tested with the exception of the (-) enantiomer of FTC.

Table 44 Sensitivity Drug Sensitivity Profile of the 3TC -Resistant Variant of HIV-1

Compound	Wild-type HIV-1 RF		3TC-Resistant Variant	
	I_{50} (μM)	TOX (μM)	I_{50} (μM)	TOX (μM)
3TC (-)	0.45	>4.57	>457	457
gsk002* (+)	1.92	45.7	0.82	45.7
AZT	0.02	>3.7	0.002	>3.7
ddC	0.14	>4.74	0.06	>4.74
ddI	7.21	424	11.02	>424
(-) FTC	0.92	>400	34	400
(+) FTC	9.6	>400	1.6	>400
R-82150	0.23	31	0.056	31
Nevirapine	0.095	>38	0.015	>38
Ro 31-8959 (saquinavir)	0.035	>1.5	0.027	>1.5
L-697,639	0.005	>0.28	0.0008	>0.28

4.2.7. High Level Resistance in vitro is due to one Amino Acid Substitution

The mechanism for the development of HIV-1 resistance of 3TC was investigated in a collaborative study with Dr [redacted] from the [redacted] (GSK Document number GVR/93/039).

Two protocols were used to generate 3TC -resistant isolates. In the first, HIV-1 strain RF was passaged in C8166 cells with increasing amounts of 3TC (initial concentration 0.003 μM). Supernatant fluids were harvested when a cytopathic effect was detectable (3 to 4 days) and used to initiate a new cycle of infection at a doubled concentration of 3TC. After approximately 10 passages, 3TC -resistant stock was prepared by passaging three times in 457 μM 3TC. In the second protocol, either HIV-1 strain HXB2 or a clinical isolate C19 were passaged in MT-2 cells with increasing amounts of 3TC (initial concentration 0.2 μM) using the formation of syncytia as a marker of virus replication. Once syncytia were detectable throughout the culture, cell-free virus was harvested and used to initiate a new cycle of infection at a doubled concentration of 3TC. 3TC -resistant virus was harvested after nine passages.

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Sensitivity of the 3TC -resistant isolates to AZT, ddC, ddI, the (+) enantiomer, 3TC, and the (+) and (-) enantiomers of FTC was examined, following the first protocol, in MT-4 cells by analysis of antiviral activity in the MTT formazan assay or, following the second protocol, in HeLa CD4 1ac Z cells by analysis of the antiviral activity in a plaque-reduction assay.

All three isolates were resistant to 3TC; the increase in IC50 ranged between 100 to 1000-fold (Table 45). HIV-1 RF and HIV-1 HXB2 were also resistant to the (-) enantiomer of FTC, but retained sensitivity to AZT, ddC, ddI, 3TC and the (+) enantiomer of FTC (the sensitivity of clinical isolate C19 to these compounds was not determined).

The nucleotide sequence of the RT gene was determined for all three 3TC -resistant strains. The sequence of the RT gene for 3TC -resistant HIV-1 HXB2 and HIV-1 RF was determined following amplification by polymerase chain reaction (PCR); the sequence of C19 was analysed by direct sequencing.

In all three 3TC -resistant strains, an amino acid change from methionine to isoleucine has occurred at codon 184 of RT (within the YMDD motif of the active site) in comparison with the respective pre-selection strain.

The biological significance of the amino acid change at codon 184 was confirmed by generation of recombinant viruses containing isoleucine at this position and subsequent testing of their sensitivity. The 184-isoleucine mutation was introduced into the RT gene of HXB2 and the RT gene obtained from an HIV-1 AZT-resistant isolate (derived from an AZT-treated individual) by site-directed mutagenesis. Sequence analysis confirmed the 184-isoleucine mutation in both RT genes and, in addition, two known AZT mutations (at position 41 and 215) in the AZT-resistant isolate gene.

Recombinant viruses with a 184-isoleucine showed a >100-fold increase in their IC50 value for GR109714X. This confirms the role of the amino acid change at codon 184 in the development of resistance to 3TC. In addition, when 184-isoleucine was introduced into the AZT-resistant clinical isolate, a decline of approximately 50-fold was measured in AZT resistance. This provides further support for the suggestion that the clinical use of 3TC and AZT together may delay the development of viral resistance.

Table 45 Drug Sensitivity Profiles of HIV Isolates Selected In Vitro

Isolate	Status	$IC_{50}(\mu M)$#							Codon at 184
		3TC	(-)FTC	AZT	ddI	gsk002*	(+) FTC	ddC	
HIV-1 RF	Wild-type selected	0.16 >437	2.02 323	0.056 0.015	7.63 12.3	3.50 3.71	2.10 7.07	0.22 0.22	Met Ile
HXB2	Wild-type selected	0.39 >437	0.105 9.29	0.02 0.001	3.18 3.82	0.91 0.57	6.85 1.7	0.42 0.4	Met Ile
C19	Wild-type selected	1.25 92	ND ND	ND ND	ND ND	ND ND	ND ND	ND ND	Met Ile

Key:

The results represent the averages of at least two experiments performed in duplicate. The error was <15%. The correlation coefficients for the data were >0.95.
ND Not Done
Met Methionine
Ile Isoleucine

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4.2.8. Activity against Viruses other than HIV

In order to evaluate the antiviral specificity of 3TC, its antiviral activity against a variety of viruses other than retroviruses was investigated GSK Document number (GVR/91/013). Preliminary studies were performed using the racemate, gsk001* . A range of human herpesviruses comprising herpes simplex types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV) and Epstein Barr virus (EBV), and the respiratory viruses, human rhinovirus types 2 and 14 (HRV-2 and HRV-14), influenza viruses A and B, and respiratory syncytial virus (RSV) were propagated in cell lines which support productive infection of the respective virus, and in which suitable antiviral compounds are active. In most virus-cell combinations, antiviral activities were evaluated by determining the dose of compound required to inhibit the formation of virus-induced cytopathic effect (syncytia formation or cell lysis) by 50% (IC50 value). Inhibition of RSV replication was investigated using viral antigen as the marker, and in the case of EBV, which does not cause a cytopathic effect, cells were analysed for the presence of EBV DNA sequences. Even at the highest concentrations employed (1314 μM against VZV, 438 μM against other viruses tested), 3TC had no antiviral activity against any of the viruses tested (Table 46).

Table 46 Antiviral Activity of 3TC against a Series of DNA and RNA Viruses

	IC50 (μM)				
Virus	**3TC**	**Acyclovir**	**Ganciclovir**	**Ribavirin**	**Amantadine**
HSV-1	>438	0.28	ND[a]	ND	ND
HSV-2	>438	8.2	ND	ND	ND
VZV	>1314	9.5	ND	ND	ND
CMV	>438	ND	0.35	ND	ND
EBV	>438	2.89 – 3.78	0.5 – 2.35	ND	ND
Influenza A	>438	ND	ND	12.3	1.6
Influenza B	>438	ND	ND	123	>27
RSV	>438	ND	ND	0.27 – 26.7	ND
HRV-2	>438	ND	ND	ND	ND
HRV-14	>438	ND	ND	ND	ND

a. ND, not done

The effect of 3TC against hepatitis B virus has also been investigated. The activity of 3TC against duck hepatitis B virus (DHBV) was evaluated in primary hepatocyte cultures from chronically infected ducklings (GSK Document number GVR/92/007,). Like human HBV, DHBV is a hepadnavirus and utilises reverse transcriptase in its replication mechanism. Primary cultures of hepatocytes were prepared from 2 week old ducklings (the progeny of infected parents) which had been screened after hatching to confirm the presence of DHBV DNA in their serum. Cells were treated with 3TC for 16 days after which intracellular DHBV DNA levels were measured by dot blot hybridisation using a [^{32}P]-labelled DHBV DNA probe followed by liquid scintillation. The data showed that 3TC decreased DHBV DNA levels in chronically infected hepatocytes with an IC50 of ≤0.1 μg/mL (0.44 μM).

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In a subsequent study, the effect of 3TC on HBV production in 2.2.15 cells (a human hepatoma cell line stably-transfected with HBV DNA) was studied over a six week period (GSK Document number GVR/93/034). Confluent 2.2.15 cells were passaged for 4 weeks in medium containing 3TC at 1 or 10 μg/mL. At the end of week 4, compound treatment was withdrawn and fresh medium was added. During the following 11 days the cells were not passaged, the medium was not changed and every second day 0.5 mL of culture supernatant was removed. On the eleventh day cellular DNA was extracted from these cells, and from cells that had been continually treated with 3TC at 1 or 10 μg/mL (total treatment period of 6 weeks). Viral DNA was also extracted from the supernatant samples taken over the 11 day period. Extracted DNA samples were studied by Southern blot analysis and hybridisation using an [α-^{32}P] dCTP-labelled HBV-DNA probe.

Treatment of 2.2.15 cells with 3TC at 1 or 10 μg/mL for 6 weeks resulted in an inhibition of the production of replicative HBV-DNA intermediates and mature virion HBV-DNA. Viral production rebounded following the withdrawal of treatment as demonstrated by the presence of replicative HBV-DNA intermediates in 2.2.15 cells and virion HBV-DNA in cell supernatant 11 days after treatment withdrawal. Viral HBV-DNA was only detected in cell supernatant from 4 days after withdrawal of treatment indicating that viral production does not rebound immediately.

4.2.9. Effects on Mammalian DNA Polymerases

The effects of 3TC 5'-triphosphate on the mammalian DNA polymerases α, β and γ have been assessed and compared with those of the triphosphates of AZT, ddC and ddA. DNA polymerase α is thought to play a major role in semi-conservative DNA replication. DNA polymerase $\beta$is thought to be involved in DNA repair synthesis. DNA polymerase γ is the polymerase activity found in mitochondria and is believed to be the enzyme responsible for the replication of mitochondrial DNA and therefore, ultimately responsible for the normal functioning of mitochondria.

DNA polymerases α, β and γ were purified from HeLa Ohio cells (a cell line derived from a human cervical carcinoma) and were characterised on the basis of known biochemical properties along with K_m values for deoxynucleotide triphosphates (dNTP) (GSK Document number GVR/91/010). The effect of 3TC 5'-triphosphate on the activity of each polymerase was investigated using radiolabelled dCTP at a concentration equal to the K_m; dATP, dGTP, dTTP at concentrations >10K_m and activated calf thymus DNA as template/primer. gsk001* 5'-triphosphate, gsk002* 5'-triphosphate, ddA 5'-triphosphate, ddC 5'-triphosphate and AZT 5'-triphosphate were also assayed using appropriate radiolabelled and non-radiolabelled dNTPs. ddA 5'-triphosphate was included as a comparator since it is believed to be the active form of ddI. IC_{50} values were determined, where possible, from plots of ([inhibitor]/fraction of inhibition) against [inhibitor]. For 3TC 5'-triphosphate with DNA polymerase α, a linear-relationship was not observed in such plots, therefore IC_{50} values were estimated from linear portions of plots of the reciprocal initial rate against inhibitor.

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The results of these experiments are presented in Table 47. All of the compounds tested were poor inhibitors of DNA polymerase α. 3TC 5'-triphosphate had a mean IC_{50} of 175 μM against this enzyme. 3TC 5'-triphosphate was also a weak inhibitor of DNA polymerase γ with a mean IC_{50} of 43.8 μM (K_i = 15.8 μM; [Hart, 1992]). The results with DNA polymerase β were qualitatively very similar to those with DNA polymerase γ, 3TC 5'-triphosphate showing only weak inhibition of this enzyme with a mean IC_{50} of 24.8 μM (K_i = 18.7 μM; [Hart,1992]).

Table 47 Effect of Triphosphates on Mammalian DNA Polymerases

Enzyme	IC_{50} at [dNTP]=K_m (μM)					
	3TC 5'-triphosphate (-)	gsk001* 5'-triphosphate (racemate)	gsk002* 5'-triphosphate (+)	ddA 5'-triphosphate	ddC 5'-triphosphate	AZT 5'-triphosphate
DNA Polymerase α	173 153 154 219	79.2 70.5 110.6	44.6 36.6	>500	>500	>850 >850
DNA Polymerase γ	30.9 64.0 50.1 30.0	0.069 0.108 0.048 0.041	0.045 0.052	0.062 0.074	0.035 0.027	130 164
DNA Polymerase β	15.5 36.8 22.1	0.62 0.22	Not Determined	0.73 0.77	0.53 0.58	>100 850

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A further study was performed to assess whether 3TC 5'-triphosphate could act as a substrate for DNA polymerase γand whether the 3'-5' exonuclease activity of DNA polymerase γ could excise any incorporated 3TC-monophosphate (GSK Document number GVR/94/007).

DNA polymerase γ, purified from HeLa Ohio cells, was used in an incorporation assay in which an oligodeoxynucleotide primer was labelled with ^{32}P prior to annealing it to its complimentary sequence on an M13mp 18 (+) DNA template. The kinetic constants K_m and k_{cat} were determined for the incorporation of 3TC-monophosphate and dCMP (from the natural substrate dCTP), into the DNA primer catalysed by DNA polymerase γ.

The data, presented in Table 48, indicated that 3TC 5'-triphosphate had a similar K_m value to the natural substrate dCTP and thus would be utilised as a substrate as efficiently by DNA polymerase γ.

Table 48 Kinetic Constants for HeLa Cell DNA Polymerase γ (DNAdepDNApol)

Substrate	K_m (μM)	k_{cat} (min^{-1})	k_{cat}/K_m (M^{-1} times min^{-1})
3TC 5'-triphosphate	3.18± 0.63	0.0232 ± 0.0009	7.3 times 10^3
3TC 5'-triphosphate	6.46 ± 0.61	0.0186 ± 0.0003	2.9 times 10^3
dCTP	1.24 ± 0.52	0.0074 ± 0.0007	6.0 times 10^3
dCTP	6.26 ± 1.32	0.0099 ± 0.0003	1.6 times 10^3

In order to investigate the potential for excision of 3TC-monophosphate from the 3' end of a primer, 16-mer oligodeoxynucleotide primers containing 3TC-monophosphate, ddCMP or dCMP were synthesised and annealed to M13 mp 18 (+) DNA. Initial velocities of the 3'-5' exonuclease activity of DNA polymerase γ was calculated for each primer from reaction time courses.

The data, presented in Table 49, showed that DNA polymerase γ was able to excise 3TC-monophosphate from the primer-template. The rate of excision of 3TC-monophosphate was similar to those for ddCMP and dCMP.

Table 49 HeLa Cell DNA Polymerase γ (3'-5' Exonuclease activity)

Substrate	Initial Velocity (moles/min/L)
5' ATGCCACTACGAAGGC 3'	11.58 ± 0.06 times 10^{-12}
5' ATGCCACTACGAAGG-ddCMP 3'	6.7 ± 0.76 times 10^{-12}
5' ATGCCACTACGAAGG-GR109714X-monophosphate 3'	7.69 ± 0.13 times 10^{-12}

The ability of DNA polymerase γ to incorporate and excise 3TC-monophosphate or dCMP sequentially was subsequently investigated in the presence and absence of 3TC 5'-triphosphate and dCTP respectively (GSK Document number GVR/94/007). The data indicated that the rate of incorporation of 3TC 5'-monophosphate increased with increasing concentrations of 3TC 5'-triphosphate, and that there was no change in the rate of 3'-5' exonuclease activity in the presence and absence of 3TC 5'-triphosphate. The same results were demonstrated for dCTP.

Overall, these studies demonstrate that although 3TC 5'-triphosphate is a substrate for the DNA-dependent DNA polymerase activity of DNA polymerase γ, the product of this reaction is also a substrate for the 3'-5' exonuclease activity of DNA polyerase γ. This may explain the low levels of mitochondrial toxicity observed with 3TC.

4.3. Clinical Virology - Dolutegravir plus Lamivudine (204861 and 205543)

Study Title: A Phase III, randomized, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults Week 48.

Study Design: This study is an ongoing, Phase III, randomized, double-blind, active-controlled, multicenter, parallel-group, non-inferiority study. The study randomized 719 (204861) 722 (205543) HIV-1 infected, ART-naïve subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. Subjects were randomized 1:1 to receive a 2-drug regimen of DTG + 3TC once daily or DTG + TDF/FTC FDC once daily. Subjects were stratified by screening HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and Screening CD4+ cell count (≤ or >200 cells/mm^3).

4.3.1. Viral Genotyping and Phenotyping

204861

Virology data from the Week 48 analyses demonstrated the following:

- Protocol-defined Confirmed Virologic Withdrawal (CVW) through Week 48 was low, with 4 subjects in the DTG + 3TC group and 2 subjects in the DTG + TDF/FTC group meeting CVW criteria at any time through Week 48.

- No subject meeting CVW in either group had treatment emergent INSTI or NRTI resistance associated mutations through Week 48.

205543

Key results of the Week 48 virology analyses include the following:

- Protocol-defined CVW through Week 48 was low, with 2 subjects in each treatment group meeting CVW criteria at any time through Week 48.
- No subject meeting CVW in either group had treatment emergent INSTI or NRTI resistance associated mutations through Week 48.

4.3.1.1. Virologic Withdrawal Criteria

Suspected Virologic Withdrawal

A single HIV-1 RNA value as defined by Virologic Non-response or Virologic Rebound below.

Confirmed Virologic Withdrawal

A second and consecutive HIV-1 RNA value meeting Virologic Non-response or Rebound.

Virologic withdrawal criteria were confirmed by a repeat and consecutive plasma HIV-1 RNA measurement between 2 and 4 weeks after the subject met a SVW criterion unless a delay was necessary to meet the requirements of confirmatory HIV-1 RNA testing For the purposes of clinical management in this study, virologic withdrawal criteria are defined as any of the following:

Virologic Non-response

- A decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 12, with subsequent confirmation, unless plasma HIV-1 RNA is <200 c/mL.
- Confirmed plasma HIV-1 RNA levels ≥200 c/mL on or after Week 24.

Virologic Rebound

- Confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

4.3.1.2. Confirmed Virologic Withdrawal Frequency

204861

A total of 4 subjects in the DTG + 3TC group met CVW criteria by Week 48; 1 subject at Week 16, 2 subjects at Week 24, and 1 subject at Week 48. Two subjects in the DTG + TDF/FTC group met CVW criteria by Week 48; 1 subject at Week 24 and the other at Week 48 All subjects meeting CVW criteria were classified as virologic rebound (Table 50).

Table 50 Cumulative Summary of Confirmed Virologic Withdrawals by Visit through Week 48 in Study 204861 (ITT-E Population)

Week	DTG + 3TC N=356 (n%)	DTG + TDF/FTC N=358 (n%)
Any time	4 (1%)	2 (<1%)
Virologic non-response	0	0
Rebound	4 (1%)	2 (<1%)
Week 16	1 (<1%)	0
Virologic non-response	0	0
Rebound	1 (<1%)	0
Week 24	3 (<1%)	1 (<1%)
Virologic non-response	0	0
Rebound	3 (<1%)	1 (<1%)
Week 36	3 (<1%)	1 (<1%)
Virologic non-response	0	0
Rebound	3 (<1%)	1 (<1%)
Week 48	4 (1%)	2 (<1%)
Virologic non-response	0	0
Rebound	4 (1%)	2 (<1%)

Data Source: 204861 Week 48 CSR Table 2.18

205543

A total of 2 subjects in each treatment group met CVW criteria by Week 48; all were at Week 24. All subjects meeting CVW criteria were classified as virologic rebound (Table 51).

Table 51 Cumulative Summary of Confirmed Virologic Withdrawals by Visit through Week 48 in Study 205543 (ITT-E Population)

Week	DTG + 3TC N=360 (n%)	DTG + TDF/FTC N=359 (n%)
Any Time	2 (<1%)	2 (<1%)
Virologic non-response	0	0
Rebound	2 (<1%)	2 (<1%)
Week 16	0	0
Virologic non-response	0	0
Rebound	0	0
Week 24	2 (<1%)	2 (<1%)
Virologic non-response	0	0
Rebound	2 (<1%)	2 (<1%)
Week 36	2 (<1%)	2 (<1%)
Virologic non-response	0	0
Rebound	2 (<1%)	2 (<1%)
Week 48	2 (<1%)	2 (<1%)
Virologic non-response	0	0
Rebound	2 (<1%)	2 (<1%)

Data Source: 205543 Week 48 CSR Table 2.18

4.3.1.3. Genotype and Phenotype

Q^2 Solutions genotypic resistance assay (PR and RT) was used to assess pre-treatment resistance for subject eligibility to enter the study as screening process. Integrase Phenosense, Integrase Geneseq and PhenoSense GT on study resistance assays were performed at [redacted] ([redacted]). Resistance testing for CVW subjects used the Day 1 sample and the initial elevated viral load ("SVW") sample.

204861

Determination of treatment emergent resistance requires successful baseline and on treatment resistance testing. All resistance testing was successful except for integrase phenotype assay on the CVW sample in one subject (Subject [redacted]) on DTG+TDF/3TC (Data source: 204861 Week 48 CSR Table 4.1 and Table 4.2).

There was no treatment emergent INSTI or NRTI resistance associated resistance observed for any subject meeting CVW criteria (Table 52 and Table 53).

Table 52 Summary of Virologic and Resistance Data through Week 48 for CVW Subjects in the DTG+3TC Arm

DTG+3TC ARM																
						HIV-RNA (c/mL)			IN GT IN RC(%)		DTG FC		NRTI GT PR/RT RC (%)		3TC FC	
Subj	HIV Subtype	CVW Visit	BL PSSf / GSS	CVW PSSf / GSS	Virologic Failure	BL	SVW/ CVW	WD	BL	CVW	BL	CVW	BL	CVW	BL	CVW
[redacted]	BF	W16	2/2	2/2	Rebound	124492	6648/ 56435	95	None NR	None NR	0.67	0.72	None 206	None 156	1.13	1.12
[redacted][a]	B	W24	2/2	2/2	Rebound	50263	348/ 206	96	None 193	None NR	0.76	0.7	None 111	None NR	0.98	0.69
[redacted]	F	W24	2/2	2/2	Rebound	368439	212/ 376	362	G193G/E 74	None 74	0.88	0.86	None 127	None NR	1.02	1.43
[redacted][b]	B	W48	2/2	2/2	Rebound	37701	43908/ 38457b		None NR	None 78	0.8	0.79	None 1.8	None NR	0.9	1.74

Data Source: 204861 Week 48 CSR Listing 85; Listing 50 (viral load); Listing 77 (HIV-1 Subtype).

a. Subject [redacted]- GenSeq Integrase Genotypic test and the PhenoSense Integrase Phenotypic test failed on the Virologic withdrawal time point sample. PhenoSense GT + Integrase test was successfully performed on this sample and is the source of the Integrase phenotype and genotype data.

b. Subject [redacted]met CVW with viral load of 38457 c/ml at withdrawal visit. No subsequent visit was performed post withdrawal.

"None" indicates no IAS-USA major mutations or IN pre-specified resistance mutations observed; NR = data not reported due to assay failure; GT = Genotype; RC = Replication Capacity; subject HIV-1 clinical isolate replication as a percentage of wildtype HIV-1 replication; FC = Fold Change compared to wild type HIV-1 virus; GSS = Standford Genotypic Susceptibility Score; PSSf = Phenotypic Susceptibility Score (with full sensitivity only)

Note: IN resistance pre-specified mutations included H51Y, T66A/I/K, L74M, E92Q/V/G, Q95K, T97A, G118R, F121Y, E138A/K/D, G140A/C/S, Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K, S230R, R263K, L68V/I, L74I, E138T, V151I, G193E; Major resistance mutations to other classes (NRTI, NNRTI, PI) are as defined by the IAS-USA most recent guidelines available at the time of DBF [www.iasusa.org, 2017].

Table 53 Summary of Virologic and Resistance Data through Week 48 for CVW Subjects in the DTG + TDF/FTC Arm

DTG + TDF/FTC ARM																		
						HIV-RNA (c/mL)			IN GT RC (%)		DTG FC		NRTI GT PR/RT RC (%)		TDF FC		FTC FC	
Subj	HIV Subtype	CVW Visit	BL PSSf / GSS	CVW PSSf / GSS	Virologic Failure	BL	SVW/ CVW	WD	BL	CVW	BL	CVW	BL	CVW	BL	CVW	BL	CVW
[redacted]	B	W24	3/3	2/3	Rebound	10930	1136/ 809	647	None 63	None NR	0.72	NR	None 24	None 15	1	0.81	0.92	0.95
[redacted]	B	W48	3/2.25	3/3	Rebound	1568	8384/ 3653	3011	G193E 69	G193G/E 47	1.05	1.05	K70K/E 59	None 60	0.76	0.77	1.14	1.28

Data Source: 204861 Week 48 CSR Listing 85; Listing 50 (viral load); Listing 77(HIV-1 Subtype).

"None" indicates no IAS-USA major mutations or IN pre-specified resistance mutations observed; NR = data not reported due to assay failure; GT = Genotype; RC = Replication Capacity, subject HIV-1 clinical isolate replication as a percentage of wildtype HIV-1 replication; FC = Fold Change compared to wild type HIV-1 virus; GSS = Standford Genotypic Susceptibility Score; PSSf = Phenotypic Susceptibility Score (with full sensitivity only)
Note: IN resistance pre-specified mutations included H51Y, T66A/I/K, L74M, E92Q/V/G, Q95K, T97A, G118R, F121Y, E138A/K/D, G140A/C/S, Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K, S230R, R263K, L68V/I, L74I, E138T, V151I, G193E; Major resistance mutations to other classes (NRTI, NNRTI, PI) are as defined by the IAS-USA most recent guidelines available at the time of DBF [www.iasusa.org, 2017].

205543

Determination of treatment emergent resistance requires successful baseline and on treatment resistance testing. All resistance testing succeeded except for integrase genotype and phenotype assays on the CVW sample in one subject ([redacted]) on DTG+TDF/FTC (Data source: 2055431 Week 48 CSR Table 4.1 and Table 4.2).

There was no treatment emergent INSTI or NRTI resistance associated mutations observed for any subjects meeting CVW criteria (Table 54 and Table 55).

Table 54 Summary of Virologic and Resistance Data through Week 48 for CVW Subjects in the DTG+3TC Arm

DTG+3TC ARM																
						HIV-RNA (c/mL)			IN GT IN RC(%)		DTG FC		NRTI GT PR/RT RC (%)		3TC FC	
Subj	HIV Subtype	CVW Visit	BL PSSf / GSS	CVW PSSf / GSS	Virologic Failure	BL	SVW/ CVW	WD	BL	CVW	BL	CVW	BL	CVW	BL	CVW
[redacted]	B	W24	2/2	2/2	Rebound	96277	451/ 9602	67	None 114	None 136	0.92	0.8	None 109	None 97	1.16	1.16
[redacted]	B	W24	2/2	2/2	Rebound	17232	461/ 251	59	None 83	None 101	0.81	0.87	None 29	None 25	1.17	1.09

Data Source: 205543 Week 48 CSR Listing 85; Listing 50 (viral load); Listing 77(HIV-1 Subtype).

"None" indicates no IAS-USA major mutations or IN pre-specified resistance mutations observed; NR = data not reported due to assay failure; GT = Genotype; RC = Replication Capacity; subject HIV-1 clinical isolate replication as a percentage of wildtype HIV-1 replication; FC = Fold Change compared to wild type HIV-1 virus; GSS = Standford Genotypic Susceptibility Score; PSSf = Phenotypic Susceptibility Score (with full sensitivity only)
Note: IN resistance pre-specified mutations included H51Y, T66A/I/K, L74M, E92Q/V/G, Q95K, T97A, G118R, F121Y, E138A/K/D, G140A/C/S, Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K, S230R, R263K, L68V/I, L74I, E138T, V151I, G193E; Major resistance mutations to other classes (NRTI, NNRTI, PI) are as defined by the IAS-USA most recent guidelines available at the time of DBF [www.iasusa.org, 2017].

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Table 55 Summary of Virologic and Resistance Data through Week 48 for CVW Subjects in the DTG + TDF/FTC Arm

DTG + TDF/FTC ARM																		
						HIV-RNA (c/mL)			IN GT RC (%)		DTG FC		NRTI GT PR/RT RC (%)		TDF FC		FTC FC	
Subj	HIV Subtype	CVW Visit	BL PSSf / GSS	CVW PSSf / GSS	Virologic Failure	BL	SVW/ CVW	WD	BL	CVW	BL	CVW	BL	CVW	BL	CVW	BL	CVW
[redacted]	B	W24	3/3	3/3	Rebound	76325	569/ 362	<50	None 35	None NR	0.68	1.38	None 60	None NR	0.95	0.61	1.13	0.67
[redacted]	B	W24	3/3	2/2	Rebound	156701	213/ 1559	97	None 79	None NR	0.9	NR	None 136	None 105	1.04	1.07	0.97	1.01

Data Source: 205543 Week 48 CSR Listing 85; Listing 50 (viral load); Listing 77 (HIV-1 Subtype).

"None" indicates no IAS-USA major mutations or IN pre-specified resistance mutations observed; NR = data not reported due to assay failure; GT = Genotype; RC = Replication Capacity, subject HIV-1 clinical isolate replication as a percentage of wildtype HIV-1 replication; FC = Fold Change compared to wild type HIV-1 virus; GSS = Standford Genotypic Susceptibility Score; PSSf = Phenotypic Susceptibility Score (with full sensitivity only)

Note: IN resistance pre-specified mutations included H51Y, T66A/I/K, L74M, E92Q/V/G, Q95K, T97A, G118R, F121Y, E138A/K/D, G140A/C/S, Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K, S230R, R263K, L68V/I, L74I, E138T, V151I, G193E; Major resistance mutations to other classes (NRTI, NNRTI, PI) are as defined by the IAS-USA most recent guidelines available at the time of DBF [www.iasusa.org, 2017].

4.3.1.4. Post-Hoc Analysis of the Proportions of Subjects with Plasma HIV-1 RNA <40 c/mL By Visit Using the Snapshot Algorithm

204861

The proportion of subjects with plasma HIV-1 RNA <40 c/mL at each visit was high and similar in both treatment groups (Table 56). Most subjects in both arms achieved plasma HIV-1 RNA <40 c/mL by Week 4. The proportion of subjects with plasma HIV-1 RNA <40 c/mL based on the Snapshot analysis was similar to those for the primary endpoint of plasma HIV-1 RNA <50 cm/L.

Table 56 Summary of the Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL by Visit - Snapshot analysis for Study 204861 (ITT-E Population)

Actual Relative Time	DTG + 3TC (N=356)	DTG + TDF/FTC (n=358)
	n/N (%)	n/N (%)
Baseline	0/356	0/358
Week 4	245/356 (69)	226/358 (63)
Week 8	288/356 (81)	291/358 (81)
Week 12	301/356 (85)	309/358 (86)
Week 16	299/356 (84)	306/358 (85)
Week 24	323/356 (91)	321/358 (90)
Week 36	312/356 (88)	322/358 (90)
Week 48	316/356 (89)	330/358 (92)

Data Source: 204861 Week 48 CSR Table 2.33

205543

The proportion of subjects with plasma HIV-1 RNA <40 c/mL at each visit was high and similar in both treatment groups (Table 57). Most subjects in both arms achieved plasma HIV-1 RNA <40 c/mL by Week 4. The proportion of subjects with plasma HIV-1 RNA <40 c/mL based on the Snapshot analysis was similar to those for the primary endpoint of plasma HIV-1 RNA <50 cm/L.

Table 57 Summary of the Proportion of Subjects with Plasma HIV-1 RNA <40 c/mL by Visit – Snapshot analysis for Study 205543 (ITT-E Population)

Actual Relative Time	DTG + 3TC (N=360)	DTG + TDF/FTC (n=359)
	n/N (%)	n/N (%)
Baseline	1/360 (<1)[a]	0/359
Week 4	240/360 (67)	239/359 (67)
Week 8	307/360 (85)	290/359 (81)
Week 12	315/360 (88)	309/359 (86)
Week 16	316/360 (88)	311/359 (87)
Week 24	325/360 (90)	317/359 (88)
Week 36	321/360 (89)	323/359 (90)
Week 48	330/360 (92)	332/359 (92)

Data Source: 205543 Week 48 CSR Table 2.33

a. Subject [redacted] had Screening plasma HIV-1 RNA of 3706 c/mL and Baseline plasma HIV-1 RNA <40 c/mL. The subject had plasma HIV-1 RNA <40 c/mL at all other time points through Week 48.

4.3.1.5. HIV-1 RNA response and HIV-1 Subtype

Some subtypes were rare and caution should be used when making interpretations when low numbers are present. Overall subgroup analyses of plasma HIV-1 RNA <50◦c/mL by Baseline HIV-1 subtype were supportive of the primary efficacy endpoint of plasma HIV-1 RNA <50◦c/mL at Week◦48 (Table 58).

Table 58 Pooled Study Outcomes (<50 c/mL) at Week 48 by HIV-1 Subtype – Snapshot analysis (ITT-E Population)

Subtype	DTG + 3TC (N with subtype=716)[a]	DTG + TDF/FTC (N with subtype=717)[b]	DTG + 3TC n (%) <50c/mL)[c]	DTG + TDF/FTC N (%<50c/mL)[c]
B	467	488	424 (91%)	452 (93%)
A	86	78	84 (98%)	74 (95%)
BF	49	50	44 (90%)	48 (96%)
AG	26	34	21 (81%)	32 (94%)
F	24	23	23 (96%)	22 (96%)
C	22	11	20 (91%)	11 (100%)
AE	13	7	12 (92%)	7 (100%)
CPX	6	2	5 (83%)	2 (100%)
D	6	2	6 (100%)	2 (100%)
BG	4	5	4 (100%)	5 (100%)
BC	3	4	3 (100%)	4 (100%)
G	3	4	2 (67%)	3 (75%)
A1	2	4	2 (100%)	3 (75%)
A1D	2	-	2 (100%)	-
AD	1	-	1 (100%)	-

Subtype	DTG + 3TC (N with subtype=716)[a]	DTG + TDF/FTC (N with subtype=717)[b]	DTG + 3TC n (%) <50c/mL)[c]	DTG + TDF/FTC N (%<50c/mL)[c]
B+F	1	-	1 (100%)	--
CRF63 02A1	1	-	1 (100%)	-
AB	-	1	-	1 (100%)
D/B	-	3	-	2 (67%)
F2	-	1	-	1 (100%)

Data Source: 204861 Week 48 CSR Table 2.32, 205543 Week 48 CSR Table 2.32,
a. Gemini-1 N=356, GEMINI-2 N=360.
b. Gemini-2 N=358, GEMINI-2 N=359.
c. Denominator for percentage based on number of subjects with specific subtype.

4.3.1.6. Discussion

This ongoing randomized double-blind non-inferiority study was conducted to evaluate the efficacy and safety of a 2-drug regimen of DTG + 3TC once daily compared with a"standard-of-care" first-line 3-drug regimen of DTG + 2 NRTIs (TDF/FTC FDC) once daily in HIV-1-infected treatment-naïve adults.

Both groups had few subjects meeting CVW criteria. In these CVW subjects, treatment with either regimen was not associated with development of treatment-emergent resistance to INSTIs (or NRTIs) after 48 weeks of therapy. The results provide support for the use of DTG + 3TC in treatment-naive adults.

Protocol-defined CVW through Week 48 in 204861 was low, with 4 subjects in the DTG + 3TC group and 2 subjects in the DTG + TDF/FTC group meeting CVW criteria at any time through Week 48.

Protocol-defined CVW through Week 48 in 205543 was low, with 2 subjects in each treatment group meeting CVW criteria at any time at any time through Week 48.

No subject meeting CVW criteria in either treatment group had treatment emergent INSTI or NRTI resistance through Week 48.

4.3.1.7. Conclusions

204861

- The incidence of protocol-defined CVW through Week 48 of 204861 was low, with 4 subjects in the DTG + 3TC group and 2 subjects in the DTG + TDF/FTC group meeting CVW criteria at any time through Week 48.
- No subject meeting CVW criteria in either treatment group of 204861 had treatment emergent INSTI or NRTI resistance through Week 48.

205543

- The incidence of protocol-defined CVW through Week 48 of 205543 was low, with 2 subjects in each treatment group meeting CVW criteria at any time through Week 48.
- No subject meeting CVW criteria in either treatment group of 205542 had treatment emergent INSTI or NRTI resistance through Week 48.

4.4. Clinical Virology - Dolutegravir

Treatment-naive (ING114467, ING113086, ING114915, ING112276): No virologic resistance was observed on DTG (50 mg once daily)-containing regimens in the treatment-naive population to either integrase or the background regimen (NRTI), whereas virologic resistance to the 3rd agent (RAL or EFV) and/or the background regimen (NRTI) has been observed on the comparator arms in three of the four studies.

Treatment-experienced, INI-naive (ING111762): Results from this Week 48 analysis show DTG has a higher barrier to resistance in this patient population. In a pre-specified key secondary endpoint analysis, there was a statistically significant difference in favor of DTG for the proportion of mITT-E subjects harboring virus with evidence of treatment emergent INI resistance by Week 48 (DTG: 4/354 [1.0%]; RAL: 17/361 [5%]; p=0.003).

A unique IN substitution was observed (R263K or R263R/K mixture) in 2 subjects with treatment emergent INI substitutions on DTG that conferred no or low fold change in susceptibility to DTG and to RAL. Clinically relevant and previously described RAL associated genotypic resistance was observed in 16/38 (42.1%) subjects with confirmed virologic failure in the RAL arm, with high fold change to RAL and limited cross-resistance to DTG demonstrated at Week 48.

As DTG/3TC is not intended to be used by patients with INI resistance, neither ING112574 (Viking 3) nor the antiviral activity of DTG by baseline resistance in integrase inhibitor-resistant patients ("Annex B") is summarized here.

4.4.1. DTG Clinical Studies

4.4.1.1. ING114467 (SINGLE)

Study Title: A Phase III, randomized, double-blind study of the safety and efficacy of DTG plus abacavir-lamivudine fixed-dose combination therapy administered once daily compared to EFV/TDF/FTC over 144 weeks in HIV-1 infected antiretroviral therapy naive adult subjects.

Study Design: ING114467 is a Phase 3 randomized, stratified, double-blind, double-dummy, active-controlled, multicentre, parallel group, fully-powered non-inferiority study. Subjects were randomized 1:1 to receive DTG 50 mg plus ABC/3TC FDC therapy once daily or EFV/TDV/FTC once daily. Subjects were stratified by screening HIV-1 RNA and CD4 cell count. PDVF required two consecutive HIV-1 RNA values ≥50 c/mL

HIV-1 RNA on or after Week 24. The primary analysis took place after the last subject completed 48 weeks on therapy; additional analyses were conducted after the last subject completed Week 144.

Viral Genotyping and Phenotyping Study Population

High response rates were observed despite the application of a strict PDVF criterion – namely, two consecutive HIV-1 RNA values ≥50 c/mL HIV-1 RNA on or after Week 24), which mandated testing for resistance (GSK Document number 2013N167896_00).

As seen in Table 59, 39/414 (9%) subjects in the DTG + ABC/3TC treatment group and 33/419 (8%) subjects in the Atripla treatment group met the definition of PDVF at 144 weeks.

Table 59 Distribution of HIV-1 RNA Results at Suspected and Confirmation of PDVF

	DTG 50 mg + ABC/3TC QD, 48 Weeks N=414 n (%)	EFV/TDF/FTC QD, 48 Weeks N=419 n (%)	DTG 50 mg + ABC/3TC QD, 144 Weeks N=414 n (%)	EFV/TDF/FTC QD, 144 Weeks N=419 n (%)
Subjects with PDVF	18 (4)	17 (4)	39 (9)	33 (8)
Suspected PDVF HIV-1 RNA (c/mL)				
50 to <200	12 (67)	11 (65)	22 (56)	22 (67)
200 to <400	3 (17)	0	4 (10)	2 (6)
400 to <1000	1 (6)	1 (6)	2 (5)	1 (3)
1000 to <10,000	2 (11)	2 (12)	5 (13)	5 (15)
10,000 to <50,000	0	2 (12)	2 (5)	2 (6)
50,000 to 100,000	0	1 (6)	0	1 (3)
>100,000	0	0	4 (10)	0
Confirmed PDVF HIV-1RNA (c/mL)				
50 to <200	16 (89)	11 (65)	29 (74)	23 (70)
200 to <400	0	3 (18)	3 (8)	5 (15)
400 to <1000	0	1 (6)	2 (5)	3 (9)
1000 to <10,000	1 (6)	1 (6)	1 (3)	1 (3)
10,000 to <50,000	1 (6)	0	2 (5)	0
50,000 to 100,000	0	0	0	0
>100,000	0	1 (6)	2 (5)	1 (3)

Data Source: ING114467 Wk 48 CSR Table 7.29; ING114467 Wk 144 CSR Table 7.29

The majority of subjects who met PDVF in the study had low-level viremia (44/72, or 61% of subjects in both treatment groups with PDVF had "suspected PDVF" with <200 c/mL HIV-1 RNA). At confirmed failure 29/39 (74%) subjects with PDVF in the DTG + ABC/3TC treatment group had <200 c/mL HIV-1 RNA, while 23/33 (70%) of subjects with PDVF in the Atripla treatment group had <200 c/mL HIV-1 RNA (Table 59). At suspected virologic failure, four (10%) subjects in the DTG + ABC/3TC treatment group had >100,000 c/mL HIV-1 RNA at PDVF (two subjects still had >100,000 c/mL at confirmed failure); no subjects in the Atripla treatment group had >100,000 c/mL HIV-1 RNA at suspected virologic failure.

Integrase Genotyping and Phenotyping Results

Nineteen subjects in the DTG + ABC/3TC treatment group had integrase genotype and phenotype data at both Baseline and at the time of PDVF, while 11 subjects in the Atripla treatment group had integrase genotype and phenotype data at both Baseline and time of PDVF.

None of the 30 subjects in either the DTG + ABC/3TC treatment group or the Atripla treatment group had treatment-emergent INI resistance mutations. One subject (Subject [redacted]) in the DTG + ABC/3TC treatment group had a treatment-emergent substitution of E157Q/P at Week 24, without accompanying DTG phenotypic resistance (Table 60).

Of note in Subject [redacted]:

- Treatment emergent IN substitution at Week 24 was E157Q/P. Replicative capacity could not be determined.
- Week 24 virus had a 1.13 fold change (FC) to DTG and 1.26 FC to RAL, as compared to 1.02 FC to DTG and 1.22 FC to RAL at Baseline.
- HIV-1 RNA at Baseline was 330,641 c/mL, reached a nadir of 79 c/mL at Week 12, and increased to 275 c/mL at Week 24.

Table 60 Treatment Emergent Genotypic or Phenotypic Evidence of Integrase Inhibitor Resistance

Subjects with PDVF	DTG + ABC/3TC, Week 48 N=18	EFV/TDF/FTC, Week 48 N=17	DTG + ABC/3TC, Week 144 N=39	EFV/TDF/FTC, Week 144 N=33
IN Genotypic Results at PDVF	N=7	N=7	19	11
IN substitution E157Q/P	1[a]	0	1[a]	0
IN Phenotypic Results at PDVF	N=7	N=7	19	11
Increase in DTG FC	0[a]	0	0	0

a. Subject [redacted]; IN E157Q/P at Week 24. DTG FC = 1.13; RAL FC = 1.26
Data Source: ING114467 Wk 48 CSR Table 12.2 and Table 12.5, ING114467 Week 144 CSR Table 12.1 and Table 12.8

Non-Nucleoside Genotyping and Phenotyping Results

Twenty-six subjects in the DTG + ABC/3TC treatment group had NNRTI genotypic and phenotypic data at both Baseline and time of PDVF. There were no treatment emergent NNRTI resistance mutations or treatment emergent NNRTI phenotypic changes in any of the subjects with PDVF in the DTG + ABC/3TC treatment group.

Sixteen subjects in the Atripla treatment group had NNRTI genotypic and phenotypic data at both Baseline and time of PDVF. Six subjects (Subjects [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]) in the Atripla treatment group had treatment emergent NNRTI resistance mutations. Phenotypic changes to EFV were observed in five of these subjects (Table 61).

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutation at Week 48 was K101E.
- Week 48 virus had a 1.9 FC to EFV, as compared to 0.75 FC at Baseline.
- HIV-1 RNA at Baseline was 2212 c/mL, reached <50 c/mL at Week 16. Suspected Virologic Failure at Week 24 was not confirmed. HIV-1 RNA was 992 c/mL at Week 48.

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutation at Week 32 was K103K/N.
- Week 48 virus had a 14 FC to EFV, as compared to 1.66 FC at Baseline.
- HIV-1 RNA at Baseline was 53,961 c/mL, reached a nadir of <50 c/mL at Week 16, and increased to 6882 c/mL at Week 32.

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutations at Week 24 were K103N and G190G/A.
- Week 24 virus had a 22 fold change (FC) to EFV, as compared to 1.03 FC to at Baseline.
- HIV-1 RNA at Baseline was 112,284 c/mL, reached a nadir of <50 c/mL at Week 16, and increased to 40,751 c/mL at Week 24.

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutation at Week 24 was G190G/A. Additional treatment emergent NNRTI mutations were K103R and V179V/D.
- Week 24 virus had a 20 fold change (FC) to EFV, as compared to 1.05 FC to at Baseline.
- HIV-1 RNA at Baseline was 5218 c/mL, reached a nadir of 89 c/mL at Week 16, and increased to 29.777 c/mL at Week 24.

Of note in Subject [redacted]

- Treatment emergent NNRTI resistance mutation at Week 60 was K103K/N.
- Week 60 virus had a 12 fold change (FC) to EFV, as compared to 0.76 FC to at Baseline.
- HIV-1 RNA at Baseline was 39,271 c/mL. This subject had unconfirmed virologic failure at Weeks 24 and 40. This subject had 2183 c/mL HIV-1 RNA at Week 60 and confirmed with 449 c/mL HIV-1 RNA.

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutation at Week 72 was K103N.
- Week 72 virus had an 11 fold change (FC) to EFV, as compared to 0.77 FC to at Baseline.
- HIV-1 RNA at Baseline was 12,078 c/mL. This subject had unconfirmed virologic failure at Week 40. This subject had 9043 c/mL HIV-1 RNA at Week 72 and confirmed with 77 c/mL HIV-1 RNA.

Table 61 Treatment Emergent Genotypic or Phenotypic Evidence of NNRTI Resistance

Subject Number	Treatment Group	Mutaation	NNRTI Phenotype
[redacted]	Atripla	K101E	1.9 FC to EFV
[redacted]	Atripla	K103K/N	14 FC to EFV
[redacted]	Atripla	K103N, G190G/A	22 FC to EFV
[redacted]	Atripla	G190G/A	20 FC to EFV
[redacted]	Atripla	K103K/N	12 FC to EFV
[redacted]	Atripla	K103N	11 FC to EFV

Data Source: ING114467 Wk 144 CSR Table 12.4, Listing 47 and Listing 48

Nucleoside Reverse Transcriptase Genotyping and Phenotyping Results

Twenty-six subjects with PDVF in the DTG + ABC/3TC treatment group had NRTI and PI genotypic and phenotypic data at both Baseline and time of PDVF, while 12 subjects with PDVF in the Atripla treatment group had NRTI and PI genotypic and phenotypic data at both Baseline and time of PDVF.

There were no treatment emergent PI resistance mutations in either treatment group.

There were no treatment emergent NRTI resistance mutations in any of the subjects with PDVF in the DTG + ABC/3TC treatment group, though one subject did experience a minor increase in FC to the NRTI DDI (Table 62).

One subject in the Atripla treatment group (Subject [redacted]) had the treatment emergent NRTI resistance mutation K65K/R. This subject did not have treatment emergent phenotypic changes, although the [redacted] predicted resistance to all NRTIs with the exception of AZT and d4T (Table 62).

Of note in Subject [redacted]:

- Treatment emergent NRTI resistance mutation at Week 24 was K65K/R.
- Week 24 virus had a 0.69 FC to TDF and 1.27 FC to FTC, although the [redacted] predicted resistance to FC to ABC, DDI, FTC, 3TC, and TDF.
- HIV-1 RNA at Baseline was 376,229 c/mL. HIV-1 RNA was 131 c/mL at Week 24.

Of note in Subject [redacted]:

- Week 32 virus had a 1.39 FC to DDI (clinical cut off = 1.3), without treatment emergent NRTI resistance mutations.
- HIV-1 RNA at Baseline was 564,854 c/mL, was <50 c/mL at Week 12 and Week 24, and increased to 66 c/mL at Week 32.

Table 62 Treatment Emergent Genotypic Evidence of NRTI Resistance

Subject number	Treatment Group	Mutation	NRTI Phenotype
[redacted]	Atripla	K65K/R	No change
[redacted]	DTG + ABC/3TC	0	1.39 FC to DDI

Data Source: ING114467 Wk 144 CSR Table 12.4, Listing 47 and Listing 48 5

Discussion

The combination of DTG + ABC/3TC, given to ART-naïve subjects, has demonstrated long-term durability through 144 weeks without the selection of treatment-emergent resistance mutations. No subjects in the DTG + ABC/3TC treatment group had any treatment-emergent resistance mutations in either integrase or RT, while six subjects in the Atripla treatment group had treatment-emergent NNRTI resistance mutations and one subject had a treatment-emergent NRTI resistant mutation.

There were 39 (9%) subjects with PDVF in the DTG + ABC/3TC treatment group and 33 (8%) subjects with PDVF in the Atripla treatment group. In this study, integrase, RT, and PR genotypes and phenotypes were attempted at Baseline and the time of PDVF for all subjects with PDVF in an effort to collect as much virology data as possible, even though the HIV-1 RNA levels were <400 c/mL for a vast majority of PDVF samples. As a result, integrase genotypes were obtained at both time points for only 19/39 subjects in the DTG + ABC/3TC treatment group. Similarly, RT/PR genotypes were obtained at

both time points for just 26/39 and 16/33 subjects in the DTG + ABC/3TC and Atripla treatment groups, respectively.

No subject in the DTG + ABC/3TC treatment group had treatment-emergent INI resistance mutations. The integrase substitution E157Q/P observed in one subject (Subject [redacted]) in the DTG + ABC/3TC treatment group was not accompanied by increased FC to either DTG or RAL. Replication capacity could not be determined for this virus. There have been no phenotypic differences in response to DTG or RAL noted for this mutation in previous studies, so the E157Q/P substitution may be a polymorphism without clinical consequence [Cahn, 2013; Raffi, 2013].

The E157P substitution has not been described, but the E157Q substitution has been observed in 5/112 (4.5%) subjects with acute HIV-1 infection [Low, 2009]. This substitution has been selected along with H51Y, E92Q, and E147G during in vitro passage with ELV [Shimura, 2008]. Shimura, et al., demonstrated that the enzyme carrying the E157Q substitution had reduced strand transfer activity relative to wild-type levels, but they were able to determine that it remained susceptible to ELV. The virus containing this substitution had only minimally decreased susceptibility to ELV.

In an analysis of clinical isolates obtained during RAL treatment, including a patient with integrase substitution E157Q, it was shown that the E157Q enzyme was almost completely inactive in both 3' processing and strand transfer. In addition, the in vitro activity of this virus was too low for antiviral activity to be tested [Malet, 2008].

Six subjects in the Atripla treatment group had treatment-emergent NNRTI resistance mutations; five of the six had treatment-emergent phenotypic resistance to EFV. Four of the six subjects had K103N or K103K/N; two of the subjects had G 190G/A (one with and one without a mutation at K103). These five subjects had 11 to 22 FC to EFV at PDVF. The sixth subject selected for K101E and had a 1.90 FC to EFV at PDVF.

No subject in the DTG + ABC/3TC treatment group had treatment-emergent NRTI resistance mutations, although one subject had 1.39 FC to DDI with no accompanying resistance mutations. This variability seen in the FC to DDI is common and of no concern.

One subject in the Atripla treatment group had treatment emergent K65K/R. While this virus did not have high level resistance to TDF, the [redacted] predicted resistance to ABC, DDI, FTC, 3TC, and TDF

Conclusions

- DTG + ABC/3TC demonstrated long term durability with a low rate of discontinuation due to virologic failure through 144 weeks.

- No treatment emergent primary INI or NRTI resistance mutations were observed through 144 weeks for those subjects on DTG plus ABC/3TC FDC with PDVF. Both EFV and NRTI primary resistance mutations were observed in subjects on Atripla with PDVF.

4.4.1.2. ING113086 (SPRING-2)

Study Title: A Phase III, randomized, double blind study of the safety and efficacy of GSK1349572 50 mg once daily compared to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naive adult subjects.

Study Design: ING113086 is a Phase III randomized, double-blind, double dummy, active-controlled, multicenter, parallel group, fully-powered non-inferiority study. Subjects were randomized to DTG 50 mg once daily or 400 mg RAL twice daily, both in combination with either abacavir/lamivudine (ABC/3TC), or tenofovir/emtricitabine (TDF/FTC). Protocol defined virologic failure (PDVF) required two consecutive HIV-1 RNA values ≥50 c/mL HIV-1 RNA on or after Week 24. At the Week 96 visit, subjects randomized to RAL are discontinued from the study, while subjects randomized to DTG are given the opportunity to remain on the study while receiving DTG 50 mg once daily during the Open-label Phase of the study.

Viral genotyping and phenotyping study population

High response rates in study ING113086 were observed despite the application of a strict PDVF criterion – namely, two consecutive HIV-1 RNA values ≥50c/mL HIV-1 RNA on or after Week 24, which mandated withdrawal from the trial (if confirmed before Week 48) and testing for resistance. The majority of subjects who met PDVF in study ING113086 through Week 96 (GSK Document number 2013N158737_00) had low-level viremia; 76 to 77% of subjects in both arms with PDVF failed with <200 c/mL HIV-1 RNA (Table 63). All 22 subjects with PDVF on DTG had <1000 c/mL HIV-1 RNA at confirmed failure, while 3 (10%) of subjects with PDVF on RAL had >10,000 c/mL HIV-1 RNA at the time of confirmed failure (Table 63).

Table 63 Distribution of HIV-1 RNA at Time of PDVF

	DTG 50 mg once daily (N=411) n (%)	RAL 400 mg BID (N=411) n (%)
Subjects with PDVF	**22 (5)**	**29 (7)**
Suspected PDVF HIV-1 RNA (c/mL)		
50 to <200	14 (64)	24 (83)
200 to <400	2 (9)	1 (3)
400 to <1000	3 (14)	0
1000 to <10,000	2 (9)	1 (3)
10,000 to <50,000	1 (5)	0
50,000 to 100,000	0	3 (10)
>100,000	0	0
Confirmed PDVF HIV-1 RNA (c/mL)		
50 to <200	17 (77)	22 (76)
200 to <400	4 (18)	2 (7)
400 to <1000	1 (5)	2 (7)
1000 to <10,000	0	0
10,000 to <50,000	0	2 (7)
50,000 to 100,000	0	0
>100,000	0	1 (3%)

Data Source: ING113086 Wk 96 CSR Table 7.23

As seen in Table 63, 22 subjects (5%) in the DTG treatment group met the definition of PDVF while 29 (7%) subjects in the RAL treatment group met the definition of PDVF. Subjects with PDVF predominantly had HIV-1 subtype B, with A1 being the next most common. In other subjects, a variety of subtypes were seen in small numbers, including AG, BF, C, F1, and G. Integrase, reverse transcriptase (RT) and protease (PR) genotypes and phenotypes were attempted at Baseline and time of PVDF for all subjects with PDVF.

Three subjects had PDVF after Week 48 (DTG 2; RAL 1). No treatment emergent IN or NRTI resistance mutations were detected in any of these subjects. Confirmation HIV-1 RNA levels were below 200 c/mL, hence all three were allowed to remain in the study as per subject management criteria of the amended protocol

Ten subjects of the 22 with PDVF in the DTG treatment arm had IN genotype at both Baseline and at the time of PDVF, while 20 subjects of the 29 with PDVF in the RAL treatment arm had IN genotype at both Baseline and time of PDVF (Table 65). Fourteen of the 22 with PDVF in the DTG treatment arm had PR/RT genotype at both BL and time of PDVF while 20 of the 29 with PDVF in the RAL treatment arm had PR/RT genotype at both Baseline and time of PDVF (Table 66).

Integrase genotyping and phenotyping results

Since the primary analysis of the study demonstrated non-inferiority, a secondary analysis testing for superiority using the same CMH weights was conducted at a two-sided 5% level of significance. The upper end of the 95% confidence interval associated

with the adjusted estimate of the difference (DTG - RAL) in proportions was not below 0% and hence superiority of DTG was not concluded (Table 64).

Table 64 Analysis of Proportion of Subjects with Genotypic or Phenotypic Evidence of INI Resistance at Time of PDVF by Week 96

	DTG 50 mg once daily N=411 n/N (%)	RAL 400 mg BID N=411 n/N (%)
Proportion meeting criteria of INI resistance	**1/411 (<1)**	**2/411 (<1)**
Difference in Proportion (95% CI) (DTG-RAL)	-0.2 (-1.1, 0.6)	
Adjusted Difference[a] in Proportion (95% CI) (DTG-RAL)	-0.2 (-1.1, 0.6)	

a. Adjusted Difference Based on Cochran-Mantel Haenszel stratified analysis adjusting for the Baseline stratification factors: Baseline HIV-1 RNA and background dual NRTI.
Data Source: ING113086 Wk 96 CSR Table 7.10

Ten subjects of the 22 with PDVF in the DTG treatment arm had IN genotype at both Baseline and at the time of PDVF, while 20 subjects of the 29 with PDVF in the RAL treatment arm had IN genotype at both Baseline and time of PDVF. None of the ten subjects in the DTG treatment arm had treatment emergent INI resistance mutations while 1/20 (5%) of the subjects on the RAL treatment arm had treatment emergent INI resistance mutations (Table 65).

Three subjects ([redacted], [redacted], and [redacted]) had genotypic or phenotypic indication of treatment emergent integrase resistance and are discussed below.

Subject [redacted] was randomized to the RAL treatment group and received TDF/FTC as the nucleoside backbone. This subject had 3,346,333 c/mL HIV-1 RNA at Baseline, reached a nadir of 11,959 c/mL HIV-1 RNA at Week 2, and increased to 88,126 c/mL HIV-1 RNA at Week 24.

Of note in Subject [redacted]:

- Treatment emergent INI resistance mutations at Week 24 were T97T/A, E138E/D, V151V/I, and N155H.
- Week 24 virus had a 34 fold change (FC) to RAL and 2.02 FC to DTG, as compared to 1.15 FC to RAL and 1.48 FC to DTG at Baseline.
- Week 24 virus also had treatment emergent NRTI mutations A62A/V, K65K/R, K70K/E, and M184V with accompanying 1.44 FC to TDF and MAX FC to FTC.

Two additional subjects ([redacted] and [redacted]) had treatment emergent elevated FC to RAL (Table 65). Subject [redacted], who was randomized to the DTG group and received TDF/FTC, had 2.01 FC to RAL (0.96 FC to DTG) at PDVF (Week 32). As there were no treatment emergent INI resistance mutations at Week 32, all IN substitutions at Baseline and Week 32 were compared.

Of note in Subject [redacted]:

- Baseline virus had IN substitutions K14R, V32I, E48E/K, V72I, Y99F, L101I, V113I, S119P, T122I, T124A, T125A, G134N, K136T, K188R, V201I, T206S, Y227F, S255N, D256E, and S283G.
- IN substitutions at Week 32 were identical to those observed at Baseline with the exception that E48K was a full substitution at Week 32.

Subject [redacted], who received RAL and TDF/FTC as the nucleoside backbone, had 1.62 FC to RAL (1.40 FC to DTG) at PDVF (Week 24). As there were no treatment emergent INI resistance mutations at Week 24, all IN substitutions at Baseline and Week 24 were compared.

Of note in Subject [redacted]:

- Baseline virus had IN substitutions E11E/D, V31I, V72I, L101I, V113I, V201I, T206S, K215T, Q216Q/K, T218I, I220L, V234L, and D256E.
- IN substitutions at Week 24 were identical to those observed at Baseline with the exceptions that E11D was a full substitution at Week 24 and Q216 was fully Q at Week 24.

Table 65 Treatment Emergent Phenotypic or Genotypic Evidence of Integrase Inhibitor Resistance

Subjects with PDVF	DTG N=22	RAL N=29
IN Genotypic Results at Baseline and PDVF	N=10	N=20
INI resistance mutations	0	1/208 (5%)[a]
Phenotypic evidence of INI resistance		
Subject [redacted]		RAL FC = 34[a]
Subject [redacted]	RAL FC = 2.01	
Subject [redacted]		RAL FC = 1.62

a. T97T/A, E138E/D, V151V/I, N155H
Data Source: ING113086 Wk 96 CSR Table 7.22, Listing 44

Reverse transcriptase genotyping and phenotyping results

Fourteen (14) of the 22 subjects with PDVF in the DTG treatment group had PR/RT genotype at both Baseline and time of PDVF, while 20 of the 29 with PDVF in the RAL treatment group had PR/RT genotype at both Baseline and time of PDVF (Table 66). None of the 14 subjects with Baseline and PDVF RT and PR genotypic data in the DTG treatment arm had treatment emergent NRTI resistance mutations while 4/20 (20%) of the subjects on the RAL treatment arm had treatment emergent NRTI resistance mutations (Table 66). In addition to Subject [redacted] (NRTI treatment emergent mutations A62A/V, K65K/R, K70K/E, and M184V) described above, subjects [redacted], [redacted], and [redacted] had treatment emergent NRTI resistance mutations at PDVF.

- Subject [redacted], who was in the RAL treatment group and received TDF/FTC as the NRTI backbone, had treatment emergent mutation M184M/I at PDVF (Week 24) with no accompanying phenotypic change to TDF or FTC.

- Subject [redacted], who was randomized to RAL and received TDF/FTC as the NRTI backbone, had treatment emergent mutation A62A/V at PDVF (Week 24) with no phenotypic change to TDF or FTC.
- Subject [redacted], who was randomized to RAL and received ABC/3TC as the NRTI backbone, had treatment emergent mutation M184M/V with 2.56 FC to ABC and MAX FC to 3TC.

Table 66 Treatment Emergent Genotypic Evidence of NRTI Resistance

Subjects with PDVF	DTG N=22	RAL N=29
RT/PR Genotype Results at BL and PDVF	14	20
Subjects with NRTI resistance mutations	0	4/20 (20%)
Genotypic Evidence of NRTI resistance		
[redacted]		A62A/V, K65K/R, K70K/E, M184V
[redacted]		M184M/I
[redacted]		A62A/V
[redacted]		M184M/V

Data Source: ING113086 Wk 96 CSR Table 7.22, Listing 43

If subjects with PDVF with <400 c/mL HIV-1 RNA are censored from this analysis, there were only 6 subjects with PDVF in the DTG treatment group, none of whom had any treatment emergent resistance mutations, and only 4 subjects with PDVF in the RAL treatment group, including the one subject with RAL resistance mutations T97T/A, E138E/D, V151V/I, and N155H and NRTI resistance mutations A62A/V, K65K/R, K70K/E, and M184V.

Discussion

In this study, IN, RT, and PR genotypes and phenotypes were attempted at Baseline and the time of PDVF for all subjects with PDVF, even though the HIV-1 RNA levels were <400 c/mL for a vast majority of PDVF samples. As a result, IN genotypes were obtained at both time points for only 10/22 subjects on the DTG treatment group and 20/29 subjects on the RAL treatment group. Similarly, RT/PR genotypes were obtained at both time points for just 14 and 20 subjects on the DTG and RAL treatment groups, respectively.

Even though subjects with PDVF after week 48 were allowed to remain on the study up to a HIV-1 RNA of 200 c/mL, no subject in the DTG treatment group had treatment emergent INI resistance mutations through Week 96, and no additional subjects on RAL developed INI resistance between Weeks 48 and 96. One subject in the RAL treatment group had treatment emergent INI resistance mutations with an accompanying high RAL FC and only a slight increase in DTG FC at Week 24. This subject received TDF/FTC as the NRTI backbone and by the time of PDVF, the virus also had genotypic and phenotypic resistance to TDF and FTC.

No subject in the DTG treatment group had treatment emergent NRTI resistance mutations. Three subjects, all in the RAL treatment arm, had treatment emergent NRTI resistance mutations prior to Week 48; only one of these subjects also had phenotypic resistance to the nucleoside backbone. Two of these three subjects, and three of the four

subjects with treatment emergent resistance mutations, had TDF/FTC as the NRTI backbone. Although numbers are small, this finding may suggest decreased NRTI mutations when NRTIs are co-administered with DTG in treatment-naive subjects.

DTG, when given to ART naive subjects along with two NRTIs, has demonstrated long term durability without the selection of treatment emergent resistance mutations.

Conclusions

- Overall, there was a low rate of discontinuation due to virologic failure in both treatment arms, with only three additional subjects with PDVF identified after Week 48. The durability of the virologic response on DTG and RAL was maintained through Week 96.
- Both INI (RAL) and NRTI primary resistance mutations were observed in subjects on RAL with PDVF up to Week 48. No treatment emergent primary INI or NRTI resistance mutations were observed for those subjects on DTG with PDVF throughout the study.

4.4.1.3. ING114915 (FLAMINGO)

Study Title: A Phase IIIb, randomized, open-label study of the safety and efficacy of GSK1349572 (dolutegravir, DTG) 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 48 weeks in HIV-1 infected antiretroviral naïve adult subjects.

Study Design: Study ING114915 is a Phase IIIb randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study being conducted in 484 human immunodeficiency virus (HIV)-1 infected, antiretroviral therapy (ART)-naïve adult subjects. This trial was designed to demonstrate the non-inferior antiviral activity of dolutegravir (DTG) 50 mg once daily versus darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily over 48 weeks (with a non-inferiority margin of 12%). Both DTG and DRV/r were given in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) therapy (abacavir/lamivudine [ABC/3TC] or tenofovir/emtricitabine [TDF/FTC]).

Viral Genotyping and Phenotyping Study Population

Four subjects (4/484, <1%) met the definition of Protocol Defined Virologic Failure (PDVF; two consecutive HIV-1 RNA values >200 c/mL HIV-1 RNA on or after Week 24) through Week 48 (GSK Document number 2013N158804_00); two in each treatment group. The two subjects in the DTG treatment group had TDF/FTC as their nucleoside backbone and had PDVF at Week 24 (Subject [redacted] had 668 c/mL HIV-1 RNA, and Subject [redacted] had 2270 c/mL HIV-1 RNA). One subject in the Darunavir and ritonavir treatment group had PDVF at Week 36 (Subject [redacted] had 61,754 c/mL HVI-1 RNA) while the other had PDVF at Week 48 (Subject [redacted] had 218 c/mL HIV-1 RNA). Both subjects in the Darunavir and ritonavir treatment arm had ABC/3TC as their nucleoside backbone.

Genotyping and Phenotyping Results

Genotype and phenotype for reverse transcriptase (RT), protease (PRO), and integrase (IN) were obtained at Day 1 and the time of PDVF for each subject who met PDVF. None of the subjects had treatment emergent resistance mutations in RT, PRO, or IN. One subject ([redacted], DTG treatment arm, TDF/FTC as the NRTI backbone) had phenotypic resistance to nelfinavir (4.12 FC), in spite of having no treatment emergent PRO resistance mutations. This subject had secondary PI resistance mutations L10V, I13V, K20R, E35D, M36I, I62I/V, L63T, and L89M at baseline and at PDVF (Week 24); no phenotypic resistance to PIs was observed at baseline (Data Source: ING114915 Wk 96 CSR Table 12.4, Table 12.6, non-ICH Listing 51 and non-ICH Listing 53).

Discussion

No treatment-emergent resistance in either treatment group was noted through Week 48.

In an effort to obtain as much virology data as possible, baseline and time of PDVF samples were evaluated for resistance for all subjects with PDVF (confirmed plasma HIV-1 RNA >200 c/mL on or after Week 24, as compared to ≥ 50 c/mL HIV-1 RNA for Spring-2 and Single).

Only two subjects in each treatment group met PDVF. No subjects had treatment-emergent INI substitutions of potential interest or treatment-emergent primary NRTI mutations. No subjects had treatment-emergent primary PI mutations; however, one subject in the DTG treatment group had phenotypic resistance to nelfinavir. Several reasons for this finding were considered. Variability of the protease (PR) phenotypic assay seems unlikely to fully explain this difference from baseline. Mixtures in the PR substitutions might account for the differences in phenotype between Baseline and Week 24 (without PI drug pressure), but only one of the PI secondary mutations for this subject was a mixture (I62I/V). Substitutions at this location are unlikely to result in phenotypic changes for nelfinavir susceptibility. Finally, re-infection with HIV containing nelfinavir resistance seems unlikely as well with no evidence of primary PI mutations at Week 24. The emergence of PI mutation in a subject receiving DTG is likely related to the presence of secondary PI mutations at Baseline and Week 24 for this subject.

This study was consistent with SPRING-2 and SINGLE where a similar lack of resistance in the DTG arms was noted.

Conclusions

- Overall, there was a low rate (<1%) of discontinuation due to virologic failure in both treatment groups.
- No treatment-emergent primary INI or NRTI resistance mutations were observed for subjects in the DTG or DRV+RTV treatment groups. One subject (in the DTG group) had phenotypic resistance to nelfinavir at PDVF, despite having no treatment emergent PI resistance mutations.

4.4.1.4. ING112276 (SPRING-1)

Study Title: A Phase IIb study to select a once daily oral dose of GSK1349572 administered with either abacavir/lamivudine or tenofovir/emtricitabine in HIV-1 infected antiretroviral therapy naive adult subjects, 96 week results.

Study Design: Study ING112276 is a Phase IIb, randomized, multicentre, parallel group, dose-ranging study conducted in HIV-1 infected ART-naïve adults. The trial was partially blinded, i.e. subjects and their investigators were blinded to the dose of DTG. Subjects received DTG, at one of three doses, or EFV once daily, both co-administered with either abacavir sulfate (abacavir, ABC) and lamivudine (3TC), (abacavir/lamivudine, ABC/3TC), or tenofovir/emtricitabine (TDF/FTC) fixed dose combinations (FDC) as background therapy. The current analysis was conducted after the last subject completed Week 96. At the Week 96 visit, subjects randomized to EFV were discontinued from the study, while subjects randomized to receive DTG were given the opportunity to remain on the study while receiving DTG 50 mg during an open-label phase of the study.

Virologic failure was defined as a less than 1.0 log10 c/mL decrease in plasma HIV-1 RNA by week 4 unless the measure was lower than 400 c/mL, failure to suppress plasma HIV-1 RNA to less than 400 c/mL on or after week 24, rebound to 400 c/mL or more after suppression to less than 400 c/mL, or rebound to greater than 0.5 log10 above nadir if 400 c/mL or greater. Participants with confirmed virologic failure (two consecutive samples 1-4 weeks apart) were assessed for study discontinuation and had samples analyzed for genotypic and phenotypic resistance.

Results: Four subjects, including one subject who received EFV, had PDVF by week 48. No additional subjects had PDVF through week 96 (GSK Document number 2011N117114_00).

Subject [redacted], who received TDF/FTC and 10 mg of DTG, had a 2.84 $\log_{10}$ c/mL decline in RNA at Week 2, but rebounded at Week 4. The only RT resistance mutation observed on treatment was M184M/V. No INI-associated substitutions or changes in susceptibility to either DTG or RAL were demonstrated. This subject was withdrawn at the time of confirmation.

Subject [redacted] received TDF/FTC and EFV, and had less than a 1 $\log_{10}$ c/mL decrease in HIV-1 RNA by Week 4. On treatment GT and PT showed no changes in RT, and the subject continued on study with subsequent suppression at Week 20.

Subject [redacted] met the definition of protocol-defined virologic failure at Week 24. The subject received ABC/3TC and DTG 25 mg and had a plasma HIV-1 RNA value of 404 c/mL at the Week 24 visit. The confirmatory plasma HIV-1 RNA value was 483 c/mL. There is documented noncompliance with study medication for this subject. At Baseline, this subject had no primary mutations in HIV reverse transcriptase or protease (RT/PRO) and no phenotypic resistance to NRTIs, NNRTIs or protease inhibitors (PIs). Genotypic data (RT/PRO) could not be generated at virologic failure (Week 24), likely due to the low level of plasma HIV-1 RNA. There were no primary INI resistance

mutations detected at either Day 1 or Week 24. This subject was withdrawn at the time of conformation.

Subject [redacted] who received ABC/3TC and 10 mg DTG, rebounded to >400 c/mL at Week 40. The subject was non-compliant with study medications at the time of virologic failure. Virologic failure was confirmed two week later prior to the subject becoming compliant with study medications. The subject began taking study medications and HIV-1 RNA was <400 c/mL three weeks after the confirmatory sample. No RT or INI mutations or changes in PT were detected at the time of virologic failure (Week 40). The subject continued in the study with continued response to therapy up to Week 108 at which time the subject withdrew.

There were no integrase inhibitor resistance mutations and no changes in DTG susceptibility at the time of virologic failure for any of the three subjects receiving DTG.

Based on data from subjects providing intensive and sparse PK at Week 2, dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve subjects was 1.20 μg/mL, 19 times higher than the estimated PA-IC90.

Discussion

A low rate of confirmed protocol-defined virological failure was observed with no treatment emergent mutations in the integrase gene detected in the three subjects receiving DTG who developed virologic failure. The rate of viral decay was much faster in the DTG treatments arms than the EFV arm, similar to what has been observed for Raltegravir, indicating a unique mechanism of the antiviral activity of integrase inhibitors.

Conclusions

- No subject in the 50 mg DTG group met protocol defined virologic failure through 96 weeks. No integrase mutations were identified in this study.
- Dolutegravir trough concentration for a single 50 mg dose in integrase inhibitor naïve subjects was 1.20 mcg/mL, 19 times higher than the estimated PA-IC90.

4.4.1.5. ING111762 (SAILING)

Study Title: A Phase III Randomized, Double-blind Study of the Safety and Efficacy of GSK1349572 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered with an Investigator-selected Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults - Week 48 Results.

Study Design: ING111762 is a Phase III randomized, double-blind, active-controlled, multicenter, parallel group, fully-powered non-inferiority study. Subjects were randomized to DTG 50 mg once daily or RAL 400 mg twice daily (BID), both in

combination with investigator selected background therapy based on Screening and historic resistance results. The background therapy was limited to no more than two antiretroviral agents. At the Week 48 visit, subjects randomized to RAL will be discontinued from the study (if RAL is approved and commercially available in the country), while subjects randomized to DTG will be given the opportunity to remain on the study while receiving DTG 50 mg once daily during the Open-label Phase of the study.

Key results of the Week 48 Virology analyses (GSK Document number 2012N154814_00) include the following:

Protocol-defined virologic failure occurred earlier and more frequently in the RAL arm, with Week 48 in 21/354 (6%) and 45/361 (12%) cumulative virologic failures for DTG and RAL respectively. A primary reason for the difference in virologic failures at Week 48 was a higher number of virologic non-responders in the RAL arm n=19/45 (42%) than in the DTG arm n=2/21 (10%).

In a pre-specified key secondary endpoint analysis, there was a statistically significant difference in favor of DTG for the proportion of mITT-E subjects harboring virus with evidence of treatment emergent INI resistance by Week 48 (DTG: 4/354 [1.0%]; RAL: 17/361 [5%]; p=0.003).

A unique IN substitution was observed (R263K or R263R/K mixture) in 2 subjects with treatment emergent INI substitutions on DTG that conferred no or low fold change in susceptibility to DTG and to RAL. Clinically relevant and previously described RAL associated genotypic resistance was observed in 16/38 (42%) subjects with confirmed virologic failure in the RAL arm, with high fold change to RAL and limited cross-resistance to DTG demonstrated at Week 48.

Protocol-defined virologic failure (PDVF) was defined as the following:

Virologic Non-response

- A decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 16, with subsequent confirmation, unless plasma HIV-1 RNA is <400 c/mL.
- Confirmed plasma HIV-1 RNA levels ≥400 c/mL on or after Week 24.

Virologic Rebound

- Confirmed rebound in plasma HIV-1 RNA levels to ≥400 c/mL after prior confirmed suppression to <400 c/mL.
- Confirmed plasma HIV-1 RNA levels >1 $\log_{10}$ c/mL above the nadir value where nadir is the lowest HIV-1 RNA value ≥400 c/mL.

Results:

Virologic failure through Week 48 occurred earlier and more frequently in the RAL arm (Table 67). At Weeks 16 and 24, there were respectively 10 (3%) and 15 (4%) confirmed virologic failures for the DTG arm and 21 (6%) and 35 (10%) for the RAL arm. The

difference through Week 24 was driven by a greater proportion of protocol defined virologic non-response in the RAL arm 5% versus <1% in the DTG arm, with a similar proportion of virologic rebound in both arms (4%). Between Week 32 and Week 48 there were no additional PDVFs in the DTG arm, and 6 additional PDVFs in the RAL arm, resulting at Week 48 in 21 (6%) and 45 (12%) cumulative virologic failures for DTG and RAL respectively.

Table 67 Cumulative Summary of Protocol-Defined Virologic Failures by Visit (mITT-E Population) Through Week 48

Week	DTG 50 mg Once Daily N=354 n/N (%)	RAL 400 mg BID N=361 n/N (%)
Week 8	1 (<1)	1 (<1)
Rebound	1 (<1)	1 (<1)
Week 12	4 (1)	6 (2)
Rebound	4 (1)	6 (2)
Week 16	10 (3)	21 (6)
Virologic non-response	0	13 (4)
Rebound	10 (3)	8 (2)
Week 24	15 (4)	35 (10)
Virologic non-response	1 (<1)	19 (5)
Rebound	14 (4)	16 (4)
Week 32	21 (6)	39 (11)
Virologic non-response	2 (<1)	19 (5)
Rebound	19 (5)	20 (6)
Week 40	21 (6)	44 (12)
Virologic non-response	2 (<1)	19 (5)
Rebound	19 (5)	25 (7)
Week 48	21 (6)	45 (12)
Virologic non-response	2 (<1)	19 (5)
Rebound	19 (5)	26 (7)

Data Source: ING111762 Wk 48 CSR Table 7.10

Genotypic and Phenotypic Accountability

Integrase PhenoSense, Integrase Geneseq, PhenoSense GT, PhenoSense Entry and Trofile assays were performed at [redacted] ([redacted]). PhenoSense GT, PhenoSense Entry and Trofile were used to assess resistance to other ARTs for eligibility purposes and to aid in the selection of the background regimen; PhenoSense Entry and Trofile tests were performed for Baseline samples only when requested by investigator. Integrase PhenoSense, Integrase Geneseq, and PhenoSense GT assays were always performed at PDVF for both the Day 1 and PDVF timepoints, and PhenoSense Entry and Trofile were performed at these same timepoints when the agents were used in the background regimen. All Baseline and On-treatment genotypic (Table 68) and phenotypic testing (Table 69) were conducted at [redacted].

Due to integrase assay failure, paired data (Baseline and time of PDVF) for IN resistance was not available for 4/21 DTG PDVF samples and 7/45 RAL PDVF samples. This is typically due to viral load < 500 c/mL, reduced viral fitness, or compromised sample collection/handling. The suspect virologic failure Week 16 sample for one subject (Subject [redacted]) in the DTG arm was inadvertently tested instead of the confirmed Week 24 sample. Additionally, the Day 1 IN resistance data needed for measure of emergent resistance was not available for Subject [redacted] as assay testing failed. The Week 16 sample IN resistance testing revealed no genotypic or phenotypic resistance. IN resistance testing at PDVF for one subject in the RAL arm (Subject [redacted]) was not available prior to database release.

Table 68 Genotypes Available in PDVF Genotypic Population through Week 48

Genotype Assessment	DTG 50 mg Once Daily N=19 n (%)	RAL 400 mg BID N=44 n (%)
Integrase		
Screen Sample	0	3 (7)
Baseline Sample	19 (100)	43 (98)
On-Treatment PDVF Sample	17 (89)	38 (86)
On-Treatment Non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	17 (89)	38 (86)
Baseline and On-Treatment Non-PDVF	1 (5)	2 (5)
Reverse Transcriptase		
Screen Sample	19 (100)	44 (100)
Baseline Sample	19 (100)	44 (100)
On-Treatment PDVF Sample	19 (100)	44 (100)
On-Treatment Non-PDVF Sample	1(5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	44 (100)
Baseline and On-Treatment Non-PDVF	1(5)	2 (5)
Protease		
Screen Sample	19 (100)	44 (100)
Baseline Sample	19 (100)	44 (100)
On-Treatment PDVF Sample	19 (100)	44 (100)
On-Treatment Non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	44 (100)
Baseline and On-Treatment Non-PDVF	1 (5)	2 (5)

Data Source: ING111762 Wk 48 CSR Table 12.5

Table 69 Phenotypes Available in PDVF Phenotypic Population through Week 48

Phenotype Assessment	DTG 50 mg Once Daily N=19 n (%)	RAL 400 mg BID N=43 n (%)
Integrase		
Screen Sample	0	3 (7)
Baseline Sample	19 (100)	42 (98)
On-Treatment PDVF Sample	17 (89)	38 (88)
On-Treatment non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	17 (89)	38 (88)
Baseline and On-Treatment non-PDVF	1 (5)	2 (5)
Reverse Transcriptase		
Screen Sample	19 (100)	43 (100)
Baseline Sample	19 (100)	43 (100)
On-Treatment PDVF Sample	19 (100)	43 (100)
On-Treatment non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	43 (100)
Baseline and On-Treatment non-PDVF	1 (5)	2 (5)
Non Reverse Transcriptase		
Screen Sample	19 (100)	43(100)
Baseline Sample	19 (100)	43 (100)
On-Treatment PDVF Sample	19 (100)	43 (100)
On-Treatment non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	43 (100)
Baseline and On-Treatment non-PDVF	1 (5)	2 (5)
Protease		
Screen Sample	19 (100)	43 (100)
Baseline Sample	19 (100)	43 (100)
On-Treatment PDVF Sample	19 (100)	43 (100)
On-Treatment non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	46 (98)
Baseline and On-Treatment non-PDVF	1 (5)	2 (5)
CCR5		
Screen Sample	16 (84)	40 (93)
Baseline Sample	16 (84)	40 (93)
On-Treatment PDVF Sample	1 (5)	6 (14)
On-Treatment non-PDVF Sample	0	0
Baseline and On-Treatment PDVF	1 (5)	6 (14)
Baseline and On-Treatment non-PDVF	0	0

Phenotype Assessment	DTG 50 mg Once Daily N=19 n (%)	RAL 400 mg BID N=43 n (%)
Fusion		
Screen Sample	12 (63)	32 (74)
Baseline Sample	12 (63)	32(74)
On-Treatment PDVF Sample	1 (5)	1 (2)
On-Treatment non-PDVF Sample	0	0
Baseline and On-Treatment PDVF	0	1 (2)
Baseline and On-Treatment non-PDVF	0	0

Data Source: ING111762 Wk 48 CSR Table 12.41

On treatment Viral Genotyping / Phenotyping

Week 48 Genotypic and Phenotypic Analyses of Virus at Protocol-Defined Virologic Failure

Genotypic evidence of emergent INI resistance was identified according to the presence of IN substitutions specified in the RAP and associated with development of resistance to relevant integrase inhibitors including RAL or DTG based on in vitro passage data as well as in vivo data and that were not present at Baseline.

Phenotypic evidence of emergent INI resistance was identified as FC in IC50 relative to wild-type, as provided by the PhenoSense HIV assays from [redacted]., above the 1.5 biological cutoff for RAL or 2.5 cutoff for DTG (standard cut-off used by [redacted]. until clinical or biological cut-off has been determined), if not above the cutoff at Baseline.

Proportion of Subjects with INI Genotypic or Phenotypic Resistance

Key secondary endpoint: For the mITT-E population, 1% of subjects receiving DTG and 5% of subjects receiving RAL had evidence of treatment emergent genotypic or phenotypic INI resistance at the time of protocol defined virologic failure by Week 48 (Table 70). The treatment difference was statistically significant in favor of DTG (p=0.003, less than the pre-specified two-sided 5% type I error cutoff) according to a pre-specified closed testing procedure.

Table 70 Summary of Analysis for Proportion of Subjects with Detectable Virus that has Treatment Emergent Genotypic or Phenotypic Evidence of INI Resistance by Week 48 (mITT-E Population)

Treatment	Number Meeting Criteria / Number Assessed	Difference in Proportion[a] % (95% CI)	Adjusted Difference in Proportion[b] % (95% CI)	P-Value[c]
DTG 50 mg Once Daily	4 / 354 (1%)			
RAL 400 mg BID	17 / 361 (5%)	-3.6 (-6.0, -1.1)	-3.7 (-6.1, -1.2)	0.003

Data Source: ING111762 Wk 48 CSR Table 7.14

a. Difference: Proportion on DTG - Proportion on RAL.
b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: Baseline HIV-1 RNA (<=50,000 vs. >50,000 c/mL), DRV/r use without primary PI mutations (yes vs. no), and Baseline PSS (2 vs. <2) to background regimen. PSS based on full susceptibility, category '2' includes two subjects with PSS=3.
c. Two-sided p-value for test of superiority. Type I error rate controlled according to a pre-specified fixed sequence testing procedure.

A statistically significant difference in favor of DTG was observed with the planned sensitivity analysis in Table 71 where the phenotypic resistance component of the endpoint was determined using a common FC cutoff of 2.5 for DTG and RAL.

Table 71 Summary of Sensitivity Analysis for Proportion of Subjects with Detectable Virus that has Treatment Emergent Genotypic or Phenotypic Evidence of INI Resistance by Week 48 (mITT-E Population)

Treatment	Number Meeting Criteria / Number Assessed (%)	Difference in Proportion[a] % (95% CI)	Adjusted Difference in Proportion[b] % (95% CI)
DTG 50 mg Once Daily	4 / 354 (<1%)		
RAL 400 mg BID	16 / 361 (4%)	-3.3 (-5.7, -0.9)	-3.4 (-5.7, -1.0)

Data Source: ING111762 Wk 48 CSR Table 7.16

a. Difference: Proportion on DTG - Proportion on RAL.
b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: Baseline HIV-1 RNA (<=50,000 vs. >50,000 c/mL), DRV/r use without primary PI mutations (yes vs. no), and Baseline PSS (2 vs. <2) to background regimen. PSS based on full susceptibility, category '2' includes two subjects with PSS=3.

A statistically significant difference in favor of DTG was observed in the second planned sensitivity analysis of Table 72, which looked at additional resistance data. Specifically, this analysis includes evidence of treatment emergent resistance from subjects whose last on-treatment HIV-1 RNA was >400 c/mL at withdrawal for a reason other than virologic

failure (DTG: Subject [redacted], discontinued at Week 4; RAL: Subject [redacted], discontinued at Week 48) or from subjects with confirmation of Week 48 PDVF occurring in the open label phase of the study (RAL: Subjects [redacted] and [redacted]), if resistance testing results were available.

Table 72 Summary of Sensitivity Analysis for Proportion of Subjects with Additional Evidence of INI Resistance by Week 48

Treatment	Number Meeting Criteria / Number Assessed (%)	Difference in Proportion[a] % (95% CI)	Adjusted Difference in Proportion[b] % (95% CI)
DTG 50 mg Once Daily	5 / 354 (1%)		
RAL 400 mg BID	20 / 361 (6%)	-4.1 (-6.8, -1.5)	-4.2 (-6.8, -1.5)

Data Source: ING111762 Wk 48 CSR Table 7.15

a. Difference: Proportion on DTG - Proportion on RAL.

b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: Baseline HIV-1 RNA (<=50,000 vs. >50,000 c/mL), DRV/r use without primary PI mutations (yes vs. no), and Baseline PSS (2 vs. <2) to background regimen. PSS based on full susceptibility, category '2' includes two subjects with PSS=3.

Proportions of INI Resistance Substitutions

At Week 48, there were 17 subjects experiencing PDVF in the DTG arm with matched Baseline and PDVF IN genotypic resistance testing results available. Integrase substitutions emerged at the RAL associated T97, E138, and polymorphic V151 positions, and at R263. At Week 48 there were 38 subjects experiencing PDVF in the RAL arm with matched Baseline and PDVF IN genotypic resistance testing results available. Integrase substitutions emerged at positions commonly observed during RAL therapy including primary resistance mutations at Y143, Q148, and N155 as well as associated secondary mutations (Table 73).

Table 73 Treatment Emergent Integrase Substitutions from Baseline (Week 48 PDVF Genotypic Population - IN results at Baseline and Time of PDVF)

Codon[a]	Treatment Emergent IN Genotype	DTG 50 mg Once Daily N=17 n (%)	RAL 400 mg BID N=38 n (%)
Any		**4 (24)**	**16 (42)**
68	L68L/V	0	1 (3)
74	L74L/M	0	1 (3)
92	E92E/Q	0	1 (3)
97	T97A, T97T/A	1 (6)	4 (11)
138	E138T/A	1 (6)	0
140	G140A, G140S	0	3 (8)
143	Y143Y/C, Y143R, Y143Y/R/H/C	0	5 (13)
148	Q148H, Q148Q/R	0	5 (13)
151	V151I, V151V/I	1 (6)	2 (5)
155	N155H, N155N/H	0	9 (24)
157	E157E/Q	0	1 (3)
163	G163K	0	2 (5)
263	R263K, R263R/K[a]	2 (12)	0

Data Source: ING111762 Wk 48 CSR Table 12.12

a. Per RAP definition RAL or DTG associated resistance mutations**:** H51Y, **T66A, T66I, T66K,** L68V, L68I, L74I, L74M, L74R4, **E92Q, E92V,** Q95K, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, **Y143C, Y143H, Y143R,** P145S, S147G, **Q148H, Q148K, Q148R**, V151I, V151L, S153F, S153Y, N155H, E157Q, G163R, G163K, G193E, R263K. IN substitutions listed above in bold were defined from the Stanford database (http://hivdb6.stanford.edu) with a score of >45. Other mutations are secondary IN resistance mutations from the Stanford database detected during INI clinical investigation, or were observed during other clinical investigation or in vitro studies with DTG.

INI Phenotypic Susceptibility by Fold Change Ranges

At PDVF within the DTG arm, 16/17 subjects with matched Baseline and PDVF IN phenotypic resistance testing results available had a DTG fold change of <2.5 ([redacted] DTG [standard] cutoff) and 16/17 RAL fold change of <1.5 ([redacted] RAL biological cutoff). The one subject (Subject [redacted]) receiving DTG with elevated DTG and RAL fold changes at PDVF enrolled with pre-existing RAL resistance mutations and with Baseline fold changes above cutoff for both DTG and RAL. Therefore, no DTG subjects had treatment-emergent INI phenotypic resistance at PDVF.

At PDVF within the RAL arm, four of the subject samples had a DTG fold change of ≥2.5 and 14 had RAL fold changes of ≥1.5 (Table 74). One of these subjects (Subject [redacted]) was also above the RAL cutoff at Baseline and enrolled with pre-existing RAL resistance mutations. Therefore, thirteen subjects receiving RAL had evidence of treatment-emergent INI phenotypic resistance to RAL at PDVF.

Table 74 Summary of Fold Change to DTG and RAL at Time of PDVF (Week 48 PDVF Phenotypic Population)

Investigational Product	Fold-Change Compared to Wildtype Virus	DTG 50 mg Once Daily N=19 n (%)	RAL 400 mg Twice Daily N=43 n (%)
DTG	n	17	38
	0 to 2.5	16 (84)	34 (79)
	>2.5 to 4	0	1 (2)
	>4 to 8	0	2 (5)
	>8 to 10	0	0
	>10 to 15	0	0
	>15 to 20	0	1 (2)
	>20 to 25	0	0
	>25	1(5)	0
	Median (Range)	0.92 (0.57 – 148.23)	1.08 (0.67 – 18.00)
RAL	n	17	38
	0 to 1.5	16 (84)	24 (56)
	>1.5 to 4	0	3 (7)
	>4 to 8	0	0
	>8 to 10	0	0
	>10 to 20	0	2 (5)
	>20 to maximum of assay limit	0	4 (9)
	>maximum of assay limit	1 (5)	5 (12)
	Median (Range)	0.93 (0.39 – 109.58)	1.13 (0.59 – 140.36)

Data Source: ING111762 Wk 48 CSR Table 12.48

Emergent Integrase Resistance and Virologic Characteristics

Subjects on DTG or RAL with emergent integrase genotypic or phenotypic resistance through Week 48 are summarized in Table 75.

There were four PDVF subjects in the DTG arm (Subjects [redacted], [redacted], [redacted], and [redacted]) with emergent integrase-defined substitutions. Three of four subjects experienced virologic rebound and one experienced non-response. Three had no defined integrase resistance substitutions at Baseline; two of these three acquired a substitution at R263 and one acquired a polymorphic V151V/I substitution in the integrase open reading frame. In all three cases the DTG fold change was < 2, as was the RAL fold change. None of the three subjects with emergent substitutions at R263 or V151V/I had RAL-associated secondary mutations at Baseline. At Baseline, one subject (Subject [redacted]) in the DTG arm harbored virus with RAL associated resistance mutations at Q148H, E138A, G140S, and elevated DTG FC of 12 at Baseline and RAL FC >Max measureable. At PDVF

integrase substitutions E138T/A and T97A emerged and DTG and RAL FCs both increased to >Max measureable.

Subject [redacted] randomized to DTG and receiving DRV/r and TDF as the background regimen experienced virologic rebound PDVF at Week 16 and had treatment emergent R263R/K in integrase without significant change in DTG susceptibility (fold change at Baseline 0.96 and at PDVF 1.12). This subjects HIV-1 RNA response varied:

	Day 1	Wk 4		Wk16	Confirm
HIV-1 RNA (c/mL)	41,179 →	<50 →	57 → 1305→	308 →	6446 → 903

The Baseline PSSf score was 2 and GSS score was 2 on a regimen of tenofovir and darunavir/r. The Week 4 C0 value was 0.5706 μg/mL. The fluctuating RNA between Day 1 and PDVF confirmation suggests adherence may have been incomplete.

Subject [redacted] randomized to DTG and receiving EFV and TDF as the background regimen experienced virologic rebound PDVF at Week 24 and had treatment emergent R263K in integrase with change in DTG susceptibility (fold change at Baseline 0.92 and at PDVF 1.93). A novel additional and conserved IN substitution V260I proximal to R263 was also present. This subject had an initial HIV-1 RNA response from Day 1: 876610 c/mL to Week 4: 1461 c/mL, followed by HIV-1 RNA 684 c/mL with sequential HIV-1 RNA values of 1852, 900, and at Week 24 PDVF timepoint HIV-1 RNA 9367 c/mL followed by confirmation timepoint HIV-1 RNA of 59400 c/mL. The BL PSSf score was 1 and GSS score was 0.75 on a regimen of tenofovir (inactive) and efavirenz. The Week 4 C0 value was below the limit of quantitation (<0.02 ug/mL) and Week 24 C0 was 0.2525. The Week 4 C0 value of <0.02 ug/mL suggests adherence may have been incomplete.

Subject [redacted] randomized to DTG and receiving ABC and EFV as the background regimen experienced virologic non-response at Week 24 and had emergent polymorphic integrase substitution V151V/I with no change in DTG susceptibility (DTG Baseline FC = 0.94 to PDVF FC = 0.92). This subject had HIV-1 RNA at Day 1 of 171,984 c/mL to Week 4: 167,931 c/mL, followed by sequential HIV-1 RNA values of 180,560 c/mL, 95,477 c/mL, 126,925 c/mL and Week 24 PDVF timepoint HIV-1 RNA of 6,832 c/mL, followed by confirmation timepoint HIV-1 RNA of 29,432 c/mL. Of note resistance testing sample was not available for testing at the Week 24 PDVF timepoint; testing was carried out on the Week 24 confirmation timepoint sample and is provided in Table 75. In addition, Week 16 timepoint sample was tested, and, the same results were obtained with emergent polymorphic integrase substitution V151V/I with no change in DTG or RAL susceptibility. The Week 4 C0 value was below the limit of quantitation (<0.02 ug/mL).

Subject [redacted] randomized to DTG and receiving ATV/r and TDF as the background regimen experienced virologic rebound at Week 16 and had treatment emergent E138T/A and T97A added onto Baseline Q148H, E138A, G140S and with change in DTG susceptibility fold change from Baseline 12 to PDVF >Max. Subject [redacted] had 6.9 years ART experience but no reported RAL experience. This subject had an initial HIV-1

RNA response from Day 1: 153,533 c/mL to Week 16 PDVF timepoint HIV-1 RNA of 266,065 c/mL, followed by confirmation timepoint HIV-1 RNA of 608,458 c/mL. The BL PSSf score was 1 and GSS score was 0.25 on a regimen of atazanavir (active) and tenofovir (inactive). The Week 4 C0 value was 0.94 ug/mL and Week 24 C0 value was below the limit of quantitation (<0.02 ug/mL).

There were 16 PDVF subjects in the RAL arm with emergent clinically relevant RAL associated genotypic integrase resistance at Week 48, seven of which were virologic non-responders, and nine were rebounders Table 75. Four of the 16 subjects in the RAL arm with emergent RAL associated genotypic integrase resistance had Baseline L74I present, one of the 16 had baseline E157Q, and one of the 16 had Baseline G193E. Five of the 16 subjects in the RAL arm had emergent DTG fold change >2 (Subjects [redacted], [redacted], [redacted], [redacted], and [redacted]). Three of these five experienced PDVF as virologic non-response, two at Week 16 and one at Week 24, and two experienced PDVF as virologic rebound. All five subjects with DTG FC >2 acquired (new) RAL associated primary resistance mutations at Y143 and/or Q148, or N155 at PDVF, plus additional secondary resistance mutations.

Table 75 Summary of Subjects with Paired Baseline and PDVF IN Genotype and/or Phenotype Exhibiting Genotypic or Phenotypic Changes Through Week 48

Arm / Subj	PDVF Visit	Baseline PSSf / GSS	Virologic Failure	HIV-1 RNA (c/mL)		DTG FC		RAL FC		IN Genotype	
				Baseline	PDVF	Baseline	PDVF	Baseline	PDVF	Baseline	PDVF
DTG / [redacted]	Week 16	2 / 2	Rebound	41179	6446	0.96	1.12	1.02	0.94	None	R263R/K
DTG / [redacted]	Week 16	1 / 0.5	Rebound	153533	266065	12	>Max[a]	>Max	>Max	E138A, G140S, Q148H	T97A,E138T/A,G140S,Q148H
DTG / [redacted]	Week 24	1 / 0.75	Rebound	876610	9367	0.92	1.93	1.11	1.12	None	R263K
DTG / [redacted]	Week 24	2 / 2	Virologic non-response	171984	6832	0.94	0.92	0.83	0.97	None	V151V/I
RAL / [redacted]	Week 16	2 / 1.25	Virologic non-response	98571	10725	0.71	18	>Max[a]	>Max	L74I/M, Y143R[b]	L68L/V, L74L/M/I, G140A, Y143Y/C, Q148Q/R, E157E/Q
RAL / [redacted]	Week 16	1 / 1	Virologic non-response	641416	84973	1.3	3.73	1.18	117	None	E92E/Q, T97T/A, V151V/I, N155H
RAL / [redacted]	Week 16	0 / 0	Virologic non-response	63449	58433	1.04	1.27	1.46	114	None	T97A, Y143R
RAL / [redacted]	Week 16	1 / 0.5	Virologic non-response	18441	2300	0.83	0.92	1.04	98	L74I	L74I, Y143Y/R/H/C, Q148Q/R
RAL / [redacted]	Week 16	2 / 1.75	Virologic non-response	47713	88989	0.98	0.9	1.25	1.6	V151I	V151I
RAL / [redacted]	Week 24	1 / 1	Virologic non-response	131377	7203	1.28	1.89	1.01	>Max	None	L74L/M, T97T/A, V151I, N155H, G163K
RAL / [redacted]	Week 24	2 / 1	Virologic non-response	856849	28931	1.13	4.12	1.23	>Max	E157Q	G140S, Q148H, E157Q
RAL / [redacted]	Week 24	1 / 1	Rebound	936821	10472	1	2.12	0.96	22	L74I	L74I, N155H
RAL / [redacted]	Week 24	1 / 0.5	Rebound	30711	47371	0.88	1.45	1.09	>Max	L74I	L74I,T97T/A,Y143Y/N/R/S/K/C
RAL /	Week	2 / 2	Virologic non-	28814	2734	1.14	0.89	1.14	1.44	None	N155N/H

Arm / Subj	PDVF Visit	Baseline PSSf / GSS	Virologic Failure	HIV-1 RNA (c/mL)		DTG FC		RAL FC		IN Genotype	
				Baseline	PDVF	Baseline	PDVF	Baseline	PDVF	Baseline	PDVF
[redacted]	24		response								
RAL / [redacted]	Week 24	1 / 1	Rebound	535742	3007185	0.92	1.38	1.09	3.78	L74I	L74I, N155N/H
RAL / [redacted]	Week 32	2 / 2	Rebound	49920	126272	0.59	0.69	0.41	0.66	None	N155N/H
RAL / [redacted]	Week 32	2 / 2	Rebound	93	1875	0.88	1.25	0.81	13	None	Y143Y/C, N155N/H,G163G/R
RAL / [redacted]	Week 32	2 / 1	Rebound	153526	2206	0.86	1.34	1	13	None	N155H
RAL / [redacted]	Week 40	2 / 2	Rebound	21403	860	0.88	4.36	0.8	>Max	G193E	G140S, Q148H, G193E
RAL / [redacted]	Week 40	2 / 2	Rebound	72029	1920	1.09	1.12	1	1.15	None	N155N/H
RAL / [redacted]	Week 40	2 / 2	Rebound	739998	879	1.08	1.13	1.02	2.34	None	Q148Q/R

Data Source: ING111762 Wk 48 CSR Table 12.59; Table 12.60

a. Greater than maximum measureable in assay fold change resistance = >Max for DTG=>148; >Max for RAL =>110.

b. Per RAP definition RAL or DTG associated resistance mutations: L74M, L74I, T97A, E92Q, E138A, E138K, G140S, Y143C, Y143H, Y143R, Q148H, Q148K, Q148R, V151I, N155H, S153Y, S153F, G163K, G163R, G193E, R263K.

Treatment Emergent Resistance to Background Regimen

There was a statistically significant difference in favor of DTG with more emergent resistance to the background regimen in the RAL arm (12/361 versus 4/354 in the DTG arm) (Table 76), based on having evidence of a descrease in background regimen genotypic or phenotypic susceptibility scores from baseline to time of PDVF.

Table 76 Summary of Emergence of Genotypic and/or Phenotypic Resistance to the Background Regimen at Time of PDVF (mITT-E Population)

Treatment	Number meeting Criteria / Total Assessed	Difference in Proportion (95% CI) (DTG - RAL)	Adjusted Difference in Proportion[a] (95% CI) (DTG - RAL)
DTG 50 mg Once Daily	4 / 354 (<1%)		
RAL 400 mg BID	12 / 361 (3%)	-2.2 (-4.3, 0.0)	-2.2 (-4.3, -0.1)

Data Source. ING111762 Wk 48 CSR Table 7.30

a. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: Baseline HIV-1 RNA (<=50,000 vs. >50,000 c/mL), DRV/r use without primary PI mutations (yes vs. no), and Baseline PSS (2 vs. <2) to background regimen. PSS based on full susceptibility, category '2' includes two subjects with PSS=3. . Statistical significance was assessed relative to a nominal 5% type I error rate, without adjustment for multiple comparisions.

Emergent Background Regimen Resistance for Subjects at PDVF

Looking at all subjects there was negligible change from Baseline in number of classes for which at least one drug was available for both DTG and RAL.

There were four subjects on DTG with emergent resistance to background regimen at PDVF; one had pre-existing RAL primary and secondary resistance mutations and additional emergent IN mutations at PDVF, and two other subjects also had emergent substitutions within the integrase open reading frame.

- **Subject[redacted]:** received TDF, ATV/r and had a PSSf score of 2 and GSS of 2.0 at Baseline. At Week 12 PDVF the PSSf score remained 2 while GSS score changed to 1.5 and the NNRTI mutation K101P/Q emerged, and no integrase substitutions emerged.
- **Subject[redacted]:** received TDF, EFV and had a PSSf of 1 and GSS of 0.75, with tenofovir inactive at Baseline. At Week 24 PDVF the PSSf score changed to zero and GSS score to 0.5 as NNRTI mutation G190S emerged, and integrase substitution R263K emerged.
- **Subject[redacted]:** received ABC, EFV and had a PSSf and GSS of 2. At Week 24 PDVF the PSSf and GSS scores changed to 1, as NNRTI mutations K101K/E/Q and G190A emerged. In addition, the polymorphic integrase substitution V151V/I emerged.
- **Subject[redacted]:** received TDF, ATV/r and had a PSSf score of 1 and GSS of 0.25. At Week 16 PDVF the PSSf and GSS scores changed to 0, and the PI mutation V32V/I

emerged. Of note Subject [redacted] also had Baseline RAL integrase mutations Q148H, E138A, G140S and treatment emergent E138T/A and T97A at PDVF.

Twelve subjects in the RAL arm had treatment emergent resistance to the background regimen. Six subjects (Subjects [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]) had treatment emergent background resistance and also emergent INI resistance (as shown in Table 75)

- **Subject [redacted]:** received ABC, TDF and had a PSSf score of 2 and GSS of 1. At Week 16 PDVF, the PSSf score was unchanged and GSS score changed to 0.75, with emergent RT mutations K70K/R and T215F. Of note, Subject [redacted] also had Baseline RAL integrase mutations Y143R, L74I/M and treatment emergent Q148Q/R, G140A, and E157E/Q at PDVF.
- **Subject [redacted]:** received received TDF, TPV/r and had a PSSf score of 2 and GSS of 2. At Week 24 PDVF, the PSSf and GSS scores changed to 1, with emergent PRO mutation I47I/V**.**
- **Subject [redacted]:** received MVC, ZDV and had a PSSf score of 2 and GSS of 2. At Week 32 PDVF, the PSSf and GSS scores changed to 1 as tropism changed from R5 to CXCR4 tropic.
- **Subject [redacted]:** received FTC, TDF and had a PSSf score of 2 and GSS of 2. At Week 40 PDVF, the PSSf score changed to 1 and the GSS score changed to 1, with emergent RT mutations K103N, P255H and M184V.
- **Subject [redacted]:** received 3TC, ABC and had a PSSf score of 1 and GSS of 0.5. At Week 24 PDVF, the PSSf score was unchanged and the GSS score changed to 0.25, without emergent IAS mutations but had increased resistance to ABC Stanford algorithm at PDVF.
- **Subject [redacted]:** received 3TC, ABC and had a PSSf score of 1 and GSS of 0.5. At Week 24 PDVF, the PSSf score changed to 0 and the GSS score changed to 0, with emergent RT mutation L74L/V.

Six other PDVF subjects in the RAL arm (Subjects [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]) with treatment emergent background resistance did not have emergent integrase resistance at PDVF.

- **Subject [redacted]:** received DRV/r, TDF and had a PSSf score of 1 and GSS of 1.5. At Week 40 PDVF, the PSSf score was unchanged and the GSS score changed to 1.25 without emergent IAS mutations but increased resistance to TDF by Stanford algorithm at PDVF.
- **Subject [redacted]:** received DRV/r, ETR and had a PSSf score of 2 and GSS of 2. At Week 24 PDVF, the PSSf score changed to 1 and the GSS score changed to 1.25, with emergent RT mutations K101K/E, Y181Y/C, M230M/L and M41M/L, M184M/V, T215T/F/I/S, K219K/E.
- **Subject [redacted]:** received DRV/r, ETR and had a PSSf score of 2 and GSS of 2. At Week 16 PDVF, the PSSf score changed to 1 and the GSS score changed to 1, with emergent RT mutation Y181Y/C.

- **Subject** [redacted]: received ETR, LPV/r and had a PSSf score of 2 and GSS of 2. At Week 24 PDVF, the PSSf score was unchanged and the GSS score changed to 1.25, with emergent RT mutation Y181Y/C.
- **Subject** [redacted]: received ATV/r, TDF and had a PSSf score of 0 and GSS of 1. At Week 16 PDVF, PSSf score was unknown due to phenotypic assay failure, and the GSS score changed to 0.5, with emergent PRO mutation I84V.
- **Subject** [redacted]: received FPV/r, TDF and had a PSSf score of 2 and GSS of 0.5. At Week 24 PDVF, the PSSf score changed to 0 and the GSS score was unchanged, without emergent IAS mutations.

Genotypic and Phenotypic Analysis of Virus for Other Samples

Subject [redacted] randomized to the DTG arm and was a virologic non-responder PDVF at Week 24. In addition to the testing at the confirmation timepoint for Week 24 PDVF due to lack of sample of actual PDVF, IN resistance testing was performed at the preceding Week 16 timepoint; as at Week 24 confirmation and provided in Table 75, the emergent polymorphic integrase substitution V151V/I was also observed with no change in DTG or RAL susceptibility.

Post Randomized Phase Results and Analyses Based on Data to Date

Protocol-Defined Virologic Failure Post Randomized Phase

Two subjects (Subjects [redacted] and [redacted]) in the DTG arm experienced suspected PDVF at the Week 48 visit which was confirmed during the open label phase of the study following the Week 48 visit. An additional 6 subjects experienced virologic rebound on DTG during the Open Label Phase: three at Week 60 (Subjects [redacted], [redacted], and [redacted]), two at Week 72 (Subjects [redacted] and [redacted]), and one at Week 84 (Subject [redacted]) (Table 77). Of note: Subject [redacted] was identified as a Protocol deviation due to non-compliance with IP treatment.

Three subjects (Subjects [redacted], [redacted], and [redacted]) in the RAL arm experienced suspected PDVF at the Week 48 visit which was confirmed during the open label phase of the study following the Week 48 visit. An additional two subjects experienced virologic rebound on RAL during the open label phase at Week 60 (Subjects [redacted] and [redacted]). Resistance testing data was not complete for Subject [redacted] before database freeze.

Table 77 IN Genotypic and Phenotypic Data for Protocol Defined Virologic Failures Confirmed During the Open-Label Phase

Arm / Subj	PDVF Visit	HIV-1 RNA (c/mL)		DTG FC		RAL FC		IN Genotype	
		Baseline	PDVF	Baseline	PDVF	Baseline	PDVF	Baseline	PDVF
DTG / [redacted]	Week 48	346	80599	0.87	0.68	0.98	0.83	None	None
DTG / [redacted]	Week 48	20153	6691	0.83	0.94	0.85	0.92	None	None
DTG / [redacted]	Week 60	14749	282669	1.11	1.11	1.11	1.02	None	None
DTG / [redacted]	Week 60	1780	6164	0.83	0.87	0.83	0.87	None	None
DTG / [redacted]	Week 72	84313	27050	0.66	2.4	0.52	113	None	T97A, N155H
DTG / [redacted]	Week 72	461	82460	0.99	1.05	1.11	1.24	None	None
DTG / [redacted]	Week 84	6977	2035	0.96	NA	0.96	NA	None	NA
RAL / [redacted]	Week 48	807	880	1.41	2.27	1.57	31	None	E92E/Q, N155H
RAL / [redacted]	Week 48	26387	1848	1.18	1.13	0.93	0.85	None	None
RAL / [redacted]	Week 48	85943	1871	0.82	2	0.82	30	L74L/I	L74I, T97T/A, N155H
RAL / [redacted]	Week 60	2417	46664	1.17	1.32	1.06	7.99	None	N155H
RAL / [redacted]	Week 60	5967	3862	1.01	NA	0.86	NA	None	NA

Data Source: ING111762 Wk 48 CSR Table 12.59, Other Listing 71

Additional Virology Results

IN Viral Genotypic and Phenotypic Data for the Last On-Study Visit

To further monitor the development of resistance to INIs, the genotypic and phenotypic susceptibilities were determined at the last time point on study meeting the following criteria: unconfirmed suspected protocol-defined virologic failure HIV-1 RNA ≥400 c/mL. At Week 48, six subjects in the DTG arm and eight subjects in the RAL arm had resistance results based on met these testing criteria (Table 78). In addition, one subject (Subject [redacted]) in the RAL arm was tested at the post Week 40 timepoint and the data is provided below, though the HIV-1 RNA is <400 c/mL for the tested timepoint.

Table 78 Summary of Subjects with Elevated HIV-1 RNA who Discontinued Without Confirmation

Arm / Subject	Visit (Week)	HIV-1 RNA Baseline (c/mL)	HIV-1 RNA Resistance Testing (c/mL)	IN Genotype		DTG Fold Change		RAL Fold Change	
				Day 1	Final	Day 1	Final	Day 1	Final
DTG / [redacted]	16	66035	19896	none	none	0.90	0.81	0.87	1.03
DTG / [redacted]	4	4155	1929	none	L74L/M/I	0.88	0.88	0.73	0.75
DTG / [redacted]	8	371109	668	L74I	L74I	1.03	0.96	1.05	1.07
DTG / [redacted]	16	171984	126925	none	V151V/I	0.94	0.92	0.83	0.91
DTG / [redacted]	16	15447	2202	none	none	1.25	1.27	0.9	0.98
DTG / [redacted]	12	433019	1486	L74I	L74I	0.91	0.94	1.02	1.06
DTG / [redacted]	2	4695	2007	T97A	none	0.70	0.87	1.85	1.01
RAL / [redacted]	48	64707	458	None	None	0.97	0.81	0.8	0.77
RAL / [redacted]	8	663584	1375311	None	None	1.41	1.07	1.09	1.2
RAL / [redacted]	4	381204	105809	L74I	L74I	1.00	0.95	1.22	1.06
RAL / [redacted]	16	233573	44202	L74I	L74I	0.93	0.86	0.97	0.87
RAL / [redacted]	8	624823	247888	None	None	0.73	0.72	0.94	0.89
RAL / [redacted]	40	625	281	None	None	1.31	0.95	1.39	1.12
RAL / [redacted]	48	64707	458	None	None	0.97	0.81	0.8	0.77
RAL / [redacted]	16	120085	17972	None	None	0.68	0.83	0.56	0.9
RAL / [redacted]	16	33112	30725	L74I	L74I	0.91	0.75	1.33	1.33
RAL / [redacted]	48	16624	1153	L74I	L74I, N155H	0.75	1.38	1.07	26

Data Source: ING111762 Wk 48 CSR Table 12.61; ICH Listing 9

Discussion

Results from this Week 48 analysis show DTG has a higher barrier to resistance in this patient population and a distinct resistance profile from RAL. A statistically significant difference in favor of DTG was demonstrated by planned virologic analyses for emergent

integrase resistance. The proportion of subjects harboring virus with evidence of INI resistance by Week 48 was statistically lower for DTG vs RAL, with 1% (4/354) of subjects receiving DTG and 5% (17/361) of subjects receiving RAL harboring treatment emergent genotypic or phenotypic INI resistance at the time of protocol-defined virologic failure. A prespecified sensitivity analysis of the same endpoint but using a common FC cutoff to determine phenotypic resistance to RAL and DTG also confirmed a statistically significant difference in favor of DTG.

DTG exhibits a higher barrier to treatment failure than RAL. PDVF occurred earlier and more frequently in the RAL arm compared with the DTG arm, which reflects the greater suppresive effect in this ART-experienced patient population for DTG versus RAL.

Four of the 16 subjects in the RAL arm with treatment emergent INI resistance had baseline L74I polymorphism present, one of 16 had baseline E157Q, and one had baseline G193E. None of these positions have been associated with decreased response or greater frequency of virologic failure during INI therapy; they were included in the pre-defined list of potential INI resistance mutations along with clinically identified INI resistance mutations (e.g., at IN positions Q148, Y143, and N155) based on in vitro passage studies with relevant INIs to be comprehensive in studying this investigational INI (DTG).

At the previous Week 24 interim analysis, 2 of the 9 (22%) subjects with confirmed virologic failure in the DTG treatment arm had treatment emergent INI resistance substitutions which were both at position R263 in the IN open reading frame, and 9 (33%) of 27 in the RAL arm had treatment emergent INI resistance mutations commonly observed during RAL therapy including the primary resistance mutations at Y134, Q148, and N155 as well as associated secondary mutations. At Week 48, four PDVF subjects on DTG and 19 subjects on RAL with matched Baseline and PDVF resistance testing developed treatment emergent integrase genotypic and/or phenotypic changes. For all subjects in the RAL arm the observed mutations were, as expected, clinically relevant INI resistance mutations commonly observed during RAL therapy, and included the primary resistance mutations at Y134, Q148, and N155 and associated secondary mutations. For subjects in the DTG arm without Baseline RAL resistance, no primary or secondary resistance mutations commonly selected during RAL therapy emerged. In one case of emergent integrase resistance for the DTG arm, the IN substitution observed was at position V151 with no increase to DTG FC compared to wildtype. For the other DTG subjects with emergent integrase resistance, the IN mutations observed were at position R263 (max PDVF FC =1.93).

The R263K mutation has been selected during passage with EVG [Jones, 2007], has been infrequently observed during RAL therapy [Brenner, 2011], and most recently was selected during *in vitro* passage with DTG [Quashie, 2012; Oliveira, 2012]. Fold changes from R263K *in vitro* studies to date demonstrate some variability with DTG fold changes ranging from 2.5 to 11.2, and the R263K substitution conferred decreased replication, strand transfer activity, and integration into host DNA in cell based assays [Oliveira, 2012; http://journals.sfu.ca/jias/index.php/jias/article/view/18447/2740, 2012; Quashie, 2012]. Fold change measures with site direct mutants HIV-1 gave DTG FC of 1.5 (2013N167276_00), similar to the FC <2 generated in this study. Position 263 is in the

C-terminal domain of the IN protein, resides within a posited integrase nuclear localization motif [De Houwer, 2012], and is distal from the typical location of strand transfer integrase inhibitor mutations which usually are positioned at or near component residues of the catalytic pocket or its sublayers. Based on a set of 2997 aligned integrase sequences selected from integrase inhibitor naive subjects, R263 was highly conserved at a 99.77% level, with 263K present at 0.11% frequency [Vavro, 2013].

Overall, RAL and EVG have strongly overlapping resistance profiles while DTG has been demonstrated to have a distinct resistance profile based on in vitro [Kobayashi, 2011] and now *in vivo* evaluations from this study.

While low levels of HIV-1 RNA were observed at PDVF for the ART-naive DTG studies ING113086 and ING114467, subjects experiencing virologic failure through Week 48 in this study typically had higher HIV-1 RNA levels that were more broadly distributed across HIV-1 RNA ranges. Most HIV-1 RNA levels were above 1000 c/mL and >40% were above 10,000 c/mL. Thus, the virologic failures in this study had sufficient viral replication for a robust assessment of integrase resistance. Despite these higher viral loads at failure, clinically relevant resistance to DTG was not observed, while clinically relevant RAL resistance was observed.

Conclusions:

- DTG exhibits a higher barrier to treatment failure than RAL.
- In a prespecified and multiplicity controlled analysis, there was a statistically significant difference in favor of DTG for the proportion of subjects who failed therapy with treatment-emergent evidence of INI resistance through Week 48.
- A unique IN substitution was observed (R263K or R263R/K mixture) in 2 subjects with treatment emergent resistance on DTG that conferred little change in susceptibility to DTG and to RAL.

4.5. Clinical Virology – Lamivudine

4.5.1. Studies in Antiretroviral Therapy Naive Subjects

4.5.1.1. EPV20001

EPV20001 is a Phase II/III 48-week, randomized, double-blind, controlled, multicenter study to evaluate the efficacy and safety of 3TC 300 mg Once Daily vs 3TC 150 mg BID in combination with ZDV 300 mg BID and EFV 600 mg Once Daily in antiretroviral naive adults with HIV-1 infection (GSK Documet number RH2002/00007/00). A total of 554 subjects (Once Daily: 275, BID: 275) were enrolled. Protocol Defined Virologic Failure (PDVF) was defined as either a failure to achieve a reduction in HIV-1 RNA to <400 c/mL by Week 24 or the achievement of a decrease in plasma HIV-1 RNA to <400 c/mL with a subsequent confirmed increase above 400 c/mL. Subjects with plasma HIV-1 RNA >400 c/mL, where no subsequent confirmed plasma HIV-1 RNA was available were also included in this population.

Genotypic data were generated at GlaxoSmithKline using the ViroSeq HIV-1 Genotyping System Kit. All phenotypic data were generated by [redacted] Using the recombinant virus assay Phenosense™ HIV.

Fifty-three (10%) subjects failed virologically by Week 48 of the study. A total of 41 (77%) subjects had paired baseline and on-treatment genotypes. Forty-eight of the 53 (91%) subjects had a baseline phenotype while only 26/53 (49%) subjects had phenotype on-treatment data post-baseline. Only 23/53 (43%) subjects had paired genotype and phenotype at post-baseline time points.

Fourteen of the 44 subjects (32%) with post-baseline genotypes had virus that developed 3TC mutations while on treatment, 8 in the Once Daily group and 6 in the BID group (Table 79). There was no statistical difference between the 2 treatment groups with respect to the development of 3TC genotypic resistance (p value = 0.747). Six of the 14 subjects (Once Daily: 4; BID: 2) had evidence of baseline resistance to one or more drugs in the study as seen by genotype and/or phenotype. Of the 14 subjects with virus that developed 3TC genotypic resistance, 8/14 had on-treatment phenotypes as well. In all 8 subjects phenotypic determinations confirmed the genotypic result. Virus isolated from three additional subjects (Once Daily: 2; BID: 1) was found to be resistant to 3TC by phenotype only with no corresponding genotype.

Table 79 Summary of On-Treatment Resistance in Virologic Failures

Treatment Category[a]	Genotypic Resistance[b]			Phenotypic Resistance[c]		
	3TC Once Daily (n=22)	3TC BID (n=22)	Total (n=44)	3TC Once Daily (n=13)	3TC BID (n=13)	Total (n=26)
Wildtype	9 (41%)	11 (50%)	20 (46%)	3 (23%)	8 (61%)	11 (42%)
EFV only	5 (22%)	3 (14%)	8 (18%)	3 (23%)	1 (8%)	4 (15%)
TAMs only	0	1 (5%)	1 (2%)	0	0	0
3TC only	1 (5%)	2 (9%)	3 (7%)	0	1 (8%)	1 (4%)
EFV and 3TC only	6 (27%)	4 (18%)	10 (23%)	8 (46%)	3 (23%)	9 (35%)
TAMs and EFV only	0	1 (5%)	1 (2%)	0	0	0
TAMs and 3TC only	1 (5%)	0	1 (2%)	0	0	0
TAMs, EFV, and 3TC	0	0	0	1 (8%)	0	1 (4%)

Source data: EPV20001 Wk 48 CSR Listing 6

a. Treatment categories are mutally exclusive

b. TAMs are M41L, D67N, K70R, V75T, L210W, T215Y/F, K219Q/E; 3TC resistance mutations are M184V/I, E44D, V118I; EFV resistance mutations are A98G, L100I, K103N, V106A, V108I, Y181C, Y188C, G190A, K101E/V

c. Phenotypic resistance was defined for samples harbouring virus with intermediate phenotypic resistance (>2.5 and <10 fold change) or high level resistance (> 10 fold change)

Conclusions

10% of subjects enrolled in EPV20001 and who received study drug were identified as PDVF through 48 weeks of treatment.

32% of subjects (n=14) identified as PDVF developed 3TC mutations (M184V/I, E44D, V118I) while on treatment, eight in the 3TC Once Daily group and six in the 3TC BID group.

4.5.1.2. COLA4005

COLA4005 was a multicenter outpatient Phase II study which used an open-label randomized (1:1), parallel group design to evaluate the efficacy and safety of Epivir 150 mg BID versus 300 mg Once Daily when administered for 24 weeks in combination with FDA-approved dosing regimens of Zerit and either Crixivan or Viracept in subjects with HIV-1 infection (GSK Document number RM2000/00094/01).

Protocol Defined Virologic Failure (PDVF) was defined as an increase in plasma HVI-1 RNA levels to ≥1,265 c/mL on 2 separate occasions at least 2-4 weeks apart. All HIV-1 RNA samples that met criteria for PDVF were confirmed by a second measurement performed 2-4 weeks from the date of the original sample.

A secondary objective of this study was to compare the development of genotypic and phenotypic resistance in subjects taking 3TC 300 mg Once Daily versus 150 mg BID in combination with continued d4T and either Crixivan or Viracept. However, because there were no PDVF, genotype and phenotype analyses were not performed for this study.

4.6. Dolutegravir/Lamivudine Conclusions

The Week 48 primary efficacy analysis (proportion of subjects with plasma HIV-1 RNA <50 c/mL) of studies 204861 and 205543 demonstrated that DTG + 3TC provided a high level of clinical efficacy. A similar proportion of subjects in each treatment group achieved plasma HIV-1 RNA <50 c/mL at Week 48. The incidence of protocol-defined CVW through Week 48 in 204861 was low, with 4 subjects in the DTG + 3TC group and 2 subjects in the DTG + TDF/FTC group meeting CVW criteria at any time through Week 48. No subject meeting CVW criteria in either treatment group of 204861 had treatment emergent INSTI or NRTI resistance through Week 48. The incidence of protocol-defined CVW through Week 48 in 205543 was low, with 2 subjects in each treatment group meeting CVW criteria at any time through Week 48. No subject meeting CVW criteria in either treatment group in 205543 had treatment emergent INSTI or NRTI resistance through Week 48.

Nonclinical Virology

- Dolutegravir (DTG) inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle.

- DTG has low nM activity against wild type HIV-1 and HIV-2 in a variety of cells lines, regardless of subtype. Human serum (100%) causes approximately 75-fold increase in DTG IC50. DTG is additive or synergistic when assayed in combination with other antiretroviral agents.

- When HIV-1 Strain IIIB was passaged in the presence of DTG for 112 days, viruses with a 4.1-fold maximum increase in IC50 and S153Y or S153F substitutions in integrase were observed. Passage of the wild type HIV-1 NL432 in the presence of 6.4 nM DTG selected for E92Q (FC=3.1) and G193E (FC=3.2) substitutions in the IN region on Day 56. Passage of HIV-1 NL432 with Q148H, Q148K, or Q148R RAL resistant mutations resulted in selection of additional mutations and an increase in DTG FC. Passage of HIV-1 subtypes B, and A/G in TZM-bl cells selected for integrase mutation R263K.

- Susceptibilities to DTG and raltegravir (RAL) were obtained from 60 RAL resistant site directed HIV-1 mutants and 6 site directed HIV-2 mutants. DTG retained activity against a vast majority of these mutants (95% had <10 FC to DTG). Additionally, susceptibilities to DTG and RAL were determined for over 700 RAL resistant clinical isolates, with DTG retaining activity (<10 FC) against >90% of them.

- The dissociation of DTG, RAL, and EVG from wild type and mutant IN proteins complexed with DNA was investigated to obtain a better understanding of INI resistance and dissociation kinetics. DTG demonstrated slower dissociation from all IN-DNA complexes tested, including those with single, double, and up to four residues clinically relevant IN substitutions.

- Analysis of site directed mutants at IN polymorphic sites (101 and 124) as either single or double mutants, demonstrated no effect on DTG susceptibility.

- Lamivudine (3TC) is a potent and selective inhibitor of HIV-1 and HIV-2 replication in vitro and appears to show synergistic antiviral activity in vitro in combination with AZT, ABC, or other inhibitors such as the protease inhibitor Saquinavir.

- 3TC has been shown to be metabolised intracellularly to the 5'-triphosphate which has a long half-life of 10.5 to 15.5 hours. 3TC 5'-triphosphate inhibits HIV-1 RT with a K_i of 12.3 μM, and but its major action is as a chain terminator of reverse transcription.

- 3TC 5'-triphosphate is a weak inhibitor of DNA polymerase α, β and γ, hence, there is little predicted toxic effect on human cell lines.

Clinical Virology

- The incidence of protocol-defined CVW through Week 48 in 204861was low, with 4 subjects in the DTG + 3TC group and 2 subjects in the DTG + TDF/FTC group meeting CVW criteria at any time through Week 48.

- No subject meeting CVW criteria in either treatment group had treatment emergent INSTI or NRTI resistance through Week 48.
- The incidence of protocol-defined CVW through Week 48 in 205543 was low, with 2 subjects in each treatment group meeting CVW criteria at any time through Week 48.
- No subject meeting CVW criteria in either treatment group had treatment emergent INSTI or NRTI resistance through Week 48.
- DTG + ABC/3TC demonstrated long term durability in ING114467 (SINGLE) with a low rate of discontinuation due to virologic failure through 96 weeks.
- No treatment emergent primary INI or NRTI resistance mutations were observed through 144 weeks in ING114467 (SINGLE) for those subjects on DTG plus ABC/3TC FDC with PDVF. Both EFV and NRTI primary resistance mutations were observed in subjects on Atripla with PDVF.
- Overall, there was a low rate of discontinuation in ING113086 (SPRING-2) due to virologic failure in both treatment arms, with only three additional subjects with PDVF identified after Week 48. The durability of the virologic response on DTG and RAL was maintained through Week 96. No treatment emergent primary INI or NRTI resistance mutations were observed for those subjects on DTG with PDVF throughout the study.
- No treatment-emergent Primary INI or NRTI resistance mutations were observed for subjects in the DTG or DRV+RTV treatment groups of ING114915 (FLAMINGO). One subject (in the DTG group) had resistance to nelfinavir at PDVF, despite having no treatment emergent PI resistance mutations.
- DTG exhibits a higher barrier to treatment failure than RAL in the study of treatment experienced, INI naive subjects, ING111762 (SAILING).
- In a prespecified and multiplicity controlled analysis of ING111762 (SAILING), there was a statistically significant difference in favor of DTG for the proportion of subjects who failed therapy with treatment-emergent evidence of INI resistance through Week 48.
- A unique IN substitution was observed (R263K or R263R/K mixture) in 2 subjects (one receiving EFV and TDF and the other receiving DRV/r and TDF as their background regimens) enrolled in ING111762 (SAILING) with little change in susceptibility to DTG and to RAL.
- 3TC selects rapidly for M184V which causes high level resistance to 3TC, reverses the effects of AZT resistance mutations, and delays the appearance of AZT resistance mutations.

Module 2.7.3

Summary of Clinical Efficacy

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ABBREVIATIONS

3TC	Lamivudine, Epivir
ABC	Abacavir
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
c/mL	copies/milliliter
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CMH	Cochran-Mantel Haenszel
CSR	Clinical Study Report
CVW	Confirmed Virologic Withdrawal
ddc	dideoxycytidine
DTG	Dolutegravir, Tivicay
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels Questionnaire
ERDF	Efficacy related discontinuation = Failure
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FTC	Emtricitabine
FSFV	First Subject First Visit
HIV	Human immunodeficiency virus
INSTI	Integrase Strand Transfer Inhibitor
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
ITT-E	Intent-to-treat exposed
Kg	Kilogram
LOCF	Last observation carried forward
LSLV	Last Subject Last Visit
MAR	Missing at Randomization
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
NRTI	Nucleoside reverse transcriptase inhibitor
PP	Per-protocol
PK	Pharmacokinetics
RAP	Reporting and Analysis Plan
RNA	Ribonucleic acid
SDAP	Summary Data Analysis Plan
SE	Standard Error
SE	Single Entity
TDF	Tenofovir disoproxil fumarate
TRDF	Treatment Related Discontinuation = Failure
UK	United Kingdom
US	United States

ZDV	Zidovudine

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1. BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

The purpose of this summary of efficacy is to provide evidence to support the efficacy of a new 2-drug regimen combining DTG and 3TC in a FDC tablet for the treatment of HIV-1 infection in patients without known or suspected resistance to either antiretroviral component. This document will summarize the efficacy findings from 2 randomized, controlled Phase III studies (GEMINI-1, Study 204861 and GEMINI-2, Study 205543) of DTG + 3TC for the treatment of HIV-1 infection in adults who are naïve to ART treatment.

The proposed recommended oral dose for adults and adolescents above 12 years of age weighing at least 40 kg is 1 tablet administered once a day without regard to meals. The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are approved doses for adolescents ≥12 years of age weighing ≥40 kg (DTG) or for pediatric patients weighing ≥25 kg (3TC). Prior studies have shown that DTG and 3TC PK exposures in adolescents are sufficiently similar to those in adults and allows extrapolation of GEMINI efficacy data to adolescents.

1.1. Current Therapies and Unmet Clinical Needs

See Clinical Overview m2.5 for a description of current available therapies for the treatment of HIV-1 infection in adults, and a summary of unmet clinical needs in this patient population.

A summary of additional trials comparing Week 48 outcomes with 2-drug regimens in treatment naïve patients, together with a justification of DTG and 3TC as a 2-drug regimen, is discussed in m2.5 Section 6.1.2.1 and m2.5 Section 6.2.1.

1.2. Overview of the Clinical Development Program

Tivicay (dolutegravir) and Epivir (lamivudine) are approved in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents. Here we present data from 2 identical, pivotal Phase III studies (GEMINI-1, Study 204861 and GEMINI-2, Study 205543), to demonstrate the efficacy of DTG + 3TC. Data from Study 204994 provides an acceptable PK bridge between the DTG/3TC FDC and the DTG + 3TC regimen used in the GEMINI studies, and is discussed in m2.7.1.

1.2.1. Pivotal Efficacy Studies

To demonstrate the efficacy of DTG + 3TC, data from 2 identical pivotal Phase III studies (GEMINI-1, Study 204861 and GEMINI-2, Study 205543), are provided. These studies are ongoing, randomized, parallel group, double-blind, 148-week studies, designed to demonstrate non-inferior antiviral activity of DTG 50 mg plus 3TC 300 mg once daily compared to DTG plus the FDC tablet of TDF/FTC once daily.

Additional details of the study design for these 2 studies are provided in Section 1.5. A brief summary of these studies also is provided in the Appendix Table 1.

1.2.2. Supportive Single-Entity Studies for Efficacy

Previously submitted studies from DTG or 3TC SE development programs support this application and are categorized as "supportive" studies:

- **Supportive SE Studies**: these studies are not essential for the FDC Benefit Risk assessment, but are considered helpful to the reviewer and supportive on the proposed indication. Supportive studies will be briefly tabulated in the module 2.7 summaries and reports will be made available upon request for the convenience of the reviewer. A table of the "supportive" SE studies for efficacy is provided in Appendix Table 3.

All single agent data that are considered not to be relevant to this FDC application, e.g. efficacy data not related to the indication, will not be provided in this FDC submission.

1.2.3. Organization of Data Presentations

In this Summary of Clinical Efficacy, efficacy data from identical studies 204861 and 205543 are presented individually in Section 2 and in a side-by-side format with the pooled analyses for comparative purposes in Section 3 when applicable.

Efficacy data are presented under the following headings:

- "Pivotal" Efficacy Studies: Study 204861 and Study 205543
- "Supportive" SE Studies (Presentation of supportive studies for efficacy is brief and limited to Appendix Table 3. Reports for these "supportive" studies will be made available upon request [no hyperlinks to module 5 are provided].)

In this document, there are references to 3 types of presentations for tables and figures. The original electronic format, location, and a description of how these tables or figures are referenced throughout this document are summarized in Table 1.

Table 1 Description of the Types of Tables and Figures Presented in this Summary of Clinical Efficacy

Table/Figure Type	Location	How Referenced
In-text	In body of this summary document	Consecutive integers (e.g., Table 1, Table 2, Figure 1, Figure 2)
Statistical Source Tables	Individual CSR and Pooled Data	Individual Study number plus statistical source table number (e.g., Study 204861 Table 3.1). Pooled data: GEMINI ISS/ISE plus statistical source table number (e.g., GEMINI ISS/ISE Table 3.1)
Appendix	In the Appendix section of this summary document (Section 6)	Consecutive integers (e.g., Appendix Table 1, Appendix Table 2)

1.3. Patient Populations in the Pivotal Efficacy Studies Contributing to the DTG + 3TC Development Program

The intention of these studies was to enrol a population of subjects naïve to ART, with no evidence of major resistance-associated mutations.

Key inclusion criteria for the 2 efficacy studies included HIV-1 infected men or women ≥18 years of age with Screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL, and ART naïve (defined as ≤10 days of prior therapy with any ART agent following a diagnosis of HIV-1 infection). The study initially enrolled subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. As permitted by the protocol, the viral load cap was increased during the study to ≤500,000 c/mL. This was done following an independent review of accumulated data from other clinical trials investigating the DTG + 3TC dual regimen, which considered the data to be supportive of this regimen.

The main exclusion criteria were women who were pregnant or breastfeeding, subjects with evidence of pre-existing viral resistance based on the presence of any major resistance-associated mutation [Günthard, 2016] in the Screening or historical resistance test result, subjects with severe hepatic impairment, subjects who were Hepatitis B positive at Screening, subjects needing Hepatitis C therapy during the first 48 weeks of the study or interferon-based therapy at any time on study, subjects with a significant suicidality risk, or subjects with creatinine clearance of <50 mL/min/1.73m^2 via the Chronic Kidney Disease Epidemiology Collaboration method at Screening.

1.3.1. Numbers of Subjects Contributing to the DTG + 3TC Development Program

For the pivotal efficacy studies, the number of subjects included in each population were similar across treatment groups in the individual studies and in the pooled analysis (Table 2).

Table 2 Summary of Analysis Populations for Studies 204861, 205543 and Pooled Data - Randomized Population

Population	204861		205543		Pooled	
	DTG + 3TC (N=359)	DTG + TDF/FTC (N=360)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=362)	DTG + 3TC (N=719)	DTG + TDF/FTC (N=722)
Intent-to-Treat, n (%)	359 (100)	360 (100)	360 (100)	362 (100)	719 (100)	722 (100)
Intent-to-Treat Exposed, n (%)	356 (>99)	358 (>99)	360 (100)	359 (>99)	716 (>99)	717 (>99)
Per-Protocol, n (%)	345 (96)	346 (96)	349 (97)	347 (96)	694 (97)	693 (96)

Data Source: Study 204861 Table 1.7, Study 205543 Table 1.7, GEMINI ISS/ISE Table 1.7.
ITT comprises of all randomized subjects; ITT Exposed comprises of all randomized subjects who receive at least one dose of study treatment; Per-Protocol' comprises of all subjects of the ITT-E population who have no significant protocol deviation that could affect the assessment of antiviral activity.

1.4. Rationale for Dose Selection in the DTG + 3TC Clinical Development Program

The new formulation being developed is a FDC of DTG/3TC 50 mg/300 mg as a 2-drug regimen with a proposed indication for the treatment of HIV-1 infection in adult and adolescent (≥40 kg) patients without known or suspected resistance to either component who are either treatment naïve or virologically suppressed (HIV-1 RNA <50 c/mL) on a stable ARV regimen and switching their current regimen.

To date, the efficacy, PK, safety, and drug interaction potential of DTG and 3TC as single agents have been evaluated in 2 individual extensive clinical development programs of Phase I to III clinical trials. As individual agents, DTG and 3TC are both approved and marketed as Tivicay 50 mg once daily for use in adults and adolescents ≥40 kg and Epivir 300 mg once daily for use in adults and children >25 kg, respectively, the doses used in the current studies (Study 204861 and Study 205543). A summary of the overall clinical development for both products is available in the Product Information for the respective products [Tivicay Product Information, 2017; Epivir Product Information, 2018]. Based on this data, there is no need for a dose adjustment from approved doses when both products are used in combination.

The efficacy, PK, safety, and drug interaction potential of TDF and FTC as individual agents and of TDF/FTC FDC have been evaluated in extensive clinical development programmes. TDF/FTC FDC is approved and marketed as Truvada 300 mg/200 mg once daily respectively, the doses used in the current studies 204861 and 205543.

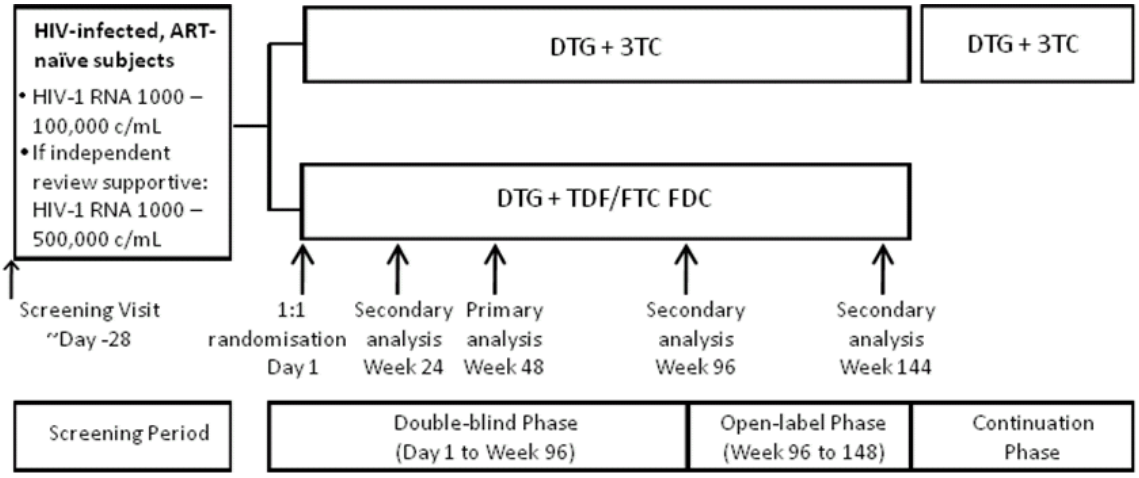
1.5. Design of Pivotal Efficacy Studies: 204861 (GEMINI-1) and 205543 (GEMINI-2)

These 2 ongoing studies are identical 148-week, Phase III, randomized, double-blind, active-controlled, multicenter, parallel-group, non-inferiority studies. They are being conducted in 719 (Study 204861) and 722 (Study 205543) (ITT Population) adult HIV-1 infected subjects who were naïve to ART. Eligible subjects were randomized 1:1 to DTG + 3TC once daily given as individual components, or DTG plus the FDC tablet of TDF/FTC once daily (Figure 1).

Over the course of the studies, at least 4 analyses will evaluate primary and secondary objectives of the protocols when all subjects have completed their visits at Week 24, Week 48, Week 96 and at Week 144. Further data cuts and analyses may be conducted as necessary after Week 144 to support regulatory submissions and publications. The Week 48 analysis is primary. The Week 24 analysis was a secondary analysis performed for regulatory purposes.

The studies include a Screening Phase (typically up to 28 days), a Double-blind Randomized Phase (Day 1 to Week 96) an Open Label Randomized Phase (Week 96 to Week 148), and a Continuation Phase. No dose reductions, modifications in dosage, or changes in the frequency of dosing were allowed at any time in the studies.

Figure 1 Study Schematic for 204861 (GEMINI-1) and 205543 (GEMINI-2)



Target enrolment N=700 randomized subjects planned/study. Subjects randomized 1:1 to receive a two-drug regimen of DTG + 3TC once daily or DTG + TDF/FTC FDC once daily. Randomization was stratified by Screening HIV-1 RNA (≤ or >100,000 c/mL) and Screening CD4+ cell count (≤ or >200 cells/mm^3).

1.6. Efficacy Endpoints in the Pivotal Efficacy Studies: 204861 (GEMINI-1) and 205543 (GEMINI-2)

The primary efficacy endpoint for the 2 pivotal studies is the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E Population.

The relevant secondary efficacy objectives and endpoints for the first 48 weeks of the study included:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24;
- Time to viral suppression (HIV-1 RNA <50 c/mL);
- Incidence of treatment-emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC in subjects meeting CVW criteria;
- Absolute values and change from Baseline in CD4+ lymphocyte count at Weeks 24 and 48;
- Incidence of disease progression (HIV-associated conditions, AIDS, and death);
- Proportion of subjects by patient subgroup(s) (e.g., by age, race, gender, Baseline CD4+ lymphocyte count) with plasma HIV-1 RNA <50 c/mL at Weeks 24 and 48 using the Snapshot algorithm for the ITT-E population;
- Change from Baseline in CD4+ lymphocyte counts at Weeks 24 and 48 by patient subgroups.

In addition to the presentation of results of the efficacy endpoints, this summary also includes a summary of Value Evidence and Outcomes results in Section 3.3.3. The endpoints for this analysis included the following:

- Change from Baseline in health-related quality of life using the EQ-5D-5L at Weeks 24 and 48 (or Withdrawal from the study).

1.7. Statistical Considerations in the Pivotal Efficacy Studies: 204861 (GEMINI-1) and 205543 (GEMINI-2)

Details of the statistical analysis methods for the individual studies are found in the individual study RAPs and a brief description is provided in this Section. Statistical methods for the pooled analysis are found in the SDAP and are also described in this Section.

1.7.1. Sample Size

Each study is designed to show that the antiviral effect of a simplified two-drug regimen of DTG + 3TC once-daily is non-inferior to a standard three-drug regimen of DTG plus TDF/FTC FDC once daily in HIV-1 infected ART-naïve adult subjects.

Non-inferiority can be concluded if the lower bound of a two-sided 95% confidence interval for the difference in response rates between the two treatment arms is greater than -10%. If r_d is the response rate on DTG plus 3TC and r_f is the response rate on DTG plus TDF/FTC FDC, then the hypotheses can be written as follows:

$$H_0: r_d - r_f \leq -10\% \qquad H_1: r_d - r_f > -10\%$$

Assuming a true response rate of 87% for the DTG + 3TC arm and an 89% response rate for the DTG plus TDF/FTC arm, the study requires 347 subjects per arm to have 90% power with a 10% non-inferiority margin and a 2.5% one-sided alpha level.

1.7.1.1. Rationale for non-inferiority margin

A non-inferiority margin -10% is a reasonable non-inferiority margin for these studies in order to demonstrate adequate preservation of treatment effect. The use of a 10% non-inferiority margin for treatment-naïve subjects is in accordance with current FDA guidance [CDER, 2015].

1.7.2. Analysis Populations

Efficacy analyses were conducted based on the ITT-E population, which consisted of all randomly assigned subjects who received at least one dose of study drug.

Sensitivity analyses of the primary efficacy endpoint, proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48, were conducted based on the ITT population (all randomized subjects) and the PP population, defined as subjects in the ITT-E population

with the exception of significant protocol violators: e.g. violations which could affect the assessment of antiviral activity, or where study drug compliance was known to be less than 90%.

1.7.3. Statistical Analysis Methods

In addition to efficacy analyses performed for the individual studies, pooled analyses were performed for the proportion of subjects with HIV-1 RNA <50 c/mL at Week 48, study outcomes and subgroups. For the primary comparison at Week 48, adjusted estimates of the difference in the rate of responders between the 2 arms were presented along with CIs based on a stratified analysis using CMH weights. All CIs were 2-sided. For the statistical analysis of non-inferiority, 4 strata (subgroups) were formed according to the combinations of levels of the following categorical variables:

- Baseline plasma HIV-1 RNA (≤ vs.>100,000 c/mL);
- Baseline CD4+ cell count (≤ vs. >200 cells/mm^3).

The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in response rates between the 2 arms as described Protocol Section 9.4.1. For the integrated analysis, Study (204861 vs. 205543) was added as an additional stratification factor.

The statistical analysis was repeated using the pooled PP and ITT populations and compared for consistency with the results from the primary ITT-E population analysis.

The following changes were made to the planned analysis specified in the SDAP:

- For Table 2.1, Table 2.2 and Table 2.3, 95% CI by treatment arm was added for the proportion of subjects with Plasma HIV-1 RNA <50 c/mL.

The following table was included in the Week 48 reporting though not specified in the SDAP:

- Treatment by Strata Tests of Homogeneity for the Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 - Snapshot Analysis.
  - A weighted least squares chi-squared statistic [Fleiss, 1981] was used to test for heterogeneity in risk difference across the following strata combination levels separately:
    - Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) and study (204861 vs. 205543.)
    - Baseline CD4+ cell count (≤ vs. >200 cells/mm^3) and study (204861 vs. 205543).
  - Following Lui and Kelly [Lui, 2000], ½ was added to each cell in any strata for which the stratum-specific differences in response proportions between the two treatment arms are zero or one, and tests will be one-sided.

- Tests of heterogeneity were assessed at the one-sided 10% level of significance.

Additional tables and figures were included in the Week 48 reporting though not specified in the SDAP. These were the same as the additional efficacy analyses specified for the individual studies.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

The data for the individual studies are included in parallel presentations of data in Section 3. Results from the pooled analysis are presented where available.

Details of the study design and key results for the individual studies also are summarized in Appendix Table 1 and Appendix Table 2, respectively. CSRs for these studies are available in m5.3.5.1.

Unless otherwise stated, efficacy analyses include data up to the Week 48 analysis cut-off date of [redacted].

2.1. Study 204861, GEMINI-1

Overall, in the ITT-E population, 90% of subjects in the DTG + 3TC group and 93% of subjects in the DTG + TDF/FTC group achieved the primary efficacy endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm). Based on a 10% non-inferiority margin, the efficacy analysis demonstrated that DTG + 3TC is non-inferior to DTG + TDF/FTC at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference [-2.6 (-6.7, 1.5)] is greater than -10%. The results for the PP and ITT Populations were supportive of those from the ITT-E (primary) population. Treatment differences across demographic (age, race, and gender) subgroups and Baseline HIV-1 RNA viral load support the primary endpoint (HIV-1 RNA <50 c/mL at Week 48). There was a lower response rate in the DTG + 3TC arm in subjects with lower Baseline CD4+ cell counts; however, the number of subjects in the ≤200 cells/mm^3 subgroup is small and as such, this result should be interpreted with caution.

The data for the 204861 study indicate that the DTG + 3TC 2-drug regimen is effective in the suppression of plasma HIV-1 RNA <50 c/mL and non-inferior to DTG + TDF/FTC at Week 48.

2.2. Study 205543, GEMINI-2

Overall, in the ITT-E population, 93% of subjects in the DTG + 3TC group and 94% of subjects in the DTG + TDF/FTC group achieved the primary efficacy endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm). Based on a 10% non-inferiority margin, the efficacy analysis demonstrated that DTG + 3TC is non-inferior to DTG + TDF/FTC at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference [-0.7 (-4.3, 2.9)] is greater than -10%. The results for the PP population and ITT Populations were supportive of those from the ITT-E (primary)

population. Treatment differences across demographic (age, race, and gender) subgroups support the primary endpoint (HIV-1 RNA <50 c/mL at Week 48). Across both the Baseline HIV-1 RNA subgroup and the Baseline CD4+ cell count subgroup, there was statistically significant evidence of heterogeneity for the difference in proportion of subjects with HIV-1 RNA <50 c/mL. This appears to be driven by a higher response rate in the DTG + 3TC group and a lower response in the DTG + TDF/FTC group in the subjects with higher Baseline plasma HIV-1 RNA (>100,000 c/mL). In the subgroup of subjects with lower Baseline CD4+ cell count, there was a lower response rate for subjects receiving DTG + 3TC. However, the number of subjects in the ≤200 cells/mm^3 subgroup is small. The reasons for subjects having Snapshot outcomes that fell into one of the "non-response" categories varied; none resulted in treatment-related discontinuation at Week 48 and as such, this result should be interpreted with caution.

The data for the 205543 study indicate that the DTG + 3TC 2-drug regimen is effective in the suppression of plasma HIV-1 RNA <50 c/mL and non-inferior to DTG + TDF/FTC at Week 48.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS PIVOTAL EFFICACY STUDIES

3.1. Study Populations in Pivotal Efficacy Studies

3.1.1. Subject Disposition

Overall and for the individual studies, the number of subjects randomized and treated was similar across treatment groups. Similar proportions of subjects in each treatment group withdrew from the study (Table 3).

Table 3 Summary of Subject Disposition for Studies 204861, 205543 and Pooled Data (ITT-E) Population

Number of subjects, n (%)	204861		205543		Pooled	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
	(N=356)	(N=358)	(N=360)	(N=359)	(N=716)	(N=717)
Randomized and treated	356	358	360	359	716	717
Ongoing	320 (90)	330 (92)	330 (92)	335 (93)	650 (91)	665 (93)
Premature Withdrawal	36 (10)	28 (8)	30 (8)	24 (7)	66 (9)	52 (7)
Primary Reason[a] for Withdrawal						
Adverse Event	6 (2)	4 (1)	8 (2)	5 (1)	14 (2)	9 (1)
Physician Decision	6 (2)	3 (<1)	2 (<1)	2 (<1)	8 (1)	5 (<1)
Lack of Efficacy	3 (<1)	1 (<1)	2 (<1)	2 (<1)	5 (<1)	3 (<1)
Lost to Follow-up	9 (3)	6 (2)	6 (2)	5 (1)	15 (2)	11 (2)
Protocol Deviation	5 (1)	4 (1)	5 (1)	2 (<1)	10 (1)	6 (<1)
Subject reached Protocol-defined stopping criteria	1 (<1)	6 (2)	0	2 (<1)	1 (<1)	8 (1)
Withdrew Consent	6 (2)	4 (1)	7 (2)	6 (2)	13 (2)	10 (1)

Data Source: Study 204861 Table 1.3, Study 205543 Table 1.3, GEMINI ISS/ISE Table 1.3.
a Subjects may have only one primary reason for withdrawal.

3.1.2. Demographic and Baseline Characteristics

3.1.2.1. Demographic Characteristics

Demographic characteristics were similar across treatment groups overall and in the individual studies (Table 4).

Table 4 Summary of Demographic Characteristics for Studies 204861, 205543 and Pooled Data (ITT-E Population)

	204861		205543		Pooled	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
	(N=356)	(N=358)	(N=360)	(N=359)	(N=716)	(N=717)
Age (y), median (range)	32.0 (1[redacted]-6[redacted])	33.0 (1[redacted]-6[redacted])	32.0 (1[redacted]-7[redacted])	33.0 (1[redacted]-7[redacted])	32.0 (1[redacted]-7[redacted])	33.0 (1[redacted]-7[redacted])
Age group (y), n (%)						
<35	211 (59)	205 (57)	209 (58)	203 (57)	420 (59)	408 (57)
35-<50	116 (33)	107 (30)	115 (32)	122 (34)	231 (32)	229 (32)
≥50	29 (8)	46 (13)	36 (10)	34 (9)	65 (9)	80 (11)
Sex, n (%)						
Female	59 (17)	52 (15)	54 (15)	46 (13)	113 (16)	98 (14)
Male	297 (83)	306 (85)	306 (85)	313 (87)	603 (84)	619 (86)
Ethnicity, n (%)						
Hispanic/Latino	120 (34)	111 (31)	95 (26)	121 (34)	215 (30)	232 (32)
Not Hispanic/Latino	236 (66)	247 (69)	265 (74)	238 (66)	501 (70)	485 (68)
Race, n (%)						
American Indian or Alaska Native	28 (8)	28 (8)	21 (6)	24 (7)	49 (7)	52 (7)
Asian						
Central/South Asian Heritage	0	4 (1)	0	3 (<1)	0	7 (<1)
Japanese/East Asian Heritage/South East Asian Heritage	37 (10)	38 (11)	34 (9)	27 (8)	71 (10)	65 (9)
Black/African American	44 (12)	36 (10)	55 (15)	40 (11)	99 (14)	76 (11)
Native Hawaiian or other Pacific Islander	2 (<1)	0	0	5 (1)	2 (<1)	5 (<1)
White						
Arabic /North African Heritage	5 (1)	6 (2)	3 (<1)	3 (<1)	8 (1)	9 (1)
White/Caucasian/European Heritage	238 (67)	242 (68)	234 (65)	246 (69)	472 (66)	488 (68)
Multiple Heritage	2 (<1)	4 (1)	13 (4)	11 (3)	15 (2)	15 (2)

Data Source: Study 204861 Table 1.11, Study 205543 Table 1.11, GEMINI ISS/ISE Table 1.11.

3.1.2.2. Baseline Characteristics

Baseline disease characteristics were similar across treatment groups overall and in the individual studies (Table 5).

Table 5 Summary of Baseline Characteristics for Studies 204861 and 205543 (ITT-E Population)

	204861		205543		Pooled	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
	(N=356)	(N=358)	(N=360)	(N=359)	(N=716)	(N=717)
Baseline HIV-1 RNA (c/mL), n (%)						
<1000	6 (2)	3 (<1)	7 (2)	6 (2)	13 (2)	9 (1)
1000 to <10,000	76 (21)	93 (26)	89 (25)	74 (21)	165 (23)	167 (23)
10,000 to <50,000	142 (40)	140 (39)	140 (39)	141 (39)	282 (39)	281 (39)
50,000 to <100,000	58 (16)	46 (13)	58 (16)	61 (17)	116 (16)	107 (15)
≥100,000 to <500,000	70 (20)	69 (19)	57(16)	69 (19)	127 (18)	138 (19)
≥500,000[a]	4 (1)	7 (2)	9 (3)	8 (2)	13 (2)	15 (2)
Baseline CD4+ (cells/mm^3)						
Median	427.0	435.5	427.5	442.0	427.0	438.0
Min., Max.	19, 1399	19, 1305	19, 1364	19, 1497	19, 1399	19, 1497
Baseline CD4+ (cells/mm^3), n (%)						
<50	5 (1)	4 (1)	3 (<1)	5 (1)	8 (1)	9 (1)
50 to <200	26 (7)	25 (7)	29 (8)	20 (6)	55 (8)	45 (6)
200 to <350	92 (26)	79 (22)	87 (24)	87 (24)	179 (25)	166 (23)
350 to <500	99 (28)	120 (34)	105 (29)	108 (30)	204 (28)	228 (32)
≥500	134 (38)	130 (36)	136 (38)	139 (39)	270 (38)	269 (38)
Hepatitis B & C Test Results, n (%)						
B only[b]	0	0	0	0	0	0
C only	26 (7)	28 (8)	13 (4)	21 (6)	39 (5)	49 (7)
B and C	0	0	0	0	0	0
Neither	329 (92)	330 (92)	347 (96)	338 (94)	676 (94)	668 (93)
Missing	1 (<1)	0	0	0	1 (<1)	0
CDC Category, n (%)						
HIV infection stage 0	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
HIV infection stage 1	128 (36)	126 (35)	129 (36)	137 (38)	257 (36)	263 (37)
HIV infection stage 2	194 (54)	204 (57)	198 (55)	189 (53)	392 (55)	393 (55)
HIV infection stage 3	33 (9)	28 (8)	33 (9)	32 (9)	66 (9)	60 (8)
HIV Subtype						
A	45 (13)	43 (12)	41 (11)	35 (10)	86 (12)	78 (11)
B	237 (67)	236 (66)	230 (64)	252 (70)	467 (65)	488 (68)
C	11 (3)	7 (2)	11 (3)	4 (1)	22 (3)	11 (2)
Others	3 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)	2 (<1)

Data Source: Study 204861 Table 1.11, Table 1.15, Table 1.16, Table 1.19, Table 1.20., Table 2.22, Study 205543 Table 1.11, Table 1.15, Table 1.16, Table 1.19, Table 1.20, Table 2.22, GEMINI ISS/ISE Table 1.11 Table 1.15, Table 1.16, Table 1.19, Table 1.20, Table 2.22.

a. Subjects were required to have a viral load <500,000 at Screening; however, viral load may have exceeded 500,000 at Baseline.

b. Subjects with Hepatitis B virus were excluded from study participation.

3.1.3. Extent of Exposure

In each study and in the pooled analysis, the overall extent of exposure to study drug was similar across the treatment groups (Data Source: Study 204861 CSR Table 3.1, Study

205543 CSR Table 3.1, GEMINI ISS/ISE Data Source Table 3.1). In the pooled analysis, the mean duration of exposure to DTG + 3TC was 412.9 days (59.0 weeks) and the mean duration of exposure to DTG + TDF/FTC was 413.8 days (59.1 weeks) (Data Source: GEMINI ISS/ISE Table 3.1).

3.2. Comparison of Efficacy Results

The primary endpoint for Studies 204861 and 205543 is the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population.

An additional sensitivity analysis was conducted post-hoc for the proportion of subjects with plasma HIV-1 RNA <40 c/mL by visit.

3.2.1. Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis)

Within each of the individual studies, the primary efficacy endpoint was achieved with the lower bound of the 95% CI for the adjusted treatment difference greater than -10% (Table 6). Based on a 10% non-inferiority margin, the analysis for each study demonstrated that DTG + 3TC is non-inferior to DTG + TDF/FTC at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference is greater than -10%. The results for the PP and ITT Populations were supportive of those from the ITT-E (primary) population (Table 7 and Data Source: Study 204861 CSR Table 2.2, Table 2.3, Study 205543 CSR Table 2.2, Table 2.3). Similar results were observed based on the pooled data (GEMINI ISS/ISE Table 2.1, Table 2.2, Table 2.3)

The proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 (Snapshot) was a study objective and secondary endpoint; results at Week 24 were consistent with results for the Week 48 primary endpoint (m5.3.5.1, Study 204861 Week 24 CSR, Study 205543 Week 24 CSR).

Table 6 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis for Studies 204861, 205543 and Pooled Data (ITT-E Population)

Treatment	Number Responded/ Total Assessed (%)	Difference in Proportion, % (95% CI)[a]	Adjusted Difference in Proportion, % (95% CI)[b]
204861			
DTG + 3TC	320/356 (90)	-2.8 (-7.0, 1.3)	-2.6 (-6.7, 1.5)
DTG + TDF/FTC	332/358 (93)		
205543			
DTG + 3TC	335/360 (93)	-0.8 (-4.4, 2.8)	-0.7 (-4.3, 2.9)
DTG + TDF/FTC	337/359 (94)		
Pooled Data			
DTG + 3TC	655/716 (91)	-1.8 (-4.6, 0.9)	-1.7 (-4.4, 1.1)
DTG + TDF/FTC	669/717 (93)		

Data Source: Study 204861 Table 2.1, Study 205543 Table 2.1, GEMINI ISS/ISE Table 2.1.

a. Difference: Proportion on DTG + 3TC – Proportion on DTG + TDF/FTC.

b. Based on CMH-stratified analysis adjusting for the following baseline stratification factors: Plasma HIV-1 RNA (≤100,000 c/mL vs. >100,000 c/mL) and CD4+ cell count (≤200 cells/mm^3 vs. >200 cells/mm^3). Pooled analysis also stratified by study.

Table 7 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis for Studies 204861, 205543 and Pooled Data (PP Population)

Treatment	Number Responded/ Total Assessed (%)	Difference in Proportion, % (95% CI)[a]	Adjusted Difference in Proportion, % (95% CI)[b]
204861			
DTG + 3TC	317/345 (92)	-2.0 (-5.9, 1.8)	-1.9 (-5.7, 1.9)
DTG + TDF/FTC	325/346 (94)		
205543			
DTG + 3TC	328/349 (94)	-0.8 (-4.2, 2.6)	-0.7 (-4.1, 2.7)
DTG + TDF/FTC	329/347 (95)		
Pooled Data			
DTG + 3TC	645/694 (93)	-1.4 (-4.0, 1.1)	-1.3 (-3.9, 1.2)
DTG + TDF/FTC	654/693 (94)		

Data Source: 204861 Table 2.2, Study 205543 Table 2.2, GEMINI ISS/ISE Table 2.2.

a. Difference: Proportion on DTG + 3TC – Proportion on DTG + TDF/FTC.

b. Based on CMH-stratified analysis adjusting for the following baseline stratification factors: Plasma HIV-1 RNA (≤100,000 c/mL vs. >100,000 c/mL) and CD4+ cell count (≤200 cells/mm^3 vs. >200 cells/mm^3). Pooled analysis also stratified by study.

3.2.2. Proportions of Subjects with Plasma HIV-1 RNA <50 c/mL By Visit

In the individual studies and the pooled analyses, the proportion of subjects with plasma HIV-1 RNA <50 c/mL by visit was high and similar in both treatment groups (Data Source: 204861 CSR Table 2.11, Study 2055543 CSR Table 2.11, GEMINI ISS/ISE Table 2.11). Most subjects in both arms achieved plasma HIV-1 RNA <50 c/mL by Week 4.

3.2.2.1. Proportion of subjects with plasma HIV-1 RNA <40 c/mL by visit

As an additional sensitivity analysis, a post-hoc analysis was carried out to evaluate a more stringent threshold for virologic success using a cut-off value of <40 c/mL (rather than <50 c/mL) for the proportion of subjects with plasma HIV-1 RNA <40 c/mL by visit (GEMINI ISS/ISE Table 2.33). The value 40 c/mL is the lower limit of quantitation detection for the Abbott RealTime HIV-1 Assay used in Study 204861 and Study 205543. In the pooled analysis at Week 48, 90% and 92% of subjects receiving DTG + 3TC and DTG + TDF/FTC, respectively, achieved virologic success at the threshold of HIV-1 RNA <40 c/mL, which represents a 1% reduction in each arm compared to the 91% and 93% of subjects in the ITT-E who achieved virologic success at the HIV-1 RNA <50 c/mL threshold.

3.2.3. Time to Viral Suppression (HIV-1 RNA <50 c/mL)

Within the individual studies and the pooled analysis, a rapid and sustained response was observed in both treatment groups (Figure 2). Kaplan-Meier estimates of the time to viral suppression (HIV-1 RNA <50 c/mL) through Week 48 indicated that subjects reached viral suppression at a similar time point in both treatment groups (median time to viral suppression = 29.0 days) (Data Source: Study 204861 CSR Table 2.17, Study 205543 CSR Table 2.17, GEMINI ISS/ISE Table 2.17).

Figure 2 Kaplan-Meier Plot of Time to Viral Suppression, Pooled Analysis (ITT-E Population)

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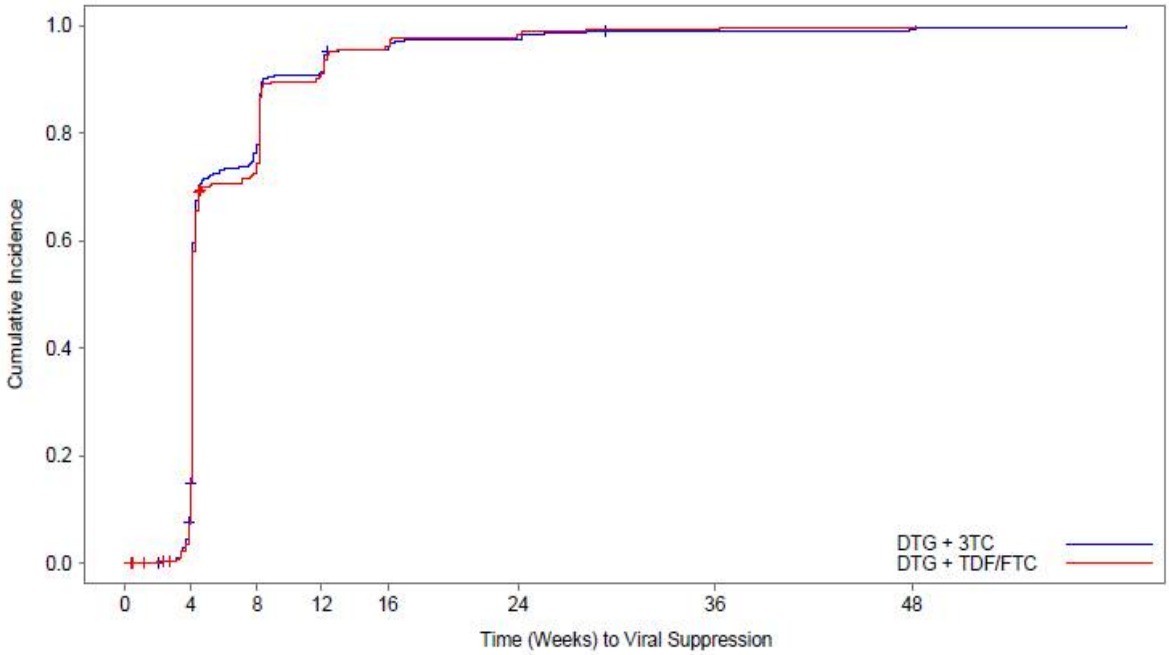
Figure 2.6
Kaplan-Meier Plot of Time to Viral Suppression



Due to the potential of informative censoring, caution required when interpreting results.

Data Source: GEMINI ISS/ISE Figure 2.6

3.2.4. Study Outcomes at Week 48: Plasma HIV-1 RNA <50 c/mL (Snapshot Analysis)

Both treatment groups had similar overall rates of success at Week 48, defined as having an HIV-1 RNA <50 c/mL (Table 8, Data Source: GEMINI ISS/ISE Table 2.4). Subjects who did not have an outcome of success, had either plasma HIV-1 RNA ≥50 c/mL, or no virologic data at Week 48. Overall, across both treatment groups in each study, there was a similar distribution across the Snapshot categories. The similarity across both treatment groups is also noted in other analysis of treatment efficacy (Table 9 and Table 10). Study outcomes for the PP and ITT populations were similar to those for the ITT-E Population (Data Source: Study 204861 CSR Table 2.5, Table 2.6, Study 205543 CSR Table 2.5, Table 2.6, GEMINI ISS/ISE Table 2.5, Table 2.6).

Table 8 Summary of Study Outcomes (Plasma HIV-1 RNA <50 c/mL) at Week 48 – Snapshot Analysis in Studies 204861, 205543 and Pooled Data (ITT-E Population)

Outcome n (%)	204861		205543		Pooled	
	DTG + 3TC (N=356)	DTG + TDF/FTC (N=358)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=359)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Plasma HIV-1 RNA <50 c/mL	320 (90)	332 (93)	335 (93)	337 (94)	655 (91)	669 (93)
Plasma HIV RNA ≥50 c/mL	13 (4)	6 (2)	7 (2)	7 (2)	20 (3)	13 (2)
Data in window and HIV-1 RNA ≥50 copies/mL	6 (2)	3 (<1)	2 (<1)	2 (<1)	8 (1)	5 (<1)
Discontinued for lack of efficacy	3 (<1)	1 (<1)	2 (<1)	1 (<1)	5 (<1)	2 (<1)
Discontinued for other reason and HIV-1 RNA ≥50 c/mL	3 (<1)	2 (<1)	2 (<1)	3 (<1)	5 (<1)	5 (<1)
Change in ART	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)	1 (<1)
No Virologic Data	23 (6)	20 (6)	18 (5)	15 (4)	41 (6)	35 (5)
Discontinued study due to AE or Death	5 (1)	9 (3)	5 (1)	4 (1)	10 (1)	13 (2)
Discontinued study for Other Reasons	17 (5)	11 (3)	12 (3)	11 (3)	29 (4)	22 (3)
On study but missing data in window	1 (<1)	0	1 (<1)	0	2 (<1)	0

Data Source: Study 204861 Table 2.4, Study 205543 Table 2.4, GEMINI ISS/ISE Table 2.4.

3.2.5. Treatment/Efficacy-Related Discontinuations

In the individual studies and the pooled analysis, the proportions of subjects without TRDF or ERDF by Week 48 were high and similar between treatment groups, supporting the Week 48 plasma HIV-1 RNA <50 c/mL results (Table 9, Table 10).

Table 9 Kaplan-Meier Estimates of Proportion of Subjects Not Meeting CVW Criteria or Discontinuing for Reasons Related to Treatment – *TREATMENT Related Discontinuation = Failure* (ITT-E Population) at Week 48

	204861		205543		Pooled	
	DTG + 3TC (N=356)	DTG + TDF/FTC (N=358)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=359)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Number of Subjects, n (%)						
Protocol Defined CVW or discontinuation due to treatment related reasons at or Prior to Week 48[a]	7 (2)	9 (3)	5 (1)	6(2)	12 (2)	15 (2)
Censored[b]	349 (98)	349 (97)	355 (99)	353 (98)	704 (98)	702 (98)
Proportion of Subjects Without Protocol Defined CVW or not discontinued due to treatment related reasons at or prior to Week 48						
Estimate (%)	98.0	97.4	98.6	98.3	98.3	97.9
95% CI (%)	(95.8, 99.0)	(95.1, 98.6)	(96.6, 99.4)	(96.2, 99.2)	(97.0, 99.0)	(96.5, 98.7)
Difference in Proportions[c]						
Estimated Difference (%)	0.6		0.3		0.4	
95% CI[d] (%)	(-1.7, 2.8)		(-1.6, 2.1)		(-1.0, 1.9)	

Data Source: Study 204861 Table 2.8, Study 205543 Table 2.8, GEMINI ISS/ISE Table 2.8.

a. Treatment related reasons are withdrawal due to drug-related AE, safety stopping criteria, or lack of efficacy.
b. Subjects who have not met CVW criteria and are ongoing in the study, or who have discontinued for non-treatment related reasons are censored.
c. Difference: Proportion on DTG + 3TC – Proportion on DTG + TDF/FTC.
d. Based on Greenwood's formula [Kalbfleisch, 1980].

Table 10 Kaplan-Meier Estimates of Proportion of Subjects Not Meeting CVW Criteria or Discontinuing for Reasons Related to Treatment – *EFFICACY Related Discontinuation = Failure* (ITT-E Population) at Week 48

	204861		205543		Pooled	
	DTG + 3TC (N=356)	DTG + TDF/FTC (N=358)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=359)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Number of Subjects, n (%)						
Protocol Defined CVW or discontinuation due to efficacy related reasons at or Prior to Week 48	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)
Censored[a]	352 (99)	356 (>99)	358 (>99)	357 (>99)	710 (>99)	713 (>99)
Proportion of Subjects Without Protocol Defined CVW or not discontinued due to efficacy related reasons at or prior to Week 48						
Estimate (%)	98.8	99.4	99.4	99.4	99.1	99.4
95% CI (%)	(96.9, 99.6)	(97.7, 99.9)	(97.7, 99.9)	(97.7, 99.9)	(98.1, 99.6)	(98.5, 99.8)
Difference in Proportions[b]						
Estimated Difference (%)	-0.6		0.0		-0.3	
95% CI[c] (%)	(-2.0, 0.8)		(-1.1, 1.1)		(-1.2, 0.6)	

Data Source: Study 204861 Table 2.9, Study 205543 Table 2.9, GEMINI ISS/ISE Table 2.9

a. Subjects who have not met the protocol defined CVW criteria and are ongoing in the study, or who have discontinued for non-treatment related reasons are censored.
b. Difference: Proportion on DTG + 3TC – Proportion on DTG + TDF/FTC.
c. Based on Greenwood's formula [Kalbfleisch, 1980].

3.2.6. Subjects Who Met CVW Criteria Through Week 48

Few subjects met protocol-defined CVW criteria in either treatment group through Week 48 (Table 11). CVW non-response criteria included a decrease in plasma HIV-1 RNA of <1 log10 c/mL by Week 12, with subsequent confirmation, unless plasma HIV-1 RNA was <200 c/mL, or confirmed plasma HIV-1 RNA ≥200 c/mL on or after Week 24. CVW rebound criteria |included confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL. Meeting CVW criteria mandated withdrawal from the trial.

The incidence of treatment-emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC in subjects meeting CVW criteria was a secondary endpoint in each study. No subject meeting CVW criteria in either group had treatment emergent INSTI or NRTI resistance through Week 48 (see m2.7.2.4 and Data Source: GEMINI ISS/ISE Table 4.5, Table 4.6).

Table 11 Cumulative Summary of Confirmed Virologic Withdrawals by Visit in Studies 204861, 205543 and Pooled Data (ITT-E Population)

Time Point	204861		205543		Pooled	
	DTG + 3TC (N=356) n (%)	DTG + TDF/FTC (N=358) n (%)	DTG + 3TC (N=360) n (%)	DTG + TDF/FTC (N=359) n (%)	DTG + 3TC (N=716) n (%)	DTG + TDF/FTC (N=717) n (%)
Week 16	1 (<1)	0	0	0	1 (<1)	0
Virologic non-response	0	0	0	0	0	0
Rebound	1 (<1)	0	0	0	1 (<1)	0
Week 24	3 (<1)	1 (<1)	2 (<1)	2 (<1)	5 (<1)	3 (<1)
Virologic non-response	0	0	0	0	0	0
Rebound	3 (<1)	1 (<1)	2 (<1)	2 (<1)	5 (<1)	3 (<1)
Week 36	3 (<1)	1 (<1)	2 (<1)	2 (<1)	5 (<1)	3 (<1)
Virologic non-response	0	0	0	0	0	0
Rebound	3 (<1)	1 (<1)	2 (<1)	2 (<1)	5 (<1)	3 (<1)
Week 48	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)
Virologic non-response	0	0	0	0	0	0
Rebound	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)

Data Source: Study 204861 CSR Table 2.18, Study 205543 CSR Table 2.18, GEMINI ISS/ISE Table 2.18

3.2.7. Change from Baseline in CD4+ Lymphocyte Count

CD4+ cell counts increased at each visit in both treatment groups (Data Source: Study 204861 CSR Table 2.22, Study 205543 Table 2.22, GEMINI ISS/ISE Table 2.22, Figure 3). At Week 48, no significant difference between treatment groups in the change in CD4+ cell counts from Baseline in either study or the pooled analysis was observed using the MAR. Results from the MMRM analysis were consistent with those using the MAR (Table 12). In the pooled analysis at Week 8, Week 12, Week 16 and Week 24, statistically significant differences were seen in the change from Baseline in CD4+ cell count, with higher increases in the DTG + 3TC group compared to the DTG + TDF/FTC group (Data Source: GEMINI ISS/ISE Table 2.21).

Table 12 Statistical Analysis of Change from Baseline in CD4+ Cell Count (cells/mm^3) - Multiple Imputed Dataset (Missing at Random) and Mixed Model Repeated Measures Analysis for Studies 204861, 205543 and Pooled Data (ITT-E Population)

Treatment	N	n	Adjusted Mean (SE)	Difference[a]	95% CI for Difference	P-value
204861						
Multiple Imputation (MI) method using a Missing at Random (MAR)[b] approach at Week 48						
DTG + 3TC	356	356	222.2 (10.31)	4.5	(-24.0, 33.0)	0.756
DTG + TDF/FTC	358	358	217.7 (10.22)			
205543						
Multiple Imputation (MI) method using a Missing at Random (MAR)[b] approach at Week 48						
DTG + 3TC	360	360	225.9 (9.42)	8.9	(-17.3, 35.2)	0.504
DTG + TDF/FTC	359	359	216.9 (9.48)			
Pooled Data						
Multiple Imputation (MI) method using a Missing at Random (MAR)[b] approach at Week 48						
DTG + 3TC	716	716	224.0 (6.96)	6.8	(-12.5, 26.1)	0.490
DTG + TDF/FTC	717	717	217.2 (6.96)			

Data Source: Study 204861 Table 2.20, Study 205543 Table 2.20, GEMINI ISS/ISE Table 2.20.

a. Differences: DTG + 3TC - DTG + TDF/FTC.

b. MAR: Adjusted mean is the estimated mean change from baseline at Week 48 in each arm calculated from ANCOVA model adjusting for the following covariates/factors: treatment, baseline plasma HIV-1 RNA (factor) and baseline CD4+ cell count. Pooled analysis also included study as a factor.

Figure 3 Line Plot of Adjusted Mean (95% CI) Change from Baseline in CD4+ Cell Count (cells/mm^3) Over Time - Repeated Measure Mixed Model – Pooled Analysis (ITT-E Population)

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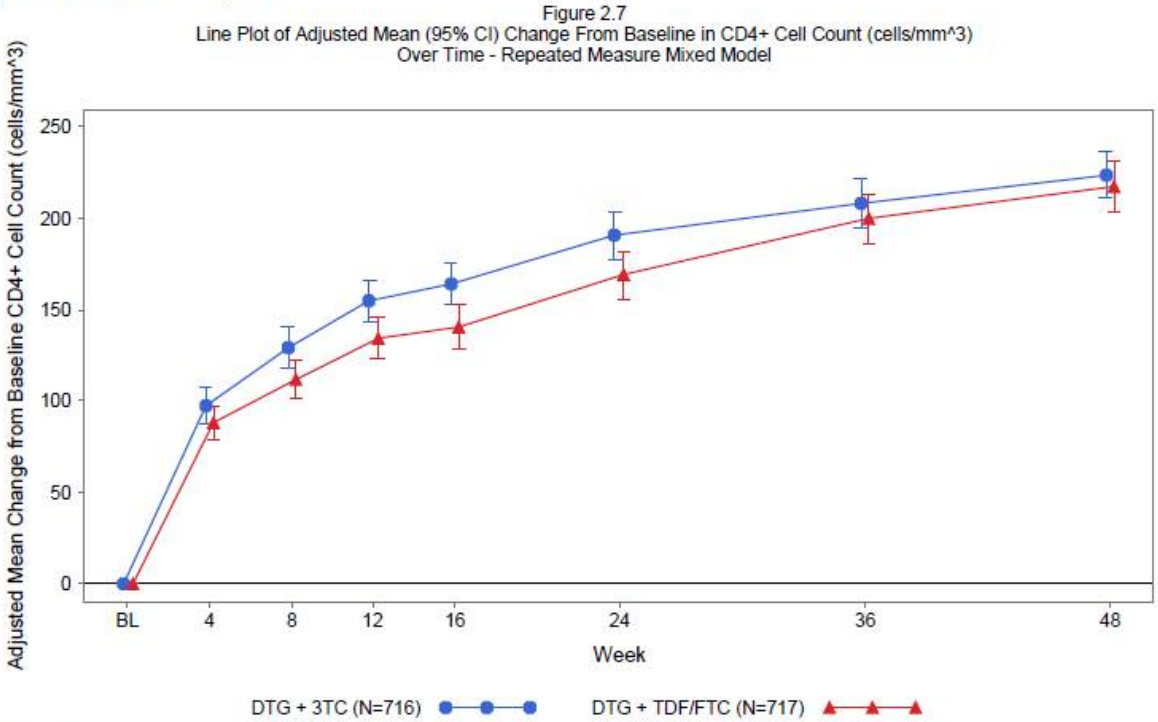
Population: Intent-to-Treat Exposed



BL= Baseline.

Data Source: GEMINI ISS/ISE Figure 2.7

3.2.8. HIV-1 Disease Progression and HIV Associated Conditions

In each study and in the pooled analysis, few subjects (≤1%) in the DTG + 3TC and DTG + TDF/FTC groups experienced HIV-1 disease progression to CDC Stage 3 clinical conditions/death through Week 48 (Table 13).

Few subjects had new Stage 3 HIV-1 associated conditions post exposure, and the proportions of subjects with these conditions were similar across the 2 treatment groups (Table 14).

Table 13 Summary of Post-Baseline HIV-1 Disease Progression – Week 48 Analysis for Studies 204861, 205543 and Pooled Data (ITT-E Population)

	204861		205543		Pooled	
	DTG + 3TC (N=356) n (%)	DTG + TDF/FTC (N=358) n (%)	DTG + 3TC (N=360) n (%)	DTG + TDF/FTC (N=359) n (%)	DTG + 3TC (N=716) n (%)	DTG + TDF/FTC (N=717) n (%)
Did subject experience disease progression to CDC Stage III or death?						
Yes	4 (1)	2 (<1)	4 (1)	1 (<1)	8 (1)	3 (<1)
No	352 (99)	356 (>99)	356 (99)	358 (>99)	708 (99)	714 (>99)
Progression						
n	4	2	4	1	8	3
from CDC Stage 1 to CDC Stage 3	0	0	0	0	0	0
from CDC Stage 2 to CDC Stage 3	2 (<1)	2 (<1)	1 (<1)	1 (<1)	3 (<1)	3 (<1)
from CDC Stage 3 to new CDC Stage 3	2 (<1)	0	1 (<1)	0	3 (<1)	0
from CDC Stage 1, 2, or 3 to Death[a]	0	0	2 (<1)	0	2 (<1)	0

Data Source: Study 204861 Table 2.27, Study 205543 Table 2.27, GEMINI ISS/ISE Table 2.27

a. Two subjects died; one event due to acute myocardial infarction; one event due to Burkitt's lymphoma. Both deaths were considered unrelated to study drug by the investigator.

Table 14 Summary of Post-Baseline HIV-1 Associated Conditions – Week 48 Analysis for Studies 204861, 205543 and Pooled Data (ITT-E Population)

	204861		205543		Pooled	
	DTG + 3TC (N=356) n (%)	DTG + TDF/FTC (N=358) n (%)	DTG + 3TC (N=360) n (%)	DTG + TDF/FTC (N=359) n (%)	DTG + 3TC (N=716) n (%)	DTG + TDF/FTC (N=717) n (%)
Including Recurrences[a, b]						
Stage 3						
Any Condition	4 (1)	2 (<1)	2 (<1)	1 (<1)	6 (<1)	3 (<1)
Cerebral chagoma	1 (<1)	0	0	0	1 (<1)	0
Herpes simplex: Chronic ulcers (>1 month's duration) or Bronchitis, Pneumonitis, or Esophagitis (onset at age >1 month)	1 (<1)	0	0	0	1 (<1)	0
Kaposi's sarcoma	1 (<1)	0	0	0	1 (<1)	0
Lymphoma, Burkitt (or equivalent term)	0	1 (<1)	0	0	0	1 (<1)
Lymphoma, immunoblastic (or equivalent term)	0	0	0	1 (<1)	0	1 (<1)
Mycobacterium tuberculosis of any site, Pulmonary, disseminated, or extrapulmonary	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)
Bacterial pneumonia	0	0	1 (<1)	0	1 (<1)	0

Data Source: Study 204861 Table 2.25, Table 2.26, Study 205543 Table 2.25, Table 2.26, GEMINI ISS/ISE Table 2.25, Table 2.26.

a. Subjects may have more than one HIV associated condition. Each condition is counted only once per subject, regardless of recurrence.
b. There were no recurrences.

3.3. Comparison of Results in Sub-Populations

The results of subgroup analyses generally were supportive of the primary efficacy endpoint of plasma HIV-1 RNA <50 c/mL at Week 48.

3.3.1. Plasma HIV-1 RNA <50 c/mL by Baseline Subgroups HIV-1 RNA and CD4+ Cell Count

Baseline HIV-1 RNA Subgroups

In Study 204861, there was no evidence of heterogeneity in the treatment differences in the proportions with plasma HIV-1 RNA <50 c/mL at Week 48 across the Baseline HIV-1 RNA subgroups (≤or >100,000 c/mL) (Table 15).

In Study 205543, there was statistically significant evidence of heterogeneity for the difference in proportion of subjects with HIV-1 RNA <50 c/mL at the 10% level of significance (p=0.03), indicating a difference in response rates between treatments across Baseline plasma HIV-1 RNA categories (Table 15). This appears to be driven by the higher response rate in the DTG + 3TC group, and lower response rate in the DTG + TDF/FTC group in the subgroup of subjects with Baseline plasma HIV-1

RNA >100,000 c/mL. In the pooled analysis, no statistically significant evidence of heterogeneity between the combinations of Baseline HIV-1 RNA subgroups (≤ or >100,000 c/mL) and Studies was observed for the primary endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 (Data Source: GEMINI ISS/ISE Table 2.7).

While the Screening HIV-1 RNA viral load for subjects participating in Study 204861 and Study 205543 was capped at ≤500,000 c/mL, 28 subjects had a Baseline HIV-1 RNA >500,000 c/mL (DTG + 3TC, 13 subjects; DTG + TDF/FTC, 15 subjects). Eleven of the 13 subjects (85%) in the DTG + 3TC group, and 12/15 (80%) of subjects in the DTG + TDF/FTC group had plasma HIV-1 RNA <50 c/mL at Week 48 (Data Source: Study 204861 CSR Listing 1, Listing 5, Listing 12, Listing 13; Study 205543 CSR Listing 1, Listing 5, Listing 12, Listing 13).

Baseline CD4+ cell count Subgroups

In each study, in the Baseline CD4+ cell count ≤200 cells/mm^3 subgroup, there was a lower response rate in the DTG + 3TC group compared to the DTG + TDF/FTC group. However, in Study 204861, the test for heterogeneity for an effect of Baseline CD4+ cell count (≤200 or >200 cells/mm^3) on the treatment difference in the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 was not significant (Table 15). In Study 205543, statistically significant evidence of heterogeneity for the difference in proportion of subjects with HIV-1 RNA <50 c/mL was observed (p=0.03), indicating a difference in response rates between treatments across Baseline CD4+ cell count categories (Table 15) that appears to be driven by the lower response rate in the DTG + 3TC arm in the subjects with lower Baseline CD4+ cell counts.

In the pooled analysis, there was statistically significant evidence of heterogeneity at the 10% level (p=0.10) across Baseline CD4+ cell count levels and Study on the treatment difference in proportion of subjects with HIV-1 RNA <50 c/mL, indicating that the difference in response rates between treatments was not consistent across Baseline CD4+ cell count categories (≤ or >200 cells/mm^3) and Study (Data Source: GEMINI ISS/ISE Table 2.7). However, the number of subjects in the pooled group is small (n=118, 8% of total ITT-E subjects). The reasons for subjects having Snapshot outcomes that fell into one of the "non-response" categories varied; except for 1 subject that met protocol-defined CVW in Study 204861, none resulted in treatment-related discontinuation at Week 48 (Data Source GEMINI ISS/ISE Table 2.14). As such, the lower response rate in the DTG + 3TC arm in the subjects with lower Baseline CD4+ cell counts should be interpreted with caution.

Table 15 Tests of Heterogeneity for the Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 by Baseline Randomization Strata, Snapshot Analysis for Studies 204861 and 205543, and Pooled Data (ITT-E Population)

	DTG + 3TC n/N (%)	DTG + TDF/FTC n/N (%)	Difference in Proportion % (95% CI)
Study 204861[a]			
HIV-1 RNA ≤100,000 c/mL	255/282 (90)	263/282 (93)	-2.8 (-7.3, 1.7)
HIV-1 RNA >100,000 c/mL	65/74 (88)	69/76 (91)	-3.0 (-12.8, 6.9)
Test of Heterogeneity[b]			**p = 0.98**
CD4+ cell count ≤200 cells/mm^3	25/31 (81)	26/29 (90)	-9.0 (-26.8, 8.8)
CD4+ cell count >200 cells/mm^3	295/325 (91)	306/329 (93)	-2.2 (-6.4, 1.9)
Test of Heterogeneity[b]			**p = 0.47**
Study 205543[a]			
HIV-1 RNA ≤100,000 c/mL	271/294 (92)	268/282 (95)	-2.9 (-6.8, 1.1)
HIV-1 RNA >100,000 c/mL	64/66 (97)	69/77 (90)	7.4 (-0.6, 15.3)
Test of Heterogeneity[b]			**p = 0.03**
CD4+ cell count ≤200 cells/mm^3	25/32 (78)	25/26 (96)	-18.0 (-34.1, -1.9)
CD4+ cell count >200 cells/mm^3	310/328 (95)	312/333 (94)	0.8 (-2.8, 4.4)
Test of Heterogeneity[b]			**p = 0.03**
Pooled Analysis (Study 204861 and Study 205543)[c]			
Baseline HIV-1 RNA			
HIV-1 RNA ≤100,000 c/mL	526/576 (91)	531/564 (94)	-2.8 (-5.9, 0.2)
HIV-1 RNA >100,000 c/mL	129/140 (92)	138/153 (90)	2.1 (-4.4, 8.5)
Test of Heterogeneity[b]			**p = 0.14**
Baseline CD4+ cell count			
CD4+ cell count ≤200 cells/mm^3	50/63 (79)	51/ 55 (93)	-13.4 (-25.5, -1.3)
CD4+ cell count >200 cells/mm^3	605/653 (93)	618/662 (93)	-0.7 (-3.5, 2.1)
Test of Heterogeneity[b]			**p = 0.10**

Data Source: Study 204861 Table 2.7, Study 205543 Table 2.7, GEMINI ISS/ISE Table 2.7.

a. Proportion on DTG + 3TC - Proportion on DTG + TDF/FTC.

b. One-sided p-value from weighted least squares chi-squared statistic. A p-value ≤0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata and study.

c. Difference: Proportion on DTG + 3TC - Proportion on DTG + TDF/FTC; data combined across studies using a Cochran-Mantel Haenszel stratified analysis.

Treatment differences in study outcomes across the categories of plasma HIV-1 RNA (≤ or >100,000 c/mL) and Baseline CD4+ cell counts (≤ or >200 cells/mm^3) generally were supportive of the primary efficacy endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 (Data Source: Study 204861 Table 2.14, Study 205543 Table 2.14, GEMINI ISS/ISE Table 2.14).

3.3.2. Plasma HIV-1 RNA <50 c/mL by Demographic and Other Subgroups

Some subgroups represent a small part of the overall population; thus, conclusions need to be made with caution. Subgroup analyses were conducted to evaluate consistency of the primary findings across subgroups.

The proportions of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 across demographic subgroups were supportive of the primary endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population (Table 16).

Table 16 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 by Demographic Subgroups, Pooled Data - Snapshot Analysis (ITT-E Population)

Analysis Strata		Treatment	Number Responded/ Total Assessed n/N (%)	Difference in Proportion[a] % (95% CI)
Pooled				
Age (years)	<35	DTG +3TC	386/420 (92)	-1.5 (-5.0, 2.1)
		DTG + TDF/FTC	381/408 (93)	
	35-<50	DTG +3TC	211/231 (91)	-3.0 (-7.7, 1.7)
		DTG + TDF/FTC	216/229 (94)	
	≥50	DTG +3TC	58/65 (89)	-0.8 (-10.8, 9.2)
		DTG + TDF/FTC	72/80 (90)	
Sex	Female	DTG +3TC	100/113 (88)	-2.3 (-10.5, 5.9)
		DTG + TDF/FTC	89/98 (91)	
	Male	DTG +3TC	555/603 (92)	-1.7 (-4.5, 1.2)
		DTG + TDF/FTC	580/619 (94)	
Race	White	DTG +3TC	447/480 (93)	-1.6 (-4.6, 1.3)
		DTG + TDF/FTC	471/497 (95)	
	African American/African Heritage	DTG +3TC	83/99 (84)	-0.4 (-11.3, 10.6)
		DTG + TDF/FTC	64/76 (84)	
	Asian	DTG +3TC	67/71 (94)	-0.1 (-7.6, 7.5)
		DTG + TDF/FTC	68/72 (94)	
	Other	DTG +3TC	58/66 (88)	-3.8 (-13.9, 6.3)
		DTG + TDF/FTC	66/72 (92)	

Data Source: GEMINI ISS/ISE Table 2.12.

a. Proportion of DTG + 3TC – Proportion of DTG + TDF/FTC (unadjusted)

Additional Baseline subgroup analyses of plasma HIV-1 RNA <50 c/mL at Week 48, such as Baseline CDC HIV classification, HCV serostatus, HIV subtype, and country, were supportive of the primary efficacy endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 (Data Source: Study 204861 CSR Table 2.12, Study 205543 CSR Table 2.12, GEMINI ISS/ISE Table 2.12). Within the individual studies and in the pooled analysis, there were some differences between treatment groups for some of the Baseline subgroup analyses; however, the number of subjects in the subgroups was small and likely to represent chance findings.

Treatment differences in study outcomes across the categories of age, sex, and race were supportive of the primary efficacy endpoint of plasma HIV-1 RNA <50 c/mL at Week 48

(Data Source: Study 204861 Table 2.14, Study 205543 Table 2.14, GEMINI ISS/ISE Table 2.14). In addition, treatment differences in study outcomes across the categories of Baseline HIV-1 RNA, HIV subtype, and country were supportive of the primary endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 (Data Source: Study 204861 Table 2.14, Study 205543 Table 2.14, GEMINI ISS/ISE Table 2.14, Table 2.32).

3.3.3. Change from Baseline in CD4+ Cell Counts by Subgroups

3.3.3.1. Baseline HIV-1 RNA and CD4+ Cell Count Subgroups

Post-baseline changes in CD4+ cell counts were similar between the treatment arms across categories of Baseline plasma HIV-1 RNA and CD4+ cell count (Table 17, Data Source: Study 204861 Table 2.23, Study 205543 Table 2.23, GEMINI Table 2.23).

Table 17 Statistical Analysis of Change from Baseline in CD4+ Cell Count (cells/mm^3) at Week 48 by Subgroup - Observed Case in Studies 204861, 205543 and Pooled Data (ITT-E Population)

Analysis Strata		Treatment	N	n	Adjusted Mean[a] (SE)	Difference[b] % (95% CI)
204861						
Baseline plasma HIV-1 RNA (c/mL)	≤100,000	DTG + 3TC	282	257	220.0 (11.72)	7.6 (-24.6, 39.8)
		DTG + TDF/FTC	282	264	212.4 (11.56)	
	>100,000	DTG + 3TC	74	67	238.5 (23.09)	3.0 (-59.8, 65.9)
		DTG + TDF/FTC	76	70	235.5 (22.70)	
Baseline CD4+ Cell Count (cells/mm^3)	≤200	DTG + 3TC	31	26	200.5 (36.97)	22.6 (-78.3, 123.5)
		DTG + TDF/FTC	29	27	177.9 (36.18)	
	>200	DTG + 3TC	325	298	225.9 (10.84)	5.2 (-24.7, 35.1)
		DTG + TDF/FTC	329	307	220.7 (10.68)	
205543						
Baseline plasma HIV-1 RNA (c/mL)	≤100,000	DTG + 3TC	294	273	215.6 (10.67)	6.9 (-22.7, 36.6)
		DTG + TDF/FTC	282	271	208.7 (10.71)	
	>100,000	DTG + 3TC	66	64	261.8 (22.27)	13.2 (-46.8, 73.2)
		DTG + TDF/FTC	77	69	248.7 (21.30)	
Baseline CD4+ Cell Count (cells/mm^3)	≤200	DTG + 3TC	32	28	210.9 (33.42)	57.7 (-37.2, 152.5)
		DTG + TDF/FTC	26	25	153.2 (35.29)	
	>200	DTG + 3TC	328	309	225.8 (10.00)	4.1 (-23.5, 31.7)
		DTG + TDF/FTC	333	315	221.7 (9.89)	
Pooled Data						
Baseline plasma HIV-1 RNA (c/mL)	≤100,000	DTG + 3TC	576	530	217.7 (7.90)	7.2 (-14.6, 29.0)
		DTG + TDF/FTC	564	535	210.5 (7.86)	
	>100,000	DTG + 3TC	140	131	249.9 (16.02)	7.4 (-35.9, 50.8)
		DTG + TDF/FTC	153	139	242.5 (15.53)	
Baseline CD4+ Cell Count (cells/mm^3)	≤200	DTG + 3TC	63	54	205.9 (24.83)	39.9 (-29.1, 108.9)
		DTG + TDF/FTC	55	52	166.0 (25.24)	
	>200	DTG + 3TC	653	607	225.8 (7.36)	4.6 (-15.7, 24.9)
		DTG + TDF/FTC	662	622	221.2 (7.26)	

Source Data: 204861 Table 2.24, Study 205543 Table 2.24, GEMININ ISS/ISE Table 2.24

a. For each subgroup, adjusted mean is the estimated mean change from Baseline at Week 48 in each arm calculated from ANCOVA model adjusting for the following covariates/factors: treatment, Baseline plasma HIV-1 RNA (factor), Baseline CD4+ cell count, subgroup, and treatment and relevant subgroup interaction. Pooled analysis also included study as a factor. For CD4+ cell count subgroup, Baseline CD4+ cell count group is included as a factor only.

b. Difference: DTG+3TC - DTG+TDF/FTC.

3.3.3.2. Demographic and Other Baseline Subgroups

Post-baseline changes in CD4+ cell counts generally were similar between treatment groups across age, race, and gender subgroups, as well as CDC category, HIV subtype, and HCV serostatus (Data Source: GEMINI ISS/ISE Table 2.23, Table 2.24).

3.4. Value Evidence and Outcomes

Mean Baseline EQ-5D-5L Utility and Thermometer scores were high and comparable in both arms (Data Source: Study 204861 Table 5.2, Table 5.3; Study 205543 Table 5.2,

Table 5.3; GEMINI ISS/ISE Table 5.2, Table 5.3). Overall, similar improvements were observed in the 2◦treatment groups in EQ-5D-5L Utility scores and Thermometer scores at Weeks◦4, 24, and 48 (Data Source: GEMINI ISS/ISE Table 5.4, Table 5.5) (Table 18).

Table 18 Statistical Analysis of Change from Baseline in EQ-5D Utility and Thermometer Scores (MMRM-LOCF Dataset) for Studies 204861, 205543 and Pooled Data (ITT-E Population)

	Treatment	N	n	Adjusted Mean[a] (SE)	Difference vs DTG + TDF/FTC[b]	95% CI for Treatment Difference	P-Value
204861							
Utility Score							
Week 48	DTG + 3TC	356	352	0.0134 (0.00384)	0.0004	(-0.0098, 0.0106)	0.934
	DTG + TDF/FTC	358	351	0.0129 (0.00349)			
Thermometer Score							
Week 48	DTG + 3TC	356	352	4.3 (0.49)	1.5	(0.1, 2.8)	0.031
	DTG + TDF/FTC	358	350	2.8 (0.49)			
205543							
Utility Score							
Week 48	DTG + 3TC	360	360	0.0189 (0.00362)	-0.0019	(-0.0117, 0.0079)	0.703
	DTG + TDF/FTC	359	358	0.0208 (0.00342)			
Thermometer Score							
Week 48	DTG + 3TC	360	359	4.0 (0.43)	-0.6	(-1.9, 0.6)	0.328
	DTG + TDF/FTC	359	358	4.6 (0.48)			
Pooled Data							
Utility Score							
Week 48	DTG + 3TC	716	712	0.0161 (0.00264)	-0.0008	(-0.0078, 0.0063)	0.834
	DTG + TDF/FTC	717	709	0.0169 (0.00244)			
Thermometer Score							
Week 48	DTG + 3TC	716	711	4.1 (0.32)	0.4	(-0.6, 1.3)	0.432
	DTG + TDF/FTC	717	708	3.7 (0.34)			

Data Source: Study 204861 Table 5.4, Table 5.5, Study 205543 Table 5.4, Table 5.5, GEMINI ISS/ISE Table 5.4, Table 5.5

a. The Mixed Model Repeated Measures (MMRM) is run on the LOCF dataset, using the observed margins (OM) option, adjusted for treatment, baseline plasma HIV-1 RNA (<=100,000 vs. >100,000 c/mL), baseline CD4+ cell count (<=200 vs. >200 cells/mm3), and baseline EQ-5D utility, treatment visit and baseline EQ-5D utility visit as factors and covariate, with visit as the repeated factor. Pooled analysis also included study as a factor.

b. Difference: DTG+3TC - DTG+TDF/FTC (adjusted).

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

The dosing of DTG 50 mg and 3TC 300 mg given once daily is based on the approved doses of the individual components DTG (Tivicay) and 3TC (Epivir) and on the absence of a drug-drug interaction between these components. The efficacy of the currently approved DTG 50 mg and 3TC 300 mg once daily dosing was demonstrated in the studies included in this submission, and this dosing is indicated in current product labelling [Tivicay Prescribing Information, 2017, Epivir Prescribing Information, 2018].

Thus, a presentation of data supporting the approved DTG 50 mg or 3TC 300 mg components is not provided here.

The BE and food effect study 204994 (m2.7.1) together with the 3TC safety data from historical dose-ranging and registrational studies that evaluated higher 3TC doses/exposures (m2.7.2 and m2.7.4) provide an acceptable PK bridge between the DTG/3TC FDC and the DTG + 3TC single entities used in GEMINI-1 and GEMINI-2 studies.

The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are approved doses for adolescents ≥12 years of age weighing ≥40 kg (DTG) or for pediatric patients weighing ≥25 kg (3TC). Prior studies have shown that DTG and 3TC PK exposures in adolescents are sufficiently similar to those in adults; these PK correlations permits the extrapolation of efficacy data in adults to adolescents.

5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

The current submission includes 48-week efficacy data for subjects receiving DTG + 3TC in 2 ongoing Phase III clinical studies. These studies will continue for 148 weeks and thus longer-term data on this 2-drug regimen will become available. At this time, longer term data are available only for each of the components from single entity studies.

HIV antiretroviral drugs are not associated with pharmacological tolerance; however, as HIV-1 is highly mutable, it can develop mutations that confer decreased susceptibility of the virus to one or more ARTs. The resistance profiles for DTG and 3TC are documented in the current product labelling [Tivicay Prescribing Information, 2017, Epivir Prescribing Information, 2018].

EFFICACY CONCLUSIONS

The primary efficacy endpoint for the 2 pivotal studies was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm. In individual and pooled analyses, a once daily, 2-drug regimen of DTG + 3TC demonstrated high efficacy and was non-inferior to a standard 3-drug regimen of DTG + TDF/FTC in treatment naïve adults with HIV-1-infection, based on a non-inferiority margin of 10%. This 2-drug regimen was able to achieve plasma HIV-1 RNA < 50 c/mL at Week 48 as effectively as the 3-drug ART regimen.

The following conclusions can be made with regard to the data from the individual studies and the pooled analysis:

- For each individual study (Study 204861 and Study 205543) at Week 48, the proportion of subjects with plasma HIV-1 RNA <50 c/mL (Snapshot; ITT-E population) was similar in both treatment arms, and demonstrated that DTG + 3TC was non-inferior to DTG + TDF/FTC, based on a 10% non-inferiority margin. The

results for the PP and ITT Populations were supportive of those from the ITT-E (primary) population. In addition, results from the pooled analysis were consistent with those for the individual studies. Results from the 2, independent, randomized, double blind Phase III studies demonstrate reproducibility of findings in meeting the non-inferiority goals and primary endpoint objectives of the pivotal efficacy studies.

- The DTG + 3TC 2-drug regimen is as effective as the 3-drug regimen in the treatment of HIV-1 infection across a diverse spectrum of ART-naïve subjects. Where subgroups are sufficiently large enough, including those with low and high and Baseline plasma HIV-1RNA (≤ or >100,000 c/mL) subgroup results are supportive of the primary endpoint of the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48.
- In Study 205543 and the pooled analysis, there was evidence of heterogeneity across Baseline CD4+ cell count subgroups (≤200 or >200 cells/mm^3), with a lower response rate in the DTG + 3TC arm in subjects with lower Baseline CD4+ cell counts. However, the number of subjects in this subgroup was small. The reasons for subjects having Snapshot outcomes that fell into one of the "non-response" categories varied; except for 1 subject that met protocol-defined CVW in Study 204861, none resulted in treatment-related discontinuation at Week 48. As such, these results should be interpreted with caution. There was no significant evidence of heterogeneity in Study 204861.
- Efficacy of the dual regimen of DTG + 3TC was further demonstrated in a more stringent analysis of the proportion of subjects with virologic success, using a viral load threshold of HIV-1 RNA <40 c/mL.
- DTG + 3TC (as a 2-drug regimen) achieved viral suppression as rapidly as the 3-drug treatment arm.
- The incidence of protocol-defined CVW through Week 48 was low in each study. Overall, the 2-drug regimen of DTG + 3TC was not associated with an increased risk of treatment-emergent resistance, as no subject meeting CVW criteria in either treatment group had treatment emergent INSTI or NRTI resistance through Week 48.
- CD4+ cell counts increased in both treatment groups from Baseline to Week 48 with no statistically significant differences between treatment groups in change from Baseline at Week 48 in either study.
- There were few subjects with Stage 3 HIV-associated events or disease progressions in both treatment groups as could be expected in this population with a high median CD4+ count, suggesting that adequate virological control provided by both treatments helps limit the development of new CDC Stage 3 qualifying conditions.
- Mean Baseline EQ-5D-5L Utility and Thermometer scores were high and comparable in both treatment groups, and similar improvements were observed in the 2 treatment groups in Utility and Thermometer scores at Week 48.
- Together with the BE data from m2.7.1 and m2.7.2, efficacy data presented here support the use of the FDC for the treatment of HIV-1 infection in treatment-naïve adults and adolescents.

6. APPENDIX

Appendix Table 1 Description of Pivotal Efficacy and Safety Studies

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date[a]; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age, (Range, years)	Primary Endpoint(s)
GEMINI-1 204861	87 centers; Argentina, Australia, Belgium, Canada, France, Germany, Italy, South Korea, Mexico, The Netherlands, Portugal, Romania, Russia, South Africa, Spain, Taiwan, UK, US	FSFV 21JUL2016; Ongoing; W48/W52 LSLV: 29MAR2018, 719/700	To demonstrate the non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks	Phase III, randomized, double-blind, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1-infected, ART-naïve adults	DTG 50 mg; tablet; oral; once daily + 3TC 300 mg; tablet; oral; once daily; 148 weeks DTG 50 mg; tablet; oral; once daily + FDC of TDF/FTC 300 mg/200 mg; tablet oral; once daily; 148 weeks	ITT-E Population: DTG + 3TC: 356/320 ongoing DTG + TDF/FTC: 358/330 ongoing	DTG + 3TC: 297/59; 34, (1[redacted]-6[redacted]) DTG + TDF/FTC: 306/52; 35, (1[redacted]-6[redacted])	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm) in ITT-E Population
GEMINI-2 205543	104 centers; Argentina, Australia, Belgium, Canada, France,	FSFV 18JUL2016; Ongoing; W48 LSLV: 27MAR2018, W52 LSLV	To demonstrate the non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48	Phase III, randomized, double-blind, active-controlled, multicenter,	HIV-1-infected, ART-naïve adults	DTG 50 mg; tablet; oral; once daily + 3TC 300 mg; tablet; oral; once daily; 148 weeks DTG 50 mg; tablet;	ITT-E Population: DTG + 3TC: 360/330 ongoing	DTG + 3TC: 306/54; 34.6, (1[redacted]-7[redacted]) DTG + TDF/FTC: 313/46; 34.4,	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date[a]; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age, (Range, years)	Primary Endpoint(s)
	Germany, Italy, Mexico, Peru, Poland, Portugal, Romania, Russia, Spain, Switzerland, Taiwan, UK, US	04APR2018; 722/700	weeks	parallel-group, non-inferiority study		oral; once daily + FDC of TDF/FTC 300 mg/200 mg; tablet oral; once daily; 148 weeks	DTG + TDF/FTC: 359/335 ongoing	(1[redacted]-7[redacted])	algorithm) in ITT-E Population

a. A confirmatory viral load measurement is performed at Week 52 for subjects presenting with HIV-1 RNA ≥50 c/mL at Week 48.

Appendix Table 2 Results of Pivotal Efficacy Studies

Study	Treatment Arm	No. Enrolled/ Completed	Primary Endpoint			Secondary Endpoints	Other Comments
			Plasma HIV-1 RNA <50 c/mL at Week 48	Difference in Proportion[a]	Adjusted Difference in Proportion[b]		
			n/N (%)	% (95% CI)	% (95% CI)		
204861 (GEMINI-1)	DTG 50 mg + 3TC 300 mg once daily	356/320 ongoing	320/356 (90%)	-2.8 (-7.0, 1.3)	-2.6 (-6.7, 1.5)	The proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 was similar in both treatment arms and demonstrated DTG +3TC was non-inferior to DTG + TDF/FTC, based on a 10% non-inferior margin. The time to viral suppression was similar between the DTG + 3TC and DTG + TDF/FTC groups. No subjects meeting CVW criteria developed treatment emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC. There was no significant difference between treatment groups in CD4+ cell counts from Baseline to Week 48. A similar proportion of subjects in each treatment group experienced HIV-1 disease progression to CDC Stage 3 clinical conditions or death through Week 48.	Based on a 10% non-inferiority margin, DTG + 3TC is non-inferior to DTG + TDF/FTC at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (- 6.7) is greater than -10%.
	DTG 50 mg + TDF/FTC FDC (TDF 300 mg/FTC 200 mg)	358/330 ongoing	332/358 (93%)				

Study	Treatment Arm	No. Enrolled/ Completed	Primary Endpoint			Secondary Endpoints	Other Comments
			Plasma HIV-1 RNA <50 c/mL at Week 48	Difference in Proportion[a]	Adjusted Difference in Proportion[b]		
205543 (GEMINI-2)	DTG 50 mg + 3TC 300 mg once daily	360/330 ongoing	335/360 (93%)	-0.8 (-4.4, 2.8)	-0.7 (-4.3, 2.9)	The proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 was similar in both treatment arms and demonstrated DTG +3TC was non-inferior to DTG + TDF/FTC, based on a 10% non-inferior margin. The time to viral suppression was similar between the DTG + 3TC and DTG + TDF/FTC groups. No subjects meeting CVW criteria developed treatment emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC. There was no significant difference between treatment groups in CD4+ cell counts from Baseline to Week 48. A similar proportion of subjects in each treatment group experienced HIV-1 disease progression to CDC Stage 3 clinical conditions or death through Week 48.	Based on a 10% non-inferiority margin, DTG + 3TC is non-inferior to DTG + TDF/FTC at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-4.3) is greater than -10%.
	DTG 50 mg + TDF/FTC FDC (TDF 300 mg/FTC 200 mg)	359/335 ongoing	337/359 (94%)				

a. Difference: Proportion on (DTG + 3TC) – Proportion on DTG + TDF/FTC.
b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for Baseline HIV-1 RNA (≤ or >100,000 c/mL) and CD4+ cell count (≤ or >200 cells/mm^3).

Appendix Table 3 Summary of Supportive SE Studies for Efficacy

Study	Study Title	SE Study Efficacy Conclusions
ING114467 (SINGLE) (DTG) GSK Document Number: 2014N198290_01 Status: Week 144 and End-of-Study CSRs Complete	A Phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects	**At Week 48**, 88% of study participants on the DTG + ABC/3TC regimen were virologically suppressed (<50 c/mL) vs. 81% of participants on the single tablet regimen Atripla [difference and 95% CI; 7.4% (+2.5% to +12.3%); difference in the primary endpoint was statistically significant, p=0.003]. **At Week 96**, 80% of study participants on the DTG + ABC/3TC regimen were virologically suppressed (<50 c/mL) vs. 72% of participants on the single tablet regimen Atripla [difference and 95% CI; 8.0% (+2.3% to +13.8%); difference in the primary endpoint was statistically significant, [p=0.006]. Response rates on DTG+ ABC/3TC and Atripla were generally consistent across demographic subgroups, including race, gender, age, HIV risk factors, and Baseline CDC category. **At Week 144**, 71% of study participants in the DTG + ABC/3TC treatment group were virologically suppressed (<50 c/mL) versus 63% of participants on the single tablet regimen of Atripla [adjusted difference and 95% CI; 8.3% (+2.0% to +14.6%); difference in the primary endpoint was statistically significant, [p=0.010]; therefore, statistical superiority at Week 144 was maintained. Differences in the Snapshot analysis were primarily driven by a lower rate of discontinuation due to AEs in the DTG + ABC/3TC treatment group. Response rates were similar between the DTG + ABC/3TC and the Atripla treatment groups across demographic subgroups, including race, gender, age, HIV risk factors, and Baseline CDC category. The longer-term end-of-study data support the safety of DTG in combination with ABC/3TC once daily in an HIV-infected treatment-naive patient population. The majority of subjects receiving DTG + ABC/3TC FDC who entered the continuation phase past Week 144 maintained viral suppression, based on an observed analysis. In the DTG + ABC/3TC FDC arm, antiviral response was sustained with 93% (193/207) of subjects with HIV-1 RNA <50 c/mL at Week 156 based on the observed data. The data from this completed study continue to support the use of DTG 50 mg + ABC/3TC once daily for the management of HIV infection in INSTI-naive subjects.
ING113086 (SPRING-2) (DTG) GSK Document Number: 2013N158737_01 Status: Week 96 CSR and End-of-Study CSRs Complete	A Phase III, randomized, double blind study of the safety and efficacy of GSK1349572 50 mg once daily compared to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in	**At Week 48,** 88% of study participants in the DTG arm versus 85% of participants in the RAL arm were virologically suppressed (HIV-1 RNA <50 c/mL) [difference and 95% CI; 2.4% (-2.2, 7.1)]. This demonstrated DTG is non-inferior to RAL at Week 48, because the lower end of the 95% CI for the treatment difference (-2.2%) is greater than the pre-specified non-inferiority margin of -10%. DTG performed as well as RAL regardless of baseline viral load, background dual NRTI, demographic subgroups, HIV risk factors, baseline CD4+ cell count and baseline CDC category. **At Week 96**, the proportion of subjects with HIV RNA <50 c/mL (81%) compared favorably with RAL (76%) through 96 weeks. DTG performed as well as RAL regardless of baseline viral load or background dual NRTI. DTG

Study	Study Title	SE Study Efficacy Conclusions
	HIV-1 infected antiretroviral naive adult subjects	performed as well as RAL across demographic subgroups, including race, gender, age, HIV risk factors, baseline CD4+ cell count and baseline CDC category. Data through 96 weeks support DTG 50 mg once daily for INSTI-naive subjects, and provide evidence for durable efficacy and tolerability for DTG in combination therapy. In this study, DTG has shown non-inferior efficacy and a safety profile similar to RAL with no evidence of treatment emergent resistance in virologic failure. DTG administered once daily with 2 NRTIs demonstrated non-inferiority to RAL at Week 96 and was associated with good treatment response.
NUCA3001 (3TC) Glaxo Document Number UCR/95/002 Status: Complete	A randomized double-blind multicenter trial to compare the safety and efficacy of 3TC monotherapy versus ZDV monotherapy versus 3TC administered concurrently with ZDV in the treatment of HIV-1 infected study participants who are ZDV naïve (≤4 weeks) with CD4+ cell counts of 200-500 cells/mm^3	**At Week 24**, there was a decrease in viral load and sustained increase in CD4+ cell counts over 24 weeks, which was not statistically significant between the two combination therapy groups. Pairwise comparisons (adjusted) showed statistically significantly greater CD4+ cell count increase from baseline in the combination groups ZDV+3TC (150 mg) and ZDV+3TC (300 mg) groups relative to the monotherapy groups. Similar adjusted pairwise comparisons of log10- HIV-1 RNA change from baseline showed statistically significantly greater log10 HIV-1 RNA reductions in the ZDV+3TC (150mg), ZDV+3TC (300 mg) and 3TC (300 mg) groups relative to the ZDV group, and in the ZDV+3TC (150 mg), ZDV+3TC (300 mg) groups relative to the 3TC (300 mg) group. In general, Bonferri-adjusted pairwise comparisons revealed superior secondary marker effects (percent CD4+ cell count, β2-microglobin, neopterin levels) in the combination therapy groups relative to the monotherapy groups.
NUCB3001 (3TC) Glaxo Document Number GIO/94/003 Randomized, double-blind Status: Complete	A randomized, Controlled 3TC double-blinded trial to compare the safety and efficacy of 3TC (300 mg BID) in combination with ZDV versus ZDV monotherapy in treating HIV-1 infected study participants who are ZDV therapy naïve with a CD4+ cell count between 100-400 cells/mm^3	The primary comparison between treatments arms evaluated the profile of surrogate markers and measures of viral load in the 2 treatment arms during the first 24 weeks of the study; these parameters included CD4+ count and HIV RNA. **At Week 24**, combination therapy showed superior treatment effects compared with monotherapy during the first 24 weeks as documented by changes in CD4+ cell counts (increase of 0.08 x 10(9)/L vs 0.02 x 10(9)/L; P < .001), ICDp24 (-88% vs -49%; P = .04), cellular viremia (-1.27 vs -0.20 log10 median tissue-culture infected dose [TCID50] per 10(6) peripheral blood mononuclear cells; P = .001), and by HIV-1 RNA using a Roche method (-1.33 vs -0.57 log10 copies/mL; P = .001) or an immune-capture method (-0.6 vs -0.14log10 copies/mL; P = .008). **At Week 48**, observed changes were sustained to 48 weeks for patients continuing to receive combination therapy. Subjects switching to receive combination therapy at week 24 showed improvements in CD4+ cell count and viral load to Week 48. Note: After 24 weeks, study participants were eligible to enter NUCB3001c, a rollover trial.

Study	Study Title	SE Study Efficacy Conclusions
NUCA3002 (3TC) Glaxo Document Number UCR/95/003 Randomized, double-blind Status: Complete	A randomized 3TC, ddC double-blind (ZDV open-labelled) multicenter trial to evaluate the safety and efficacy of 3TC (150 mg low dose) administered concurrently with ZDV versus 3TC (300 mg high dose) administered concurrently with ZDV versus dideoxycytidine (ddC) administered concurrently with ZDV in the treatment of HIV-1 infected ZDV-experienced (≥24 weeks) study participants with CD4+ cell counts of 100-300 cells/mm^3	**At Week 24**, high- and low-dose ZDV+3TC combination therapies produced similar and sustained absolute and percent CD4+ cell count increases, and decreases in ICD p24 antigen, ~2-microglobulin, and neopterin, all of which were superior to those of ZDV+DDC (0.75 mg). ZDV+3TC (300 mg) effected statistically significantly greater 10gl0 HIV-I RNA reductions relative to the ZDV+DDC (0.75 mg) group, however ZDV+3TC (I50 mg) did not. In general, marker responses for patients who completed 24 weeks of treatment were superior to those of patients who permanently discontinued study drug prior to 24 weeks. Both ZDV+3TC therapies provided superior CD4+ and 10gl0 HIV-I RNA effects regardless of age, gender, or race, relative to ZDV+DDC (0.75 mg) however, Caucasians exhibited higher CD4+ cell count values and lower HIV-I RNA values than did Non-Caucasians.
NUCB3002 (3TC) Glaxo Report Number GIO/94/005 Randomized, double-blind Status: Complete	A randomized, controlled, Lamivudine (3TC) double-blinded trial to compare the safety and efficacy of ZDV monotherapy versus Lamivudine plus ZDV in combination in treating HIV-1 infected patients who are ZDV Therapy-experienced with a CD4+ cell counts between 100 cells/mm^3 to 400 cells/mm^3.	**At Week 24**, efficacy was measured using both immunological parameters (CD4+ count, p2-microglobulin, neopterin) and measures of viral load (HIV-I p24 antigen, HIV-I RNA PCR, plasma viral load, cellular viremia). The combination of 3TC (150mg or 300mg BID) and ZDV (200mg TID) showed significantly greater and more sustained responses over ZDV monotherapy in immunological and viral load parameters measured over the 24 week study period. No significant differences were shown between the two doses of 3TC (150 mg BID or 300 mg BID) in combination with ZDV. Note: After 24 weeks, study participants were eligible to enter NUCB3002c, a rollover trial.
Adolescent Extrapolation GSK Document Number 2018N363795_00 Status: Complete	Adolescent Extrapolation report for GSK3515864	Week 24 analysis of GEMINI-1 and GEMINI-2 Phase III studies conducted with the single entity tablets Tivicay and Epivir showed that DTG plus 3TC is highly efficacious and well tolerated in HIV-infected, ART-naïve patients. The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are adult doses that have already been authorized as individual agents in adolescents ≥12 years of age weighing ≥40 kg (DTG) or in pediatric patients weighing ≥25 kg (3TC). The available PK data from pediatric subjects (both observed and modelled), including adolescents ≥12 to <18

Study	Study Title	SE Study Efficacy Conclusions
		years, demonstrate that DTG and 3TC exposures are sufficiently similar to adults to permit extrapolation of efficacy data from pharmacokinetic correlation. The data from pivotal BE Study 204994, combined with data from the 3TC historical studies, provides an acceptable PK bridge to the single entities used in GEMINI-1 and GEMINI-2 Phase III trials, ensures similarity in terms of safety and efficacy and supports the adolescent indication for the DTG/3TC FDC product. The totality of evidence supports the rationale of an extrapolation approach from adults to adolescents and from the individual DTG plus 3TC to the DTG/3TC FDC. The DTG/3TC 50mg/300mg FDC is recommended as a once-daily complete regimen administered with or without food for the treatment of HIV-1 infection in ART-naïve adolescents (.12 years to <18 years of age, weighing at least 40 kg).

Note: Supportive studies are tabulated briefly in this efficacy summary, but reports will be made available upon request for the convenience of the reviewer.

Module 2.7.4

Summary of Clinical Safety

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ABBREVIATIONS

204861	GEMINI-1 study
205543	GEMINI-2 study
3TC	Lamivudine
ABC	Abacavir
ADHD	Attention deficit hyperactivity disorder
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immunodeficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
BE	Bioequivalence
BMI	Body mass index
c/mL	Copies/milliliter
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum observed concentration
CPK	Creatine phosphokinase
CRF	Case report form
CSR	Clinical Study Report
CT	Computed tomography
DAIDS	Division of Acquired Immune Deficiency Syndrome
DILI	Drug-induced liver injury
DTG	Dolutegravir
ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
eGFR	Estimated glomerular filtration rate
ER	Emergency room
EU	European Union
FDC	Fixed-dose combination
FTC	Emtricitabine
GDS	Global Data Sheet
GFR	Glomerular filtration rate
GI	Gastrointestinal
HBV	Hepatitis B virus
HbsAg	Hepatitis B virus surface antigen
HAV	Hepatitis A virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus

HIV-1	Human immunodeficiency virus type 1
IMS	Intercontinental Medical Statistics
INR	International normalized ratio
INSTI	Integrase strand transfer inhibitor
IRIS	Immune Reconstitution Inflammatory Syndrome
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT-E	Intent-to-Treat Exposed
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LOCF	Last observation carried forward
LSLV	Last subject last visit
MAH	Marketing Authorization Holder
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
NCEP	National Cholesterol Education Program
NASH	Nonalcoholic steatohepatitis
OCT-2	Organic cation transporter 2
PCR	Polymerase chain reaction
PJP	Pneumocystis jirovecii pneumonia
PMFU	Person-months of follow-up
RAP	Reporting and Analysis Plan
RMP	Risk Management Plan
RNA	Ribonucleic acid
RSI	Reference Safety Information
SAE	Serious adverse event
SDAP	Summary Document Analysis Plan
SOC	System organ class
TAF	Tenofovir alafenamide
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TID	Three times daily
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information

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1. EXPOSURE TO THE DRUG

1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

This Summary of Clinical Safety is intended to provide evidence to support the safety of a new 2-drug regimen combining dolutegravir and lamivudine in a fixed-dose combination tablet for the treatment of HIV-1 infection in patients without known or suspected resistance to either antiretroviral component.

Dolutegravir (DTG; TIVICAY, GSK1349572) is an HIV INSTI approved for use in combination with other ARVs for treatment-naïve and treatment-experienced HIV-infected adults and adolescents at a dose of 50 mg once daily or 50 mg twice daily (when certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance are present). Lamivudine (3TC; EPIVIR, GR109714) is a cytidine nucleoside analog HIV-1 reverse transcriptase inhibitor approved for the use in combination with other ARV agents for the treatment of HIV-1 infection at a dose of 300 mg once daily in adults and adolescents.

Both DTG and 3TC are commercially available products in many markets worldwide, and are also available as part of a FDC product (ABC/DTG/3TC, TRIUMEQ). Post-marketing information for these products is provided in Section 6.

Safety data for the combination of DTG + 3TC are gathered from 2 identical, pivotal studies (204861 [GEMINI-1] and 205543 [GEMINI-2]) conducted in HIV-1-infected, ART-naïve adults. The studies evaluated the use of single-entity DTG 50 mg in combination with single-entity 3TC 300 mg, administered once daily as a complete regimen for the treatment of HIV-1 infection in ART-naïve adults. Subjects in the comparator arm for each of these studies received DTG 50 mg + fixed-dose combination TDF 300 mg/FTC 200 mg once daily.

Safety data through at least Week 48 for the two pivotal studies are available and are described herein in support of a marketing authorization for this 2-drug regimen. Full study data are available in the 204861 Week 48 CSR and the 205543 Week 48 CSR, both located in m5.3.5.1.

1.1.1. Strategy for Establishing the Safety Profile for DTG/3TC FDC

The DTG/3TC FDC contains the active substances DTG and 3TC at the same once daily doses as marketed for the individual components (i.e., 50 mg and 300 mg, respectively).

Establishing the risk/benefit profile of a FDC tablet includes an assessment of the safety of each individual component taken alone as well as the safety of the components when used in combination. The Applicant's strategy for providing a robust safety package to support the DTG/3TC FDC is outlined below.

1.1.1.1. Pivotal Safety Studies

Data from the Phase III clinical trials (204861 and 205543, including a pooled analysis of data from both studies) conducted under the DTG/3TC FDC development program provide pivotal safety data for this application. These studies and the pooled analysis of these two studies are summarized as follows:

- **204861** (GEMINI-1) and **205543** (GEMINI-2) – 2 identical, pivotal, ongoing randomized, parallel group, double-blind, 148-week, Phase III studies, designed to demonstrate non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC in HIV-1-infected, ART-naïve subjects.
- **GEMINI ISS/ISE** (Pooled Analysis of 204861 and 205543) – pooled data from these 2 studies, comprising a total of 716 subjects receiving DTG + 3TC as part of 204861 and 205543 (and compared with 717 subjects in the DTG + TDF/FTC groups). This analysis, described in the SDAP, supplements the individual study data analyses described in the 204861/205543 RAP.

1.1.1.2. Other Safety Data

A Phase I relative bioavailability study (204993) and a Phase I bioequivalence study (204994) were also conducted under the DTG/3TC FDC development program; these studies are summarized as follows:

- **204993** (RBA study) – a relative bioavailability (RBA) study in healthy volunteers to evaluate the relative bioavailability of a single dose of DTG 50 mg and 3TC 300 mg when administered together in each of two experimental FDC tablet formulations compared to the co-administration of a single dose of the single-entity DTG and 3TC products. Safety data from this study are summarized in Section 5.5.1.
- **204994** (BE study) – an open-label, randomized, two-way crossover, single dose, pivotal BE study of two formulations of DTG/3TC FDC tablets versus DTG and 3TC single entities and food effect assessment in healthy volunteers. Safety data from this study are summarized in Section 5.5.2.

Additionally, previously submitted studies from DTG or 3TC single-entity development programs support the assessment of safety for this application. For the purposes of this submission, studies categorized as "supportive" are defined as follows:

- **Supportive single-entity studies**: these studies are not essential for the FDC benefit-risk assessment, but are considered helpful to the reviewer and supportive on the proposed indication. Supportive studies will be briefly tabulated in the module 2.7 summaries and reports will be made available upon request for the convenience of the reviewer. A table of the "supportive" single-entity studies for safety is provided in Appendix Table 1.

As both DTG and 3TC are marketed products, safety data collected from post-marketing experience will also contribute to the FDC benefit-risk assessment (see Section 1.1.1.3).

1.1.1.3. Data from Post-Marketing Experience for the DTG and 3TC Single Entities

No post-marketing experience is available with the DTG/3TC FDC, as it is an investigational product and is not marketed or authorized for sale in any country at the time of this report. However, both DTG and 3TC have been marketed for a number of years. An overview of any significant post-marketing information for DTG and 3TC and any information, for example from the literature, describing the use of DTG and 3TC together is provided in Section 6.

Post-marketing data relating to the use of DTG in pregnancy is reviewed in Section 5.4, and information related to neural tube defects following the preliminary analysis of a birth outcomes study in Botswana is summarized in Section 6.1.

1.1.2. Nonclinical Data Relevant to Human Safety

To support initial separate marketing, DTG and 3TC have each been tested individually in comprehensive nonclinical development programs. There is no known overlapping toxicity for DTG and 3TC, and the single-entities components have been used together in combination with ABC as TRIUMEQ. Thus, no nonclinical combination toxicity studies have been conducted on the combination of DTG and 3TC as combination toxicity studies are not generally warranted for HIV products unless there is a specific cause for concern under clinically relevant conditions.

Refer to the Nonclinical Overview (m2.4) for information on nonclinical toxicology and pharmacology.

1.1.3. Clinical Development Program Overview

The overall clinical development and reporting strategy for the DTG/3TC FDC is summarized in m2.5 Section 1.2.

1.1.4. Description Types of m2.7.4 Tabular Data Presentations

In this document, there are references to 3 types of presentations for tables and figures. The original electronic format, location, and a description of how these tables or figures are referenced throughout this document are summarized in Table 1.

Table 1 Table, Figure, and Listing Types and Descriptions

Table/Figure Type	Location	How Referenced
In-text	In body of this summary document	Consecutive integers (e.g., Table 1, Table 2, Figure 1, Figure 2)
Statistical Source Tables	Individual CSRs (for individual study outputs) and m5.3.5.3 (for pooled analysis outputs)	For individual study data: Individual study number plus statistical source table number (e.g., Study 204861 Table 3.1). Pooled study data: GEMINI ISS/ISE plus statistical source table number (e.g., GEMINI ISS/ISE Table 3.1)
Appendix	In the Appendix section of this summary document (Section 7)	Consecutive integers (e.g., Appendix Table 1, Appendix Table 2)

1.1.5. Description of Studies

Studies 204861 and 205543 are identical in terms of study design. A narrative description of the 204861 and 205543 study design is provided in m2.7.3 Section 1.5, and a tabular summary of the design is provided in Appendix Table 2 (Description of Pivotal Efficacy and Safety Studies).

1.1.6. Data Cut-Off Date

This submission contains safety data collected and analyzed for the Week 48 primary analysis for 204861 and 205543. LSLV dates for these analyses were 29 March 2018 for 204861 and 04 April 2018 for 205543. Safety analyses summarized in this document for both studies used a data cut-off date of [redacted] (for Week 48 database freeze). The pooled analysis database contains identical data compared to the individual study databases.

Additionally, information included in the CSR case narratives (located in 204861 CSR Section 13 and 205543 CSR Section 13), for events occurring up to the cut-off date of [redacted], may include updated information on these cases up to a cut-off date of [redacted] for 204861 and [redacted] for 205543.

1.1.7. Analysis Populations Included

This Summary of Clinical Safety includes data from the 204861 and 205543 ITT-E and Safety populations.

1.1.7.1. ITT-E Population

Assessments of subject disposition and demographic and other characteristics used the ITT-E populations of 204861 and 205543. The ITT-E population for each study consisted of all randomized subjects who received at least one dose of study medication. Subjects were assessed according to their randomized treatment, regardless of the treatment they received.

1.1.7.2. Safety Population

Unless otherwise stated, safety analyses were conducted based on the Safety populations of 204861 and 205543, which, for both studies, consisted of all subjects who received at least one dose of study medication. Subjects were analyzed according to the actual treatments received.

1.1.8. Statistical Methods

Studies 204861 and 205543 are identical in terms of analysis plan. Complete details of the planned statistical analyses for the individual studies are provided in the Reporting and Analysis Plan for 204861 (identical to the Reporting and Analysis Plan for 205543).

In addition to safety analyses performed for the individual studies, a pooled analysis of 204861 and 205543 was performed. Refer to the Summary Document Analysis Plan for DTG + 3TC for complete details of the planned pooled analyses. This pooled output uses the most recent version of MedDRA and GSKDrug dictionaries at the time of the database freeze within each study; individual study datasets and pooled datasets were created at the same time using the same dictionary version.

Safety analyses are summarized by treatment group and for some outputs are also summarized overall (i.e., total of DTG + 3TC and DTG + TDF/FTC groups together); these analyses include summaries of extent of exposure, AEs, and laboratory tests, including special interest categories for AEs and laboratory tests.

Additional tables and figures were included in the Week 48 reporting though not specified in the SDAP. These were the same as the additional safety analyses specified for the individual studies.

1.1.9. Subject Disposition

The subject disposition for 204861 is summarized in 204861 Week 48 CSR Section 5.2; the subject disposition for 205543 is summarized in 205543 Week 48 CSR Section 5.2. In each study, similar proportions of subjects in the ITT-E population withdrew from the study for the DTG + 3TC group compared with the DTG + TDF/FTC group. In the combined analysis, 8% of subjects overall withdrew early (DTG +3TC 9%; DTG + TDF/FTC 7%) (Data Source: GEMINI ISS/ISE Table 1.3).

A tabular summary of subject disposition for each study and the total pooled group is provided in m2.7.3 Section 3.1.1. Primary reasons for withdrawal were similar between the two studies and between the treatment groups. In the total pooled group, the most common primary reason for withdrawal was “lost to follow-up” (26 [2%] subjects overall) (Data Source: GEMINI ISS/ISE Table 1.3). In total, 14 (2%) subjects in DTG + 3TC group and 9 (1%) subjects in the DTG + TDF/FTC group withdrew with “adverse event” noted by the investigator as the primary reason for withdrawal. (Note: subjects may be withdrawn for more than one reason; however, the investigator must designate a single primary reason on the CRF. In some cases, a subject may have

experienced an AE leading to withdrawal, but the investigator may have indicated withdrawal for a different primary reason than "adverse event" on the CRF.)

1.2. Overall Extent of Exposure

Across these 2 identical Phase III studies, 204861 and 205543, 1433 subjects were exposed to DTG 50 mg – 716 subjects received at least 1 dose of DTG + 3TC and 717 subjects received at least 1 dose of DTG + TDF/FTC (Data Source: GEMINI ISS/ISE Table 3.1).

For the individual studies and the pooled analysis, the overall mean extent of exposure to study drug was similar across the 2 treatment groups (Data Source: 204861 Week 48 CSR Table 3.1; 205543 Week 48 CSR Table 3.1; GEMINI ISS/ISE Table 3.1). In the pooled analysis, the mean exposure was 412.9 days (59.0 weeks) in the DTG + 3TC group and 413.8 days (59.1 weeks) in the DTG + TDF/FTC group up to the data cut-off used for the Week 48 database freeze of [redacted].

1.3. Demographic and Other Characteristics of Study Population

Refer to m2.7.3 Section 3.1.2 for tabular summaries of demographic and baseline characteristics for studies 204861 and 205543 and for the pooled analysis. For both studies, demographic and baseline characteristics were similar across the treatment groups.

2. ADVERSE EVENTS

The AE and SAE definitions used in studies 204861 and 205543 are provided in Section 7.2 and Section 7.3, respectively. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0 (November 2014) [DAIDS, 2014] was used to assess the severity of clinical adverse events. This DAIDS grading version uses Grades 1-5, with Grade 5 indicating death (the previous version used Grades 1-4, with death included within Grade 4 along with potentially life-threatening events).

2.1. Analysis of Adverse Events

2.1.1. Unreported Adverse Events due to a GCP Non-Compliance Finding

In addition to the AEs reported in the Week 48 analysis outputs, 8 additional AEs (reported in a total of 5 subjects at a single study center [redacted] in study 204861) were identified that had an onset prior to the data cut-off date of [redacted] used for the Week 48 database freeze. These 8 AEs do not appear in the Week 48 source tables, figures, and listings as they were not originally captured in the subjects' eCRFs (see 204861 CSR Section 5.3.2.1). The reporting discrepancy has been corrected, and these events will be included in the planned Week 96 analysis.

Table 2 lists the 8 AEs that are not captured in the Week 48 analysis outputs. Most of these AEs were infections or were skin related. All of the events were Grade 2 in intensity and were resolved or resolving, and all subjects are continuing on study drug. None of the events were serious, drug-related, or led to withdrawal. None of the events were AESIs. The reported candidiasis does not change the findings reported in m2.7.3 Section 3.2.8 of HIV-associated conditions.

Of the 5 subjects listed in Table 2 with unreported events, which had not been captured in the Week 48 analysis outputs, 3 of these subjects had previously reported other events that were captured in the Week 48 analysis outputs, and the other 2 subjects had not previously reported any other additional events to those shown in Table 2. Thus, these latter 2 subjects represent 2 additional subjects that need to be added to the total numbers of subjects reporting "any AE" and "any Grade 2-5 AE" in the Week 48 analysis outputs. Both of these subjects were in the DTG + 3TC group (Subject [redacted] with Grade 2 syphilis and Subject [redacted] with 2 events of Grade 2 gonorrhea). In-text tables in this document with data that are impacted by the missing subjects/events this will be footnoted to indicate what data is missing.

Neither the previously unreported 8 AEs nor the 2 subjects not accounted for in total subject numbers of the Week 48 outputs significantly impacts the safety data or the overall safety conclusions of the study.

Table 2 Listing of Adverse Events Occurring Prior to the Week 48 Analysis Cut-off Date that were Not Reported in the Week 48 Analysis Outputs by Study Center [redacted]

Subject ID	AE Preferred Term(s)	Onset (Study Day)	Maximum Grade	Serious AE (Yes or No)	Drug Related (Yes or No)
Subjects Randomized to DTG + 3TC					
[redacted]	Atopic dermatitis[a]	585	2	No	No
[redacted]	Syphilis[b]	225	2	No	No
[redacted]	Gonorrhoea[b]	13	2	No	No
	Gonorrhoea[b]	330	2	No	No
Subjects Randomized to DTG + TDF/FTC					
[redacted]	Perineal abscess[b]	161	2	No	No
	Vitamin D deficiency[c]	197	2	No	No
	Secondary erectile dysfunction[d]	392	2	No	No
[redacted]	Oral erythematous candidiasis[b]	211	2	No	No

Note: All events occurred at a single study center and were identified following reconciliation of the site's clinic EMR database (where these AEs had been recorded) with the site's research EMR database (where these AEs had not been recorded and which served as site's data source for CRFs).

Note: No subject was withdrawn and study drug was not interrupted due to any of the listed AEs.

a. Skin and subcutaneous tissue disorders SOC
b. Infections and infestations SOC
c. Metabolism and nutrition disorders SOC
d. Reproductive system and breast disorders SOC

2.1.2. Common Adverse Events

2.1.2.1. Overall Adverse Event Frequencies

Table 3 provides an overall summary of adverse events up to the Week 48 analysis cut-off date for 204861 and 205543. In both studies and in the pooled analysis, a moderately lower proportion of subjects in the DTG + 3TC group compared with the DTG + TDF/FTC group reported drug-related AEs, though, most of these were Grade 1 events. Drug-related AEs are further described in Section 2.1.2.4.

The most commonly reported AEs for the DTG + 3TC and DTG + TDF/FTC groups in the pooled analysis are shown in Figure 1 and in Table 4 (which also displays these most commonly reported AEs by individual study). Fewer subjects in the DTG + 3TC group compared with the DTG + TDF/FTC group reported nasopharyngitis, insomnia, and nausea (relative risk bounds of the 95% CI did not include 1 in Figure 1). There were no other notable differences between the 2 treatment groups when comparing individual preferred terms.

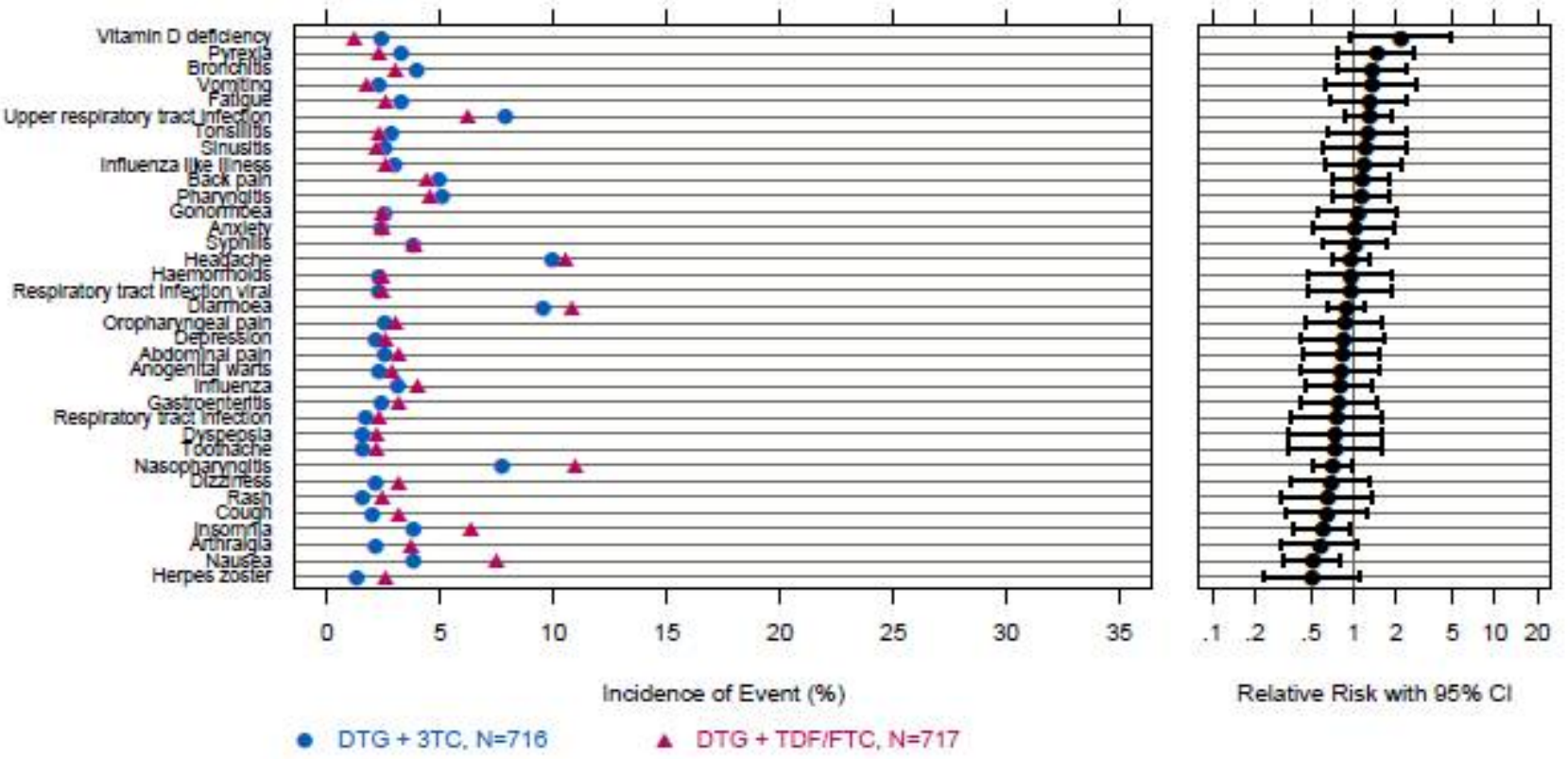
Table 3 Overall Summary of Adverse Events for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Any AE	276 (78)[a]	295 (82)	267 (74)	284 (79)	543 (76)[a]	579 (81)	1122 (78)[a]
Drug-related AEs	71 (20)	94 (26)	55 (15)	75 (21)	126 (18)	169 (24)	295 (21)
Grade 2 to 5 AEs	216 (61)[a]	234 (65)	188 (52)	191 (53)	404 (56)[a]	425 (59)	829 (58)[a]
Drug-related Grade 2 to 5 AEs	21 (6)	25 (7)	21 (6)	22 (6)	42 (6)	47 (7)	89 (6)
AEs Leading to Withdrawal	7 (2)	8 (2)	8 (2)	8 (2)	15 (2)	16 (2)	31 (2)
Drug-related AEs Leading to Withdrawal	3 (<1)	5 (1)	3 (<1)	4 (1)	6 (<1)	9 (1)	15 (1)
Any SAE	21 (6)	22 (6)	29 (8)	33 (9)	50 (7)	55 (8)	105 (7)
Drug-related SAEs	2 (<1)	1 (<1)	2 (<1)	3 (<1)	4 (<1)	4 (<1)	8 (<1)
Fatal AEs	0	0	2 (<1)	0	2 (<1)	0	2 (<1)
Drug-related Fatal AEs	0	0	0	0	0	0	0

Data Source:
204861 Week 48 CSR Table 3.2, Table 3.4, Table 3.7, Table 3.9, Table 3.19, Table 3.76, Table 3.16, Table 3.17, Table 3.14, and Table 3.15;
205543 Week 48 CSR Table 3.2, Table 3.4, Table 3.7, Table 3.9, Table 3.19, Table 3.76, Table 3.16, Table 3.17, Table 3.14, and Table 3.15;
GEMINI ISS/ISE Table 3.2, Table 3.4, Table 3.7, Table 3.9, Table 3.19, Table 3.76, Table 3.16, Table 3.17, Table 3.14, and Table 3.15.

a. As described in Section 2.1.1, there were 2 additional subjects in the DTG + 3TC group of 204861 with AEs meeting criteria for reporting as "Any AE" and "Grade 2 to 5 AEs"; these AEs had not been reported by the data cut-off date and were not included in the analyses due to a GCP noncompliance issue at a single study center; updated data would be as follows:
204861 DTG + 3TC column, n (%) = 278 (78) for Any AE and 218 (61) for Grade 2 to 5 AEs;
POOLED DTG + 3TC column, n (%) = 545 (76) for Any AE and 406 (57) for Grade 2 to 5 AEs;
POOLED Total column, n (%) = 1124 (78) for Any AE and 831 (58) for Grade 2 to 5 AEs.

Figure 1 Plot of Common Adverse Events and Relative Risk for Pooled Data (204861 and 205543) (Safety Population)



Data Source: GEMINI ISS/ISE Figure 3.1.

Note: Common adverse events are those reported by ≥2% in at least one treatment. For events that occurred in only one treatment group the CI for relative risk was calculated using Proc Freq with the exact statement.

Note: Data used to generate this figure do not include 2 events of gonorrhoea (DTG + 3TC group; both reported in the same subject), 1 event of syphilis (DTG + 3TC group), and 1 event of vitamin D deficiency (DTG + TDF/FTC group) that occurred in 204861, which, as described in Section 2.1.1, had not been reported by the data cut-off date and were not included in the analyses due to a GCP noncompliance issue at a single study center.

Table 4 Summary of Common Adverse Events (Reported in >=5% of Subjects in Any Pooled Treatment Group) by Preferred Term for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Any AE	276 (78)[a]	295 (82)	267 (74)	284 (79)	543 (76)[a]	579 (81)	1122 (78)[a]
Headache	40 (11)	44 (12)	31 (9)	31 (9)	71 (10)	75 (10)	146 (10)
Diarrhoea	33 (9)	42 (12)	35 (10)	35 (10)	68 (9)	77 (11)	145 (10)
Nasopharyngitis	33 (9)	37 (10)	22 (6)	41 (11)	55 (8)	78 (11)	133 (9)
Upper respiratory tract infection	24 (7)	22 (6)	32 (9)	22 (6)	56 (8)	44 (6)	100 (7)
Nausea	12 (3)	30 (8)	15 (4)	23 (6)	27 (4)	53 (7)	80 (6)
Insomnia	16 (4)	29 (8)	11 (3)	16 (4)	27 (4)	45 (6)	72 (5)
Pharyngitis	23 (6)	13 (4)	13 (4)	19 (5)	36 (5)	32 (4)	68 (5)

Data Source: 204861 Week 48 CSR Table 3.6; 205543 Week 48 CSR Table 3.6; GEMINI ISS/ISE Table 3.6.

a. As described in Section 2.1.1, there were 2 additional subjects in the DTG + 3TC group of 204861 with AEs meeting criteria for reporting as "Any AE"; these AEs had not been reported by the data cut-off date and were not included in the analyses due to a GCP noncompliance issue at a single study center; updated data would be as follows:
204861 DTG + 3TC column, n (%) = 278 (78) for Any AE;
POOLED DTG + 3TC column, n (%) = 545 (76) for Any AE;
POOLED Total column, n (%) = 1124 (78) for Any AE.

2.1.2.2. Adverse Events by System Organ Class

AE reporting by SOC is presented in Table 5. Proportions of subjects reporting events were generally similar across the SOCs, although minor differences were observed for some SOCs (e.g., GI disorders). In the case of the GI disorders SOC, the higher reporting rate in the DTG + TDF/FTC was largely driven by differences in the incidence of nausea (DTG + 3TC: 27 [4%]; DTG + TDF/FTC: 53 [7%]) and, to some extent, diarrhea (DTG + 3TC: 68 [9%]; DTG + TDF/FTC: 77 [11%]); however, in most instances, there were no noteworthy differences between the groups in reporting rates for any individual preferred terms within the SOC (Data Source: GEMINI ISS/ISE Table 3.2).

Table 5 Summary of Adverse Events by System Organ Class for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Any AE	276 (78)[a]	295 (82)	267 (74)	284 (79)	543 (76)[a]	579 (81)	1122 (78)[a]
Infections and infestations	183 (51)[b]	187 (52)	180 (50)	204 (57)	363 (51)[b]	391 (55)	754 (53)[b]
Gastrointestinal disorders	103 (29)	127 (35)	105 (29)	118 (33)	208 (29)	245 (34)	453 (32)
Nervous system disorders	57 (16)	76 (21)	53 (15)	57 (16)	110 (15)	133 (19)	243 (17)
Psychiatric disorders	54 (15)	60 (17)	41 (11)	45 (13)	95 (13)	105 (15)	200 (14)
Skin and subcutaneous tissue disorders	51 (14)[c]	52 (15)	42 (12)	48 (13)	93 (13)[c]	100 (14)	193 (13)[c]
Musculoskeletal and connective tissue disorders	41 (12)	55 (15)	53 (15)	44 (12)	94 (13)	99 (14)	193 (13)
Respiratory, thoracic and mediastinal disorders	36 (10)	53 (15)	34 (9)	39 (11)	70 (10)	92 (13)	162 (11)
General disorders and administration site conditions	41 (12)	48 (13)	44 (12)	34 (9)	85 (12)	82 (11)	167 (12)
Injury, poisoning and procedural complications	33 (9)	25 (7)	37 (10)	36 (10)	70 (10)	61 (9)	131 (9)
Metabolism and nutrition disorders	19 (5)	11 (3)[d]	35 (10)	21 (6)	54 (8)	32 (4)[d]	86 (6)[d]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	15 (4)	18 (5)	14 (4)	17 (5)	29 (4)	35 (5)	64 (4)
Investigations	15 (4)	10 (3)	16 (4)	21 (6)	31 (4)	31 (4)	62 (4)
Reproductive system and breast disorders	12 (3)	15 (4)[d]	22 (6)	12 (3)	34 (5)	27 (4)[d]	61 (4)[d]
Renal and urinary disorders	14 (4)	15 (4)	13 (4)	12 (3)	27 (4)	27 (4)	54 (4)
Vascular disorders	11 (3)	11 (3)	6 (2)	7 (2)	17 (2)	18 (3)	35 (2)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	**DTG + TDF/FTC N=358 n (%)**	**DTG + 3TC N=360 n (%)**	**DTG + TDF/FTC N=359 n (%)**	**DTG + 3TC N=716 n (%)**	**DTG + TDF/FTC N=717 n (%)**	**Total N=1433 n (%)**
Blood and lymphatic system disorders	6 (2)	6 (2)	8 (2)	7 (2)	14 (2)	13 (2)	27 (2)
Immune system disorders	8 (2)	10 (3)	5 (1)	2 (<1)	13 (2)	12 (2)	25 (2)
Eye disorders	4 (1)	14 (4)	7 (2)	3 (<1)	11 (2)	17 (2)	28 (2)
Hepatobiliary disorders	4 (1)	5 (1)	5 (1)	9 (3)	9 (1)	14 (2)	23 (2)
Cardiac disorder	6 (2)	7 (2)	3 (<1)	3 (<1)	9 (1)	10 (1)	19 (1)
Ear and labyrinth disorders	3 (<1)	3 (<1)	6 (2)	5 (1)	9 (1)	8 (1)	17 (1)
Endocrine disorders	0	1 (<1)	2 (<1)	1 (<1)	2 (<1)	2 (<1)	4 (<1)
Pregnancy, puerperium and perinatal conditions	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)
Congenital, familial and genetic disorders	0	1 (<1)	2 (<1)	0	2 (<1)	1 (<1)	3 (<1)
Social circumstances	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Surgical and medical procedures	0	1 (<1)	0	1 (<1)	0	2 (<1)	2 (<1)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)

Data Source: 204861 Week 48 CSR Table 3.2; 205543 Week 48 CSR Table 3.2; GEMINI ISS/ISE Table 3.2.

a. As described in Section 2.1.1, there were 2 additional subjects with AEs in the DTG + 3TC group of 204861 meeting criteria for reporting as "Any AE"; these AEs had not been reported by the data cut-off date and were not included in the analyses due to a GCP noncompliance issue at a single study center; updated data would be as follows:
204861 DTG + 3TC column, n (%) = 278 (78) for Any AE;
POOLED DTG + 3TC column, n (%) = 545 (76) for Any AE;
POOLED Total column, n (%) = 1124 (78) for Any AE.

b. There were 2 additional subjects in the DTG + 3TC group of 204861 (Subject [redacted] and Subject [redacted]; see Section 2.1.1) with AEs from the Infections and infestations SOC that had not been reported by the data cut-off date and were not included in the analysis due to a GCP noncompliance issue at a single study center; neither subject had previously reported any other AEs from this SOC; updated data would be as follows:
204861 DTG + 3TC column, n (%) = 185 (52) for Infections and infestations;
POOLED DTG + 3TC column, n (%) = 365 (51) for Infections and infestations;
POOLED Total column, n (%) = 756 (53) for Infections and infestations.

c. There was 1 additional subject in the DTG + 3TC group of 204861 (Subject [redacted]; see Section 2.1.1) with an AE from the Skin and subcutaneous tissue disorders SOC that had not been reported by the data cut-off date and was not included in the analysis due to a GCP noncompliance issue at a single study center; the subject had not previously reported any other AEs from this SOC; updated data would be as follows:
204861 DTG + 3TC column, n (%) = 52 (15) for Skin and subcutaneous tissue disorders;
POOLED DTG + 3TC column, n (%) = 94 (13) for Skin and subcutaneous tissue disorders;
POOLED Total column, n (%) = 194 (14) for Skin and subcutaneous tissue disorders.

d. There was 1 additional subject in the DTG + TDF/FTC group of 204861 (Subject [redacted]; see Section 2.1.1) with an AE from the Metabolism and nutrition disorders SOC and an AE from the Reproductive system and breast disorders SOC that had not been reported by the data cut-off date and were not included in the analysis due to a GCP noncompliance issue at a single study center; this subject had not previously reported any other AEs from either SOC. (Of note, this subject also had an unreported event from the Infections and infestations SOC, but had previously reported another AE from the Infections and infestations SOC and therefore the data in the table already reflect reporting in this SOC for this subject.). Updated data would be as follows:
204861 DTG + TF/FTC column, n (%) = 12 (3) for Metabolism and nutrition disorders and 16 (4) for Reproductive system and breast disorders;
POOLED DTG + TF/FTC column, n (%) = 33 (5) for Metabolism and nutrition disorders and 35 (5) for Reproductive system and breast disorders;
POOLED Total column, n (%) = 87 (6) for Metabolism and nutrition disorders and 62 (4) for Reproductive system and breast disorders.

2.1.2.3. Adverse Events by Grade

For the individual studies and the pooled analysis, the majority of events reported had a maximum intensity of Grade 1 or Grade 2 for both treatment groups (Table 6). Overall, there were similar proportions of subjects reporting any Grade 2-5 AE in the DTG + 3TC and DTG + TDF/FTC groups (Table 7).

Across the studies, a total of 2 Grade 5 events (deaths) were reported, both in the DTG + 3TC group (see Section 2.1.3).

Table 6 Summary of Adverse Events by Maximum Grade for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Any AE	276 (78)[a]	295 (82)	267 (74)	284 (79)	543 (76)[a]	579 (81)	1122 (78)[a]
Grade 1	60 (17)	61 (17)	79 (22)	93 (26)	139 (19)	154 (21)	293 (20)
Grade 2	195 (55)[a]	210 (59)	161 (45)	159 (44)	356 (50)[a]	369 (51)	725 (51)[a]
Grade 3	19 (5)	22 (6)	19 (5)	29 (8)	38 (5)	51 (7)	89 (6)
Grade 4	2 (<1)	2 (<1)	6 (2)	3 (<1)	8 (1)	5 (<1)	13 (<1)
Grade 5[b]	0	0	2 (<1)	0	2 (<1)	0	2 (<1)

Data Source: 204861 Week 48 CSR Table 3.3; 205543 Week 48 CSR Table 3.3; GEMINI ISS/ISE Table 3.3.

a. As described in Section 2.1.1, there were 2 additional subjects in the DTG + 3TC group of 204861 with AEs meeting criteria for reporting as "Any AE" and "Grade 2"; these AEs had not been reported by the data cut-off date and were not included in the analyses due to a GCP noncompliance issue at a single study center; updated data would be as follows:
204861 DTG + 3TC column, n (%) = 278 (78) for Any AE and 197 (55) for Grade 2;
POOLED DTG + 3TC column, n (%) = 545 (76) for Any AE and 358 (50) for Grade 2;
POOLED Total column, n (%) = 1124 (78) for Any AE and 727 (51) for Grade 2.

b. Grade 5 (fatal) events are described in Section 2.1.3.

Table 7 Most Common (Reported in >=2% of Subjects in Either Pooled Treatment Group) Grade 2-5 Adverse Events by Overall Frequency for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Any Grade 2-5 AE	216 (61)[a]	234 (65)	188 (52)	191 (53)	404 (56)[a]	425 (59)	829 (58)[a]
Headache	22 (6)	25 (7)	12 (3)	6 (2)	34 (5)	31 (4)	65 (5)
Nasopharyngitis	15 (4)	19 (5)	9 (3)	13 (4)	24 (3)	32 (4)	56 (4)
Pharyngitis	19 (5)	12 (3)	8 (2)	13 (4)	27 (4)	25 (3)	52 (4)
Upper respiratory tract infection	10 (3)	15 (4)	15 (4)	10 (3)	25 (3)	25 (3)	50 (3)
Diarrhoea	16 (4)	17 (5)	8 (2)	4 (1)	24 (3)	21 (3)	45 (3)
Syphilis	14 (4)[b]	13 (4)	8 (2)	7 (2)	22 (3)[b]	20 (3)	42 (3)[b]
Bronchitis	15 (4)	8 (2)	0	0	21 (3)	15 (2)	36 (3)
Influenza	13 (4)	7 (2)	4 (1)	8 (2)	17 (2)	15 (2)	32 (2)
Back pain	11 (3)	12 (3)	0	0	17 (2)	14 (2)	31 (2)
Insomnia	6 (2)	15 (4)	0	0	9 (1)	18 (3)	27 (2)
Influenza like illness	9 (3)	7 (2)	0	0	15 (2)	9 (1)	24 (2)
Sinusitis	9 (3)	5 (1)	0	0	15 (2)	7 (<1)	22 (2)

Data Source: 204861 Week 48 CSR Table 3.7; 205543 Week 48 CSR Table 3.3, Table 3.7; GEMINI ISS/ISE Table 3.7.

a. As described in Section 2.1.1, there were 2 additional subjects in the DTG + 3TC group of 204861 with AEs meeting criteria for reporting as "Any Grade 2 to 5 AE"; these AEs had not been reported by the data cut-off date and were not included in the analyses due to a GCP noncompliance issue at a single study center; updated data would be as follows:
204861 DTG + 3TC column, n (%) = 218 (61) for Any Grade 2 to 5 AE;
POOLED DTG + 3TC column, n (%) = 406 (57) for Any Grade 2 to 5 AE;
POOLED Total column, n (%) = 831 (58) for Any Grade 2 to 5 AE.

b. As described in Section 2.1.1, an additional AE of syphilis (Grade 2) was reported in the DTG + 3TC group of 204861; this AE had not been reported by the data cut-off date and was not included in the analyses due to a GCP noncompliance issue at a single study center; updated data would be as follows:
204861 DTG + 3TC column, n (%) = 15 (4) for Syphilis;
POOLED DTG + 3TC column, n (%) = 23 (3) for Syphilis;
POOLED Total column, n (%) = 43 (3) for Syphilis.

In the DTG + 3TC group, a total of 9 Grade 4 events were reported in 8 subjects, with 1 related to study drug. In the DTG + TDF/FTC group, a total of 6 Grade 4 events were reported in 5 subjects, with 2 related to study drug (both in the same subject) (Table 8).

Table 8 Listing of Subjects Who Experienced a Grade 4 AE in 204861 or 205543 (Safety Population)

Subject Number	Grade 4 AE	Serious	Led to Withdrawal	Related to Study Drug	Resolved
DTG + 3TC Group					
[redacted]	Acute Hepatitis C	Yes	Yes	No	Yes
	Hepatitis A	Yes	Yes	No	Yes
[redacted]	Suicide attempt[a]	Yes	Yes	No	Yes
[redacted]	Lipids increased	No	No	No	No
[redacted]	Hepatitis A	Yes	No	No	Yes
[redacted]	Suicide attempt[a]	Yes	No	No	Yes
[redacted]	Lipase increased	No	No	Yes	Yes
[redacted]	Suicide attempt[a]	Yes	No	No	Yes
[redacted]	Suicide attempt[a]	Yes	No	No	Yes
DTG + TDF/FTC Group					
[redacted]	Hepatitis A	Yes	No	No	Yes
[redacted]	Hypertriglyceridemia	No	No	No	Yes (resolving)
[redacted]	Penetrating abdominal trauma	Yes	No	No	Yes
[redacted]	Overdose (paracetamol and tramadol)	No	Yes	Yes	Yes
	Suicide attempt[a]	Yes	Yes	Yes	Yes
[redacted]	Hepatitis A	No	No	No	Yes

Data Source: 204861 Week 48 CSR Listing 15, 205543 Week 48 CSR Listing 15.
a. See Section 2.1.6.3.

2.1.2.4. Drug-Related Adverse Events

For the individual studies and the pooled analysis, most drug-related AEs had a maximum intensity of Grade 1 or Grade 2 for both treatment groups (Table 9).

The most frequently reported drug-related AEs are shown in Table 10. A lower proportion of subjects in the DTG + 3TC group compared with the DTG + TDF/FTC group reported at least 1 drug-related AE, with this difference driven primarily by larger numbers of subjects reporting drug-related Grade 1 events, notably nausea, in the DTG + TDF/FTC group.

Table 11 summarizes drug-related events with a maximum intensity of Grade 2 to 5; all events with a maximum intensity of Grade 3 or higher are footnoted in the table.

Table 9 Summary of Drug-Related Adverse Events by Maximum Grade for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Any drug-related AE	71 (20)	94 (26)	55 (15)	75 (21)	126 (18)	169 (24)	295 (21)
Grade 1	50 (14)	69 (19)	34 (9)	53 (15)	84 (12)	122 (17)	206 (14)
Grade 2	18 (5)	22 (6)	17 (5)	17 (5)	35 (5)	39 (5)	74 (5)
Grade 3	3 (<1)	3 (<1)	3 (<1)	4 (1)	6 (<1)	7 (<1)	13 (<1)
Grade 4	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Grade 5	0	0	0	0	0	0	0

Data Source: 204861 Week 48 CSR Table 3.5; 205543 Week 48 CSR Table 3.5; GEMINI ISS/ISE Table 3.5.

Table 10 Most Common (Reported in >=1% of Subjects in Either Pooled Treatment Group) Drug-Related Adverse Events by Preferred Term for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Any drug-related event	71 (20)	94 (26)	55 (15)	75 (21)	126 (18)	169 (24)	295 (21)
Nausea	8 (2)	23 (6)	6 (2)	16 (4)	14 (2)	39 (5)	53 (4)
Headache	14 (4)	19 (5)	7 (2)	11 (3)	21 (3)	30 (4)	51 (4)
Diarrhoea	6 (2)	14 (4)	8 (2)	5 (1)	14 (2)	19 (3)	33 (2)
Insomnia	7 (2)	12 (3)	6 (2)	6 (2)	13 (2)	18 (3)	31 (2)
Dizziness	5 (1)	6 (2)	3 (<1)	7 (2)	8 (1)	13 (2)	21 (1)
Fatigue	6 (2)	3 (<1)	4 (1)	3 (<1)	10 (1)	6 (<1)	16 (1)
Somnolence	7 (2)	5 (1)	1 (<1)	2 (<1)	8 (1)	7 (<1)	15 (1)
Anxiety	3 (<1)	1 (<1)	5 (1)	4 (1)	8 (1)	5 (<1)	13 (<1)

Data Source: 204861 Week 48 CSR Table 3.4; 205543 Week 48 CSR Table 3.4; GEMINI ISS/ISE Table 3.4.

Table 11 Summary of Drug-Related Grade 2-5 Adverse Events for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Any drug-related Grade 2-5 event	21 (6)	25 (7)	21 (6)	22 (6)	42 (6)	47 (7)	89 (6)
Headache	4 (1)	7 (2)	4 (1)	1 (<1)	8 (1)	8 (1)	16 (1)
Insomnia	0	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	8 (<1)
Nausea	0	3 (<1)	2 (<1)	3 (<1)	2 (<1)	6 (<1)	8 (<1)
Diarrhoea	2 (<1)	4 (1)	1 (<1)	0	3 (<1)	4 (<1)	7 (<1)
Sleep disorder	3 (<1)	2 (<1)	0	2 (<1)	3 (<1)	4 (<1)	7 (<1)
Anxiety	1 (<1)	0	1 (<1)[a]	2 (<1)	2 (<1)	2 (<1)	4 (<1)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Suicidal ideation	2 (<1)[b]	0	1 (<1)[c]	1 (<1)[d]	3 (<1)	1 (<1)	4 (<1)
Creatinine renal clearance decreased	0	1 (<1)[e]	0	2 (<1)[f]	0	3 (<1)	3 (<1)
Fatigue	0	2 (<1)	1 (<1)	0	1 (<1)	2 (<1)	3 (<1)
Depression	0	0	1 (<1)[a]	1 (<1)[g]	1 (<1)	1 (<1)	2 (<1)
Dyslipidaemia	0	0	2 (<1)	0	2 (<1)	0	2 (<1)
Dyspepsia	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)	2 (<1)
Gastritis	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Gastrooesophageal reflux disease	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Myopathy	0	0	2 (<1)[h]	0	2 (<1)	0	2 (<1)
Paraesthesia	0	2 (<1)	0	0	0	2 (<1)	2 (<1)
Pruritus	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Renal impairment	0	2 (<1)[i]	0	0	0	2 (<1)	2 (<1)
Vitamin D deficiency	2 (<1)	0	0	0	2 (<1)	0	2 (<1)
Abdominal pain	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Abnormal dreams	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Alopecia	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Anogenital warts	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Anxiety disorder due to a general medical condition	0	0	1 (<1)	0	1 (<1)	0	1 (<1)
Arthralgia	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Biliary colic	0	0	0	1 (<1)[j]	0	1 (<1)	1 (<1)
Blood creatinine increased	0	0	1 (<1)	0	1 (<1)	0	1 (<1)
Bronchitis	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Cholelithiasis	0	0	0	1 (<1)[j]	0	1 (<1)	1 (<1)
Confusional state	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Constipation	0	0	1 (<1)	0	1 (<1)	0	1 (<1)
Dermatitis acneiform	0	1 (<1)	0	0	0	1 (<1)	1 (<1)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Dizziness	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Eyelid oedema	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Faeces soft	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Flushing	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Glomerular filtration rate decreased	0	0	0	1 (<1)[k]	0	1 (<1)	1 (<1)
Glucose tolerance impaired	0	0	1 (<1)	0	1 (<1)	0	1 (<1)
Hepatic steatosis	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Herpes zoster	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Hypertension	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Impaired fasting glucose	0	0	1 (<1)	0	1 (<1)	0	1 (<1)
Irritable bowel syndrome	0	0	1 (<1)	0	1 (<1)	0	1 (<1)
Lipase increased	0	0	1 (<1)[l]	0	1 (<1)	0	1 (<1)
Myalgia	0	0	1 (<1)	0	1 (<1)	0	1 (<1)
Nightmare	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Osteoporosis	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Overdose	0	0	0	1 (<1)[g]	0	1 (<1)	1 (<1)
Pain in extremity	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Pharyngeal paraesthesia	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Pruritus generalised	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Psychotic disorder	1 (<1)[m]	0	0	0	1 (<1)	0	1 (<1)
Rash	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Respiratory tract infection viral	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Rhabdomyolysis	0	1 (<1)[n]	0	0	0	1 (<1)	1 (<1)
Somnolence	0	1 (<1)	0	0	0	1 (<1)	1 (<1)
Substance-induced psychotic disorder	1 (<1)[o]	0	0	0	1 (<1)	0	1 (<1)
Suicide attempt	0	0	0	1 (<1)[g]	0	1 (<1)	1 (<1)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Thrombocytopenia	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Urticaria	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Vomiting	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
Weight increased	0	0	0	1 (<1)	0	1 (<1)	1 (<1)

Data Source:
204861 Week 48 CSR Table 3.5, Table 3.78, Listing 16;
205543 Week 48 CSR Table 3.5, Table 3.78, Listing 16;
GEMINI ISS/ISE Table 3.5.

Note: All drug-related events reported as Grade 3, 4, or 5 are footnoted below; all other events listed were Grade 2.

a. Grade 3 (for both) anxiety and depression (Subject [redacted]) (see Section 2.1.6.3).
b. One event was Grade 2, the other event was Grade 3 suicidal ideation (Subject [redacted]) (see Section 2.1.6.3).
c. Grade 3 suicidal ideation (Subject [redacted]) (see Section 2.1.4.1).
d. Grade 3 suicidal ideation (Subject [redacted]) (see Section 2.1.4.1).
e. Grade 3 creatinine renal clearance decreased (Subject [redacted]) (see Section 3.3).
f. Grade 3 creatinine renal clearance decreased (Subject [redacted]) (see Section 3.3).
g. Grade 3 depression, Grade 4 overdose, and Grade 4 suicide attempt all in the same subject (Subject [redacted]) (see Section 2.1.6.3).
h. Grade 3 myopathy (Subject [redacted]) (see Section 2.1.3).
i. One event was Grade 2, the other event was Grade 3 renal impairment (Subject [redacted]) (see Section 3.3).
j. Grade 3 (for both) biliary colic and cholelithiasis in the same subject (Subject [redacted]) (see Section 2.1.4.1).
k. Grade 3 glomerular filtration rate decreased (Subject [redacted]) (see Section 3.3).
l. Grade 4 lipase increased (Subject [redacted]) (see Section 2.1.2.3).
m. Grade 3 psychotic disorder (Subject [redacted]) (see Section 2.1.4.1).
n. Grade 3 rhabdomyolysis (Subject [redacted]) (see Section 2.1.4.1).
o. Grade 3 substance-induced psychotic disorder (Subject [redacted]) (see Section 2.1.4.1).

2.1.2.5. Labelling and Adverse Drug Reactions

The adverse reactions section of the DTG/3TC company data sheet and prescribing information will describe all the events reported from clinical trial or post-marketing surveillance that have been assessed as being at least possibly causally related to either of the individual components (DTG or 3TC). Adverse reactions will be reported regardless of whether they were observed in the GEMINI (204861/205543) clinical trial program, as assessment of ADRs for the individual components were based on a larger pool of data (integrated data from several studies or extensive post-marketing experience). Furthermore, events reported with a lower frequency in the GEMINI studies will retain the frequency category from the individual component label. An analysis of pooled data for DTG + 3TC has also been conducted to identify any differences between the adverse reactions or their frequencies observed in the GEMINI studies compared to the known adverse reaction profiles for the individual components when each was administered with other antiretroviral agents.

Adverse events in the GEMINI studies considered to be drug-related by the investigator and observed at a frequency of ≥1% across the DTG + 3TC group were headache, dizziness, somnolence, diarrhea, nausea, fatigue, insomnia, and anxiety. Somnolence was the only common drug-related event observed with the combination that is not already listed in the prescriber information for the individual components. The adverse reaction of somnolence was noted in the DTG/ABC/3TC studies and was added to the DTG/ABC/3TC product information with a frequency of "common". The proposed DTG/3TC FDC prescribing information will also report somnolence as a common ADR.

Three adverse events were noted with a slightly higher frequency in the GEMINI studies compared to the individual component prescribing information: weight increased in 9/716 subjects compared with frequency category of "uncommon"; peripheral neuropathy and paraesthesia in 3/716 subjects each, designated as "very rare" for 3TC. Seven of the 9 cases of weight increased were not considered to be related to study drug and none of the cases of peripheral neuropathy or paraesthesia were considered drug-related. Therefore, no change to the frequency categories are proposed from that originally assigned to the individual component.

The event of suicidal ideation was observed in 1% of subjects on DTG + 3TC. Most were not considered to be drug-related and were generally explained by other medical or psychosocial factors; however, due to the serious nature of this event, the company proposes changing the frequency category from "uncommon", assigned in the DTG and DTG/ABC/3TC labels, to "common" for the DTG/3TC FDC label.

Grade 3 to 4 laboratory toxicities observed at ≥1% in the DTG + 3TC pooled analysis were identified and compared to the product labels for the individual components. The common Grade 3 to 4 laboratory toxicities of ALT, AST, CK, and GFR observed for the GEMINI studies were consistent with observations from the pivotal studies for DTG or 3TC and are all considered adequately labelled. A 2% incidence of Grade 3 to 4 direct bilirubin was observed in the pooled DTG + 3TC group though total bilirubin Grade 3 to 4 elevations were <1%. The slight increase in direct bilirubin toxicity is considered a consequence of the relatively high number of subjects with acute Hepatitis A which was

related to a concurrent Hepatitis A epidemic in several countries participating in these studies (see Section 3.2). Grade 3 to 4 triglyceride and LDL elevations each occurred in 1% of subjects on DTG + 3TC and most likely represents the known changes in lipids and glucose that may occur as a result of antiretroviral treatment; these changes are therefore considered adequately labelled in the Warnings and Precautions text relating to lipid changes on therapy.

2.1.3. Deaths

Across the two studies and up to the data cut-off date for the Week 48 analysis, a total of 2 subjects died, both in the DTG + 3TC arm of 205543 (Data Source: 204861 Week 48 CSR Listing 17, 205543 Week48 CSR Listing 17). Neither fatality was related to study drug:

- **Subject [redacted] (DTG + 3TC group)** was age 30 to 40 years and was withdrawn on Study Day 206 due to a fatal adverse event. The subject reported left axillary pain and was admitted to hospital on Study Day 158. Ultrasound, then CT, confirmed an axillary mass. Fine needle aspiration of the mass showed reactive lymphadenitis only. Subsequently, the subject started complaining of myopathy. Serum CK and LDH were reported as mildly elevated. The subject developed severe abdominal pain starting on Study Day 189, which became severe requiring hospitalization. A CT abdomen revealed hepatosplenomegaly, a lymph node mass in the lower curvature of the stomach and splenic, pancreatic tail and suprarenal lesions, and nephrolithiasis. The subject underwent an esophagogastroduodenal endoscopy, which showed gastric fundal and duodenal ulcers. Lab findings were notable for a hemoglobin of 12.7 g/dL during admission that fell to 8.4 g/dL 4 days later. There was no melaena or obvious GI blood loss. The subject became hypotensive, went into cardiac arrest, and died. The reason for the cardiac arrest is unclear, but considerations included hypovolemia due to GI bleeding or septic shock. An autopsy was not performed. The final biopsy result of the left axillary mass was Burkitt's lymphoma, and the overall assessment was that the cause of death was Burkitt's lymphoma. The event was not related to study drug.
- **Subject [redacted] (DTG + 3TC group)** was age 40 to 50 years and experienced a fatal event of acute myocardial infarction on Study Day 357. Concurrent medical conditions included possible drug abuse by the subject in the week prior to the death. The subject visited the emergency room with chest pain, had a cardiac arrest and died. The subject was a smoker and autopsy found acute myocardial infarction of the posterior wall of the left ventricle with additional findings suggestive of untreated hypertension. The investigator did not consider the event related to study drug.

Case narratives for these two fatal events are provided in 205543 Week 48 CSR Section 13.

2.1.4. Other Serious Adverse Events

For both studies and in the total pooled group, the incidence of subjects reporting any SAE was similar between treatment groups (Table 12). All SAE preferred terms were reported in <1% of subjects in any pooled group.

Of 115 SAEs reported in 105 subjects across the 2 studies, there were 8 SAEs (all non-fatal) that were considered drug-related (Data Source: GEMINI ISS/ISE Table 3.18), which are described in Section 2.1.4.1.

Full narratives for all SAEs are presented in 204861 Week 48 CSR Section 13 and 205543 Week 48 CSR Section 13.

Table 12 Summary of Serious Adverse Events (Reported in >=2 Subjects in the Total Pooled Group) for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED		
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=358 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)	Total N=1433 n (%)
Any serious adverse event	21 (6)	22 (6)	29 (8)	33 (9)	50 (7)	55 (8)	105 (7)
Hepatitis A	3 (<1)	4 (1)	3 (<1)	3 (<1)	6 (<1)	7 (<1)	13 (<1)
Anogenital warts	1 (<1)	0	2 (<1)	3 (<1)	3 (<1)	3 (<1)	6 (<1)
Suicide attempt	1 (<1)	0	3 (<1)	1 (<1)[a]	4 (<1)	1 (<1)	5 (<1)
Pneumonia	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)	4 (<1)
Acute hepatitis C	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)
Cholecystitis acute	0	1 (<1)	0	2 (<1)	0	3 (<1)	3 (<1)
Suicidal ideation	0	0	1 (<1)[a]	2 (<1)[a]	1 (<1)	2 (<1)	3 (<1)
Abdominal pain	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
Anal abscess	0	1 (<1)	0	1 (<1)	0	2 (<1)	2 (<1)
Appendicitis	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)	2 (<1)
Asthma	0	1 (<1)	0	1 (<1)	0	2 (<1)	2 (<1)
B cell lymphoma	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)
Cholelithiasis	0	1 (<1)	0	1 (<1)[a]	0	2 (<1)	2 (<1)
Head injury	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)	2 (<1)
Sciatica	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)

Data Source: 204861 Week 48 CSR Table 3.16; 205543 Week 48 CSR Table 3.16; GEMINI ISS/ISE Table 3.16.

a. Considered drug-related (see Section 2.1.4.1); 2 of the 3 suicidal ideation events were considered drug-related (1 in each group).

Two SAEs (in 1 subject each) that were not related to study drug and are not elsewhere discussed are noted below as they represent potential sentinel events:

- **Subject [redacted] (Generalised tonic-clonic seizure; DTG + 3TC group)** was age 20 to 30 years, with a history of grand mal seizure who was non-compliant with lamotrigine. The subject experienced a Grade 2 event of generalized tonic-clonic seizure on Study Day 58. There was no history of alcohol or illicit drug use at the time of the event. The investigator considered the event unrelated to study drug, it did not lead to withdrawal, and the event resolved.
- **Subject [redacted] (Seizure; DTG + TDF/FTC group) (**see also Section 2.1.6.3 for a description of an SAE of intentional overdose in this subject**)** was age 20 to 30 years and experienced a Grade 2 seizure reported on Study Day 269. The subject had fallen the previous week while drinking alcohol, and had also stopped taking concurrent medications of oxazepam and amphetamine / dextroamphetamine. The seizure was considered due to a concussion and possibly also due to withdrawal of oxazepam and amphetamine / dextroamphetamine. The investigator considered the event unrelated to study drug, it did not lead to withdrawal, and the event resolved.

2.1.4.1. Drug-Related SAEs

As summarized in Table 3, for both studies, the incidence of subjects reporting any drug-related SAE was comparable between treatment groups and across the 2 studies (<1% of subjects in any individual study group or pooled group).

There were no drug-related fatal SAEs (Data Source: GEMINI ISS/ISE Table 3.15).

Eight subjects (DTG + 3TC 4; DTG + TDF/FTC 4) experienced a drug-related non-fatal SAE (Data Source: GEMINI ISS/ISE Table 3.17). Brief descriptions are provided below; additional details are provided as full narratives in 204861 Week 48 CSR Section 13 and 205543 Week 48 CSR Section 13.

- **Subject [redacted] (Substance-induced psychotic disorder; DTG + 3TC group)** was age 20 to 30 years and reported Grade 3 substance-induced psychotic disorder starting on Study Day 1. The subject developed visual hallucinations and paranoid ideation, was admitted to an ER, and was diagnosed with toxic psychosis. Methamphetamine hydrochloride (crystal meth) was a co-suspect product, and it is unknown whether the subject was ingesting other drugs or alcohol. The subject had a past history of crystal meth use. The subject self-discontinued study treatment because of the subject's own concerns about an adverse reaction to crystal meth that might have been triggered by study treatment. The treating physician could not exclude a contributory role of study treatment. The subject had a relapse of crystal meth use and was withdrawn from the study.

- **Subject [redacted] (Psychotic disorder; DTG + 3TC group)** was age 30 to 40 years and reported a Grade 3 event of psychotic disorder on Study Day 353. The subject had a history of psychiatric disorder (not further specified) and depression; current medical conditions at Baseline included insomnia, generalized anxiety disorder, and low mood. The subject experienced a worsening of depression on study, including agitation and psychosis; the subject presented at the clinic in an extremely agitated state and was hyperventilating. The subject reported often hearing voices, and indicated no illicit drug or alcohol use. The subject was reported to have been given "strong" medication by the psychiatric team. The investigator considered there to be a reasonable possibility the psychosis was related to study drug. The subject was withdrawn from the study. The event outcome was considered not recovered.
- **Subject [redacted] (Suicidal ideation; DTG + 3TC group)** was age 30 to 40 years and reported Grade 3 (i.e., with a plan) suicidal ideation on Study Day 137. There was no relevant past history reported at study entry, but questioning at the time of the event revealed that the subject had a history of suicidal thoughts prior to the study, which had recently increased, triggered by current psychosocial stressors ([redacted]). The subject was reportedly also still coping with the acceptance of [HIV] diagnosis. The subject reported not feeling well and having thoughts of jumping in front of a car. The subject was contacted a few hours later and reported feeling better since talking to a friend. The subject did not have current use of illicit drugs or alcohol. The investigator could not rule out a role for DTG in the event, and the event was therefore considered drug-related. The subject was withdrawn from the study. The event resolved.
- **Subject [redacted] (Hepatotoxicity; DTG + 3TC group)** was age 20 to 30 years and reported an event of Grade 1 hepatotoxicity on Study Day 60; the event was associated with a possible dolutegravir-related DILI as no clear alternative cause could be demonstrated. The subject was withdrawn from the study. Details of this case are summarized in Section 3.2.
- **Subject [redacted] (Rhabdomyolysis; DTG + TDF/FTC group)** was age 50 to 60 years and developed worsening arthralgias and new onset Grade 3 myalgias on Study Day 13. The subject had Grade 1 arthralgias prior to study entry. Local labs performed on Study Day 20 revealed elevated CPK (11732 u/L; > 100xULN), AST (260 u/L; 9.6xULN), and ALT (62 u/L; 2.4xULN). There was no renal impairment or hematuria. Study treatment was discontinued on Study Day 20, and symptoms resolved by Study Day 27. The subject was withdrawn from the study on Study Day 28. Central laboratory results on Study Day 27 showed mildly elevated CPK (267 u/L) and normal AST and ALT. The subject did not have any history of fevers, upper respiratory tract infection symptoms, or autoimmune or thyroid disorders. The subject did not use alcohol or drugs. There was no history of unusual exercise, trauma, or seizure. The subject was not hospitalized; the investigator categorized this as a serious event due to the medical significance of the event. The outcome of the event was resolved. The clinical details provided for this case would be more consistent with a myolysis occurring without renal impairment; although rhabdomyolysis lacks a clear definition, a degree of renal impairment due to

myoglobinuria may be expected in such cases. Of note, rhabdomyolysis has been reported in the post-marketing phase for the TDF/FTC FDC, referenced in the USPI.

- **Subject [redacted] (Cholelithiasis; DTG + TDF/FTC group)** was age 30 to 40 years and reported Grade 3 cholelithiasis on Study Day 98. The subject presented on 2 occasions with biliary colic. Abdominal ultrasound was performed with the second occurrence, which showed cholelithiasis; the subject had a cholecystectomy on the same day and was released the next day. Because there was no family history of cholelithiasis or biliary colic and subject had not previously undergone abdominal imaging, the investigator could not eliminate a relationship to study drug. The subject continued on study. The event resolved.
- **Subject [redacted] (Suicide attempt; DTG + TDF/FTC group)** was age 30 to 40 years and reported Grade 4 suicide attempt on Study Day 512 that was considered drug related. The subject with withdrawn from the study. This event is described in Section 2.1.6.3 along with other relevant events for this subject (non-serious, drug-related events of depression and overdose; also see Table 13).
- **Subject [redacted] (Suicidal ideation; DTG + TDF/FTC group)** was age 20 to 30 years and reported Grade 3 suicidal ideation on Study Day 111; the subject ingested [redacted] and experienced suicidal ideations. The subject had a history of previous suicide attempt ([redacted], drug overdose) that required hospitalization; the subject had been suffering from depression since at least that time and had received intermittent psychological assistance and anti-depression medications, both were reported as discontinued in the year prior to the current event. At study entry, the subject had current depression and mood disorder, and paroxetine was noted as a concurrent medication during the first two months of study. After 2 weeks of psychiatric follow-up, the subject was hospitalized due to a persistent and severe depression. The investigator could not eliminate a relationship to study drug. The subject was withdrawn from the study. The event outcome was resolved.

2.1.5. Other Significant Adverse Events

2.1.5.1. Adverse Events Leading to Withdrawal

AEs leading to discontinuation were most commonly from the Psychiatric disorders or Infections and infestations SOCs, and the proportion of subjects with AEs leading to discontinuation were balanced between treatment groups (Data Source: GEMINI ISS/ISE Table 3.19.) Across the 2 studies, up to the data cut-off date for the Week 48 analysis, a small number of subjects in either treatment group experienced an AE leading to withdrawal/permanent discontinuation of study drug (either through investigator or subject discretion or through meeting liver/renal stopping criteria). All subjects who withdrew due to an AE (DTG + 3TC: 15 [2%]; DTG +TDF/FTC: 16 [2%]) are listed in Table 13.

Additionally, in 2 cases, subjects were withdrawn after meeting liver stopping criteria (Subject [redacted]; see Table 17) or renal stopping criteria (Subject [redacted]; see Section 3.3); since in both cases the laboratory abnormalities were

not deemed clinically significant by the investigator, the primary reason for withdrawal was not considered to be an AE (i.e., they do not appear in Table 13).

Table 13 Listing of Subjects Who Experienced AEs Leading to Withdrawal/Permanent Discontinuation of Study Treatment in 204861 or 205543 (Safety Population)

Subject ID	AE Preferred Term(s)	Onset (Study Day)	Grade	Serious AE (Yes or No)	Drug Related (Yes or No)
Subjects Randomized to DTG + 3TC					
[redacted]	Hepatitis A	164	2	No	No
[redacted]	Acute hepatitis C	31	4	Yes	No
	Hepatitis A	31	4	Yes	No
[redacted]	Substance-induced psychotic disorder	1	3	Yes	Yes
[redacted]	Sleep disorder	1	2	No	Yes
[redacted]	Suicide attempt	427	4	Yes	No
[redacted]	Pulmonary tuberculosis	169	2	No	No
[redacted]	Insomnia	353	2	No	No
	Psychotic disorder	353	3	Yes	Yes
[redacted]	Burkitt's lymphoma[a]	158	5	Yes	No
[redacted]	Suicidal ideation	137	3	Yes	Yes
[redacted]	Acute myocardial infarction[a]	357	5	Yes	No
[redacted]	Anxiety	312	3	No	Yes
	Depression	312	3	No	Yes
[redacted]	Hepatitis alcoholic	337	3	No	No
[redacted]	Hepatotoxicity	60	1	Yes	Yes
[redacted]	Tuberculous pleurisy	131	2	Yes	No
[redacted]	Renal impairment	85	2	No	No
Subjects Randomized to DTG + TDF/FTC					
[redacted]	Osteoporosis	30	2	No	Yes
[redacted]	Creatinine renal clearance decreased	29	3	No	Yes
[redacted]	B-cell lymphoma	28	3	Yes	No
[redacted]	Hepatitis C	172	3	No	No
[redacted]	Drug-induced liver injury[b]	114	3	No	No
[redacted]	Renal impairment	58	2	No	Yes
[redacted]	Renal impairment	27	3	No	Yes
[redacted]	Rhabdomyolysis	13	3	Yes	Yes
[redacted]	Alcoholic psychosis	101	2	Yes	No
[redacted]	Depression	490	3	No	Yes
	Overdose	512	4	No	Yes
	Suicide attempt	512	4	Yes	Yes
[redacted]	Hepatitis A	54	2	Yes	No
[redacted]	Anxiety	135	2	No	Yes
[redacted]	Non-Hodgkin's Lymphoma	62	3	Yes	No
[redacted]	Hepatitis alcoholic	106	3	No	No

Subject ID	AE Preferred Term(s)	Onset (Study Day)	Grade	Serious AE (Yes or No)	Drug Related (Yes or No)
[redacted]	Suicidal ideation	111	3	Yes	Yes
[redacted]	Glomerular filtration rate decreased	322	3	No	Yes

Data Source: 204861 Week 48 CSR Listing 20; 205543 Week 48 CSR Listing 20.
a. Subject died (see Section 2.1.3 for details of the 2 fatal events).
b. Verbatim text: toxic hepatitis caused by drug abuse.

2.1.6. Analysis of Adverse Events by Organ System or Syndrome

AESIs have been determined for DTG + 3TC based on: non-clinical and/or clinical safety data for DTG and 3TC; labelling and/or regulatory authority interest for approved integrase inhibitors; and/or regulatory authority requirements.

Liver chemistries and hepatobiliary adverse events are discussed in Section 3.2.

Renal-related adverse events, clinical chemistry, and urinalysis data are discussed in Section 3.3

2.1.6.1. Drug Hypersensitivity

Drug hypersensitivity-related AESIs were identified by searching a pre-defined list of events coded to the following preferred terms:

- Anaphylactic reaction;
- Anaphylactic shock;
- Anaphylactoid reaction;
- Anaphylactoid shock;
- Anaphylaxis treatment;
- Drug hypersensitivity;
- Hypersensitivity.

Across the studies, there were very few reports of hypersensitivity-related AESI preferred terms (Data Source: GEMINI ISS/ISE Table 3.24). Events were reported in 4 (<1%) subjects in the DTG + 3TC group and 1 (<1%) subject in the DTG + TDF/FTC group. Verbatim text for 3 of the events in the DTG + 3TC group were "nonspecific allergic reaction", "allergy to sulfa", and "environmental allergy", and the fourth event was Grade 3 drug hypersensitivity to a concomitant respiratory medication. The verbatim text for the event in the DTG + TDF/FTC group was "worsen allergic reaction" (Data Source: 204861 Week 48 CSR Listing 15, 205543 Week 48 CSR Listing 15).

Other than the Grade 3 drug hypersensitivity to a concomitant respiratory medication, all other events were Grade 1 or 2. None of the events recurred, were serious, were considered study drug-related, or led to withdrawal.

Median time to onset for the 4 events in the DTG + 3TC group was 237.0 days (range: 47 to 324 days). Time to onset of the single event in the DTG + TDF/FTC group was 241 days (Data Source: GEMINI ISS/ISE Table 3.25)

2.1.6.2. Rash

To evaluate for rash-related AESIs (distinct from "rash" as a single preferred term), events related to a rash were identified by searching a pre-defined list of events coded to the following preferred terms:

- Dermatitis;
- Dermatitis allergic;
- Genital rash;
- Photosensitivity reaction;
- Rash;
- Rash erythematous;
- Rash macular;
- Rash maculo-papular;
- Rash papular;
- Rash pruritic;
- Rash pustular;
- Urticaria;
- Urticaria chronic.

The number of subjects experiencing a rash AESI term was low and consistent with current labelling.

In both studies and in the pooled analysis, the reporting rate for any rash AESI was similar between the treatment groups (DTG + 3TC 31 [4%] subjects reported 35 events; DTG + TDF/FTC 44 [6%] subjects reported 51 events) (Data Source: GEMINI ISS/ISE Table 3.21). All events were Grade 1 or 2. Most of the events were not related to study drug; 2/31 subjects in the DTG + 3TC group and 7/44 subjects in the DTG + TDF/FTC group had events considered drug-related. No subjects had an event that led to withdrawal.

The time to onset was similar between the treatment groups, with 77% of subjects in the DTG + 3TC group and 80% of subjects in the DTG + TDF/FTC group had a time to onset >35 days after starting study drug. The median time to onset for the DTG + 3TC group was 113.0 days (range: 1 to 452 days) and for the DTG + TDF/FTC group was 111.0 days (range: 1 to 419 days) (Data Source: GEMINI ISS/ISE Table 3.22).

Severe (Grade 3 or 4) or Serious Rash

No rash-related events (using preferred terms as listed above) were Grade 3 or Grade 4 and none were considered serious (Data Source: GEMINI ISS/ISE Table 3.21). There were no reports of Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis or erythema multiforme.

2.1.6.3. Psychiatric Disorders

Reporting rates of AEs from the Psychiatric disorders SOC were consistent between the treatment groups (DTG + 3TC: 95 [13%], DTG + TDF/FTC: 105 [15%]) (Data Source: GEMINI ISS/ISE Table 3.2). Insomnia (5%), anxiety (2%), depression (2%), and suicidal ideation (1%; see Section 2.1.2.5) were the most commonly reported AEs from this SOC overall, with no notable differences between the 2 treatment groups. All other events were reported in <1% of subjects in the total pooled population.

The majority of the events reported from the Psychiatric disorders SOC across the treatment groups had a maximum intensity of Grade 1 or Grade 2 (Data Source: GEMINI ISS/ISE Table 3.3). Thirteen (<1%) subjects reported events with a maximum intensity of Grade 3 (DTG + 3TC: 8, DTG + TDF/FTC: 5), 5 subjects (<1%) reported events with a maximum intensity of Grade 4 (DTG + 3TC: 4; DTG + TDF/FTC: 1), and no Grade 5 events (deaths) were reported from the Psychiatric disorders SOC.

Similar proportions of subjects in each treatment groups reported drug-related AEs from the Psychiatric disorders SOC (DTG + 3TC: 36 [5%]; DTG + TDF/FTC 37 [5%]) (Data Source: GEMINI ISS/ISE Table 3.4). The most common drug-related event was insomnia (2%); all other drug-related events occurred in <1% of subjects. In both treatment groups, the majority of subjects with events from this SOC reported drug-related events that were Grade 1 (Data Source: GEMINI ISS/ISE Table 3.5).

Six subjects (DTG + 3TC: 5; DTG + TDF/FTC: 1) reported drug-related events with a Grade 3 maximum intensity and 1 subject (DTG + TDF/FTC group) reported a Grade 4 drug-related event from this SOC:

- **Subject [redacted] (Grade 3 Substance-induced psychotic disorder; DTG + 3TC group)**; see Section 2.1.4.1 for details.
- **Subject [redacted] (Grade 3 Psychotic disorder; DTG + 3TC group)**; see Section 2.1.4.1 for details.
- **Subject [redacted] (Grade 3 Suicidal ideation; DTG + 3TC group)** was age 20 to 30 years and reported Grade 3 suicidal ideation on Study Day 80. At Baseline, the subject had current conditions of generalized anxiety disorder and panic attack, and was on escitalopram and lorazepam. The subject reported via the Baseline eC-SSRS evaluation, 2 previous (lifetime) suicide attempts as well as suicidal ideation in the 2 months prior to study start. The latter triggered a positive alert, which the investigator, after evaluating the subject, considered as a false positive. The subject developed worsening of anxiety on Study Day 4, which did not resolve. At Study Day 80, the subject reported suicidal ideation once per week but no attempts. The subject had psychosocial stressors and reported that ideation improved after stopping study drug on Day 114 (the reason for stopping on Day 114 is not known). The subject was lost to follow-up at Study Day 139. The event was considered related to study drug and was not resolved.

- **Subject [redacted] (Grade 3 Anxiety and Depression; DTG + 3TC group)** was age 30 to 40 years, and reported Grade 3 drug-related events of anxiety and depression, both on Study Day 312. The subject had a medical history of anxiety and depression, which failed to settle with standard psychological interventions. The events led to withdrawal.
- **Subject [redacted] (Grade 3 Suicidal ideation; DTG + 3TC group)** reported Grade 3 drug-related suicidal ideation. There was no relevant past history reported at study entry, but questioning at the time of the event revealed that the subject had a history of suicidal thoughts prior to the study. See Section 2.1.4.1 for additional details.
- **Subject [redacted] (Grade 3 Suicidal ideation; DTG + TDF/FTC group)** reported Grade 3 drug-related suicidal ideation. The subject had a history of previous suicide attempt and depression. See Section 2.1.4.1 for additional details.
- **Subject [redacted] (Grade 3 Depression; Grade 4 Suicide Attempt; DTG + TDF/FTC group)** reported Grade 3 drug-related depression and, at a later date, reported Grade 4 drug-related suicide attempt by a Grade 4 drug-related overdose on the same day. See "Suicide Attempts" below for additional details.

Higher rates of depression- or suicide-related events were observed in subjects with a past history of depression. The incidence of emergent depression and/or suicide-related events in subjects recording a past medical condition of depression at baseline was examined (Data Source: GEMINI◦ISS/ISE◦Table◦3.70). A total of 86/716 (12%) subjects in the DTG + 3TC group and 72/717 (10%) subjects in the DTG + TDF/FTC group reported a past history of depression at Baseline. Among these subjects with a past history of depression, the incidence of emergent depression was 10% (9/86) for the DTG + 3TC group and 11% (8/72) for the DTG + TDF/FTC group; by comparison, in subjects without a past history of depression, emergent depression events occurred in 2% (13/630) of subjects in the DTG + 3TC group and 2% (16/644) of subjects in the DTG + TDF/FTC group. On-treatment suicide-relate events were also more frequently noted in those with a past history of depression, observed in 10/86 (12%) of subjects in the DTG + 3TC group and 5/72 (7%) of subjects in the DTG + TDF/FTC group compared with 7/630 (1%) and 7/644 (1%), respectively, for those without a past history of depression. However, the majority of subjects with a past history of depression did not experience a recurrence of depression on study before the Week 48 cut-off date; of the total of 158 subjects with a past history of depression, 17 (11%) experienced depression on study, meaning that 89% of subjects did not experience a recurrence over the 48-week study period.

Suicidal Ideation and Behaviors

Events coded to the following pre-defined list of preferred terms were assessed as AEs related to suicidal ideation and behaviors:

- Intentional overdose;
- Self-injurious ideation;
- Suicidal behavior;
- Suicidal ideation;
- Suicide attempt.

The reporting rates for AEs relating to suicidality and self-injury were similar between the treatment groups (DTG + 3TC: 17 [2%] subjects reported 1 event each; DTG + TDF/FTC: 12 [2%] subjects reported a total of 13 events) (Data Source: GEMINI ISS/ISE Table 3.63).

Across both treatment groups, reporting of these events generally occurred in subjects with a past history of psychiatric disorder or previous suicidal ideation or behavior (20/29 subject had a relevant past history). In addition, these cases generally had additional psychosocial stressors reported at the time of the event. One subject in the DTG + TDF/FTC group reported 2 occurrences; all other subjects reported single occurrences. Nine subjects had serious events (DTG + 3TC: 5; DTG + TDF/FTC: 4), 2 subjects in each group had an event leading to withdrawal. There were no completed suicides.

In both groups, most events were Grade 1 or 2. In the DTG + 3TC group, 2 subjects reported events with a maximum Grade 3 intensity and 4 subjects reported Grade 4 events. In the DTG + TDF/FTC group, 4 subjects reported events with a maximum Grade 3 intensity and 1 subject reported a Grade 4 event.

Few subjects reported events considered drug related (DTG + 3TC 3; DTG + TDF 2). All of these subjects had co-morbid psychiatric conditions and/or psychosocial stressors at the time of the event.

The majority of subjects had events occurring >35 days after starting study drug (DTG + 3TC: 14 [82%]; DTG + TDF/FTC: 9 [75%]). The median time to onset for the DTG + 3TC group was 86.0 days (range: 1 to 427 days) and for the DTG + TDF/FTC group was 120.0 days (range: 25 to 512 days) (Data Source: GEMINI ISS/ISE Table 3.66).

Suicide Attempts

The 6 events of suicide attempt and one event of intentional overdose are described below.

- **Subject [redacted] (Suicide attempt; DTG + 3TC group)** was age <20 years and reported a suicide attempt (i.e., DAIDS Grade 4 event, but had been designated as Grade 1 by the investigator) on Study Day 27. The subject had a history of depression, anxiety, ADHD, and suicidal behavior. The subject reported to the investigator that he was playing with a razor knife and was uncertain whether he meant to harm himself or not. The subject had a current psychiatric condition and psychosocial stressors and was encouraged to contact his psychiatrist. The event was not considered to be related to study drug, and did not lead to withdrawal from the study.

- **Subject [redacted] (Suicide attempt; DTG + 3TC group)** was age 20 to 30 years with ongoing generalized anxiety disorder reported at Baseline. Medications at Baseline included alprazolam, clonazepam, gabapentin, quetiapine, and trazodone, which were all stopped at Study Day 34. The subject had a history of previous suicidal ideation triggered by family conflict. On Study Day 427, the subject took an overdose of lorazepam, and dolutegravir and blinded study drug (30 tablets each of DTG and of 3TC). The subject was admitted to the emergency room 30 minutes after the overdose and was treated with gastric lavage and activated charcoal. During subsequent follow-up, the subject was asymptomatic and did not develop any laboratory abnormalities. The subject was also treated with lorazepam and ongoing risperidone. No further psychological treatment was deemed necessary as the event was considered related to family conflict. The events were deemed as unrelated to study drug but the subject was withdrawn from the study and started a DTG-containing regimen.
- **Subject [redacted] (Suicide attempt; DTG + 3TC group)** was age 30 to 40 years with no past psychiatric history. The subject experienced adjustment disorder, traumatic head injury, and suicide attempt on Study Day 82, the same day as ingestion of [redacted], [redacted], and alcohol. Psychiatric review considered events related to social circumstances. Events were not related to study drug and resolved on continuing study treatment.
- **Subject [redacted] (Suicide attempt; DTG + 3TC group)** was age 20 to 30 years with no psychiatric history, and attempted suicide at Study Day 73. The subject was treated with haloperidol and lorazepam and underwent psychiatric evaluation. The suicide attempt was related to bereavement over a death in the family and was not related to study drug. The subject remained on study.
- **Subject [redacted] (Suicide attempt; DTG + TDF/FTC group)** was age 30 to 40 years with a past history of depression but was not on any psychiatric medication at Baseline. The subject developed depression on Study Day 490 with a suicide attempt by overdose of paracetamol/acetaminophen and tramadol on Study Day 512. The subject was referred for psychiatric assessment and commenced sertraline. The event was considered most likely to relate to social stress, but the investigator could not rule out a contribution from study drug and the subject was withdrawn from the study.
- **Subject [redacted] (Intentional overdose; DTG + TDF/FTC group) (**see also Section 2.1.4 for a description of an SAE of seizure in this subject) was age 20 to 30 years, and entered the study with current depression and a history of suicidal ideation but no attempts. On Study Day 25, a Grade 3 intentional overdose of antihistamine was reported, which, in the opinion of the investigator, was of minor severity and suggestive of seeking attention rather than a serious suicide attempt. There was possible alcohol abuse in the week preceding the event, and the event was considered to have been triggered by personal circumstances.
- **Subject [redacted] (Suicide attempt; DTG + 3TC group)** was age 30 to 40 years and reported an AE of substance abuse on Study Day 76 followed by a suicide attempt on Study Day 90. The subject reported a history of mania and suicidal ideation and was experiencing ongoing depression at Baseline. Suicidal ideation was

reported as being present at Baseline prior to ingestion of study drug. There were clear psychosocial stressors at the time of the event, and the event was not considered related to study drug.

In addition to all the drug-related Grade 3 AEs of suicidal ideation described above, one additional drug-related event of suicidal ideation was reported, which had a maximum intensity of Grade 2:

- **Subject [redacted] (Grade 2 Suicidal ideation; DTG + 3TC group)** was age 40 to 50 years with a current condition of depression at Baseline. The subject experienced Grade 2 suicidal ideation on Study Day 38. A number of contributing factors were reported; psychosocial stressors, current psychiatric conditions, medical condition, concomitant medications, and investigational product were considered as possible contributors. Treatment with aripiprazole and lamotrigine was commenced and remained ongoing. The subject did not withdraw from study and events resolved with no further episodes.

Depression

Events coded to the following pre-defined list of preferred terms were assessed as AEs related to depression:

- Adjustment disorder with depressed mood;
- Bipolar disorder;
- Depressed mood;
- Depression;
- Major depression;
- Persistent depressive disorder.

In the pooled analysis, reporting rates for AESIs related to depression were consistent between the treatment groups (DTG + 3TC: 22 [3%] subjects reported 1 event each; DTG + TDF/FTC 24 [3%] subjects reported 1 event each) (Data Source: GEMINI ISS/ISE Table 3.62). There were 8 subjects with drug-related events (DTG + 3TC: 3; DTG + TDF/FTC: 5). Two subjects in each group reported events with a maximum Grade 3 intensity, and all other subjects reported events with a maximum intensity of Grade 1 or 2. One subject had a depression-related AESI reported as an SAE:

- **Subject [redacted] (Major depression; DTG + 3TC group)** was age 50 to 60 years and reported serious Grade 3 major depression on Study Day 32, including auditory hallucinations encouraging suicide. The subject had a past history of schizophrenia and depression. The subject was hospitalized due to the event. [redacted]. The subject was treated with sertraline and mirtazapine. The event was not considered drug-related, and the event resolved.

There were 2 withdrawals (1 in each group) for a depression-related AESI. In the DTG + 3TC group, events in 16/22 subjects were resolved or resolving, and in the DTG + TDF/FTC group, events in 14/24 subjects were resolved or resolving.

Median time to onset was 98.5 days (range: 1 to 442 days) in the DTG + 3TC group and 86.5 days (range: 1 to 490 days) in the DTG + TDF/FTC group (Data Source: GEMINI ISS/ISE Table 3.65).

Anxiety

Events coded to the following pre-defined list of preferred terms were assessed as AEs related to anxiety:

- Anxiety;
- Anxiety disorder;
- Anxiety disorder due to a general medical condition;
- Nervousness.

The reporting rate for AEs related to anxiety was similar between the treatment groups (DTG + 3TC: 23 [3%] subjects reported 1 event each; DTG + TDF/FTC: 18 [3%] subjects reported a total of 20 events) (Data Source: GEMINI ISS/ISE Table 3.61). Two subjects (both in the DTG + TDF/FTC group) had a second occurrence, and all other events for both treatment groups were single occurrences. Fourteen subjects had anxiety events considered drug-related (DTG + 3TC: 9; DTG + TDF/FTC: 5). Three subjects reported events with a maximum Grade 3 intensity (all in the DTG + 3TC group); all other events had a maximum intensity of Grade 1 or 2. No events were serious. Two subjects (1 in each group) had an anxiety-related AESI that led to withdrawal.

In the DTG + 3TC group, events in 16/23 subjects were resolved or resolving, and in the DTG + TDF/FTC group, events in 11/18 subjects were resolved or resolving.

Median time to onset was 57.0 days (range: 1 to 486 days) in the DTG + 3TC group and 175.0 days (range: 27 to 430 days) in the DTG + TDF/FTC group (Data Source: GEMINI ISS/ISE Table 3.64).

2.1.6.4. Sleep Disorders

Insomnia

Events coded to the following list of pre-defined preferred terms were assessed:

- insomnia;
- initial insomnia;
- middle insomnia;
- terminal insomnia.

The rate of insomnia was slightly higher in the DTG + TDF/FTC group compared with the DTG + 3TC group (DTG + 3TC: 27 [4%] subjects reported a total of 28 events; DTG + TDF/FTC: 45 [6%] subjects reported a total of 51 events) (Data Source: GEMINI ISS/ISE Table 3.27). All events were Grade 1 or 2. Six subjects (DTG + 3TC: 1; DTG + TDF/FTC: 5) had 2 or more occurrences of insomnia-related AESIs, and all other subjects reported a single occurrence. In the DTG + 3TC group, 13/27 subjects reported drug-related events, and in the DTG + TDF/FTC group, 18/45 subjects reported drug-related events. None of the subjects had a serious event. One subject (DTG + 3TC

group) had an insomnia-related AESI that led to withdrawal. In the DTG + 3TC group, events for 16/27 subjects were resolved or resolving, and in the DTG + TDF/FTC group, events for 33/45 subjects were resolved or resolving.

The median time to onset was 24.0 days (range: 1 to 441 days) for the DTG + 3TC group and 44.0 days (range: 1 to 416 days) for the DTG + TDF/FTC group (Data Source: GEMINI ISS/ISE Table 3.28).

Nightmares and Abnormal Dreams

Events coded to the preferred terms of "Abnormal dreams" and "Nightmare" were assessed.

The reporting rate for AEs related to nightmare/abnormal dreams slightly higher in the DTG + 3TC group compared with the DTG + TDF/FTC group (DTG + 3TC: 11 [2%] subjects reported a total of 13 events; DTG + TDF/FTC: 6 [<1%] subjects reported 1 event each) (Data Source: GEMINI ISS/ISE Table 3.30). Two Grade 2 events were reported (both in the DTG + 3TC group), and all other events had a maximum intensity of Grade 1. Two subjects (both in the DTG + 3TC group) had 2 occurrences, and all other events for both treatment groups were single occurrences. There were 9 subjects reporting a drug-related event in the DTG + 3TC group and 3 in the DTG + TDF/FTC group. No nightmare/abnormal dreams-related AESIs were serious or led to withdrawal.

In the DTG + 3TC group, events for all 11 subjects were resolved, and in the DTG + TDF/FTC group, 5/6 subjects had events that were resolved.

Median time to onset was 3.0 days (range: 1 to 65 days) in the DTG + 3TC group and 33.5 days (range: 1 to 103 days) in the DTG + TDF/FTC group (Data Source: GEMINI ISS/ISE Table 3.31).

2.1.6.5. Immune Reconstitution Inflammatory Syndrome

Compared with regimens that do not contain an integrase inhibitor, a higher rate of IRIS with regimens containing DTG may be a possible outcome due to faster rate of viral load decline.

Subjects with HIV-related medical conditions occurring up to the Week 48 Database Release were identified. These cases, along with any AEs or SAEs potentially suggestive of IRIS were reviewed by two senior company physicians from GSK/ViiV, who remained blinded to treatment and had no contact with sites or investigators, using definitions derived from the literature [Robertson, 2006; Walker, 2015].

A total of 39 subjects experienced HIV-associated conditions, AEs, or SAEs that may be associated with IRIS. Four subjects were adjudicated as having possible IRIS (2 in each treatment group). One case reporting molluscum contagiosum at Study Day 66 was deemed not possible to adjudicate due to lack of information on extent of disease. The remaining cases were adjudicated as unlikely to be IRIS.

The 4 adjudicated cases of possible IRIS are summarized as follows:

- **Subject [redacted] (DTG + 3TC group)** had a Baseline CD4+ cell count of <20 cells/mm^3. The subject was hospitalized on Study Day 12 for cerebral chagoma. At Week 8, the subject had a >3 log_{10} c/mL decrease from Baseline in HIV-1 RNA and minimal change from Baseline in CD4+ cell count. The subject was treated with benznidazole following initial empirical treatment for toxoplasmosis. The events were considered not resolved. The subject was discharged from the hospital, but had sequelae of mild facial paralysis.
- **Subject [redacted] (DTG + 3TC group)** experienced a case of possible TB IRIS. The subject had a Baseline CD4+ cell count of 320 cells/mm^3. The subject developed tuberculous pleurisy at Study Day 131. At Week 4, the subject had a >3 log_{10} c/mL decrease from Baseline in HIV-1 RNA and an increase in CD4+ cell count of 69 cells/mm^3. The subject was withdrawn from the study for rifampin-based TB treatment.
- **Subject [redacted] (DTG + TDF/TFC group)** had a Baseline CD4+ cell count of 371 cells/mm^3. The subject first reported an enlarged inguinal lymph node on Study Day 29. At Week 4, the subject had a 3.05 log_{10} c/mL decrease from Baseline in HIV-1 RNA and an increase from Baseline in CD4+ cell count of 239 cells/mm^3. The subject was admitted to hospital on Study Day 147 for an excision biopsy, which showed granulomatous change with no organism growth. The events resolved with sequelae.
- **Subject [redacted] (DTG + TDF/TFC group)** experienced a case of likely PJP pneumonia (or bacterial pneumonia). The subject had a Baseline CD4+ cell count of <20 cells/mm^3, and was receiving PJP prophylaxis prior to Screening and while on study. At Week 4, the subject had a 3.4 log_{10} c/mL decrease from Baseline in HIV-1 RNA and an increase from Baseline in CD4+ cell count of 123 cells/mm^3. The subject was hospitalized for bacterial pneumonia on Study Day 101. The subject received treatment for PJP pneumonia, although PJP PCR results were negative. The events resolved.

2.1.6.6. Other Adverse Events of Special Interest

Cardiovascular Disorders

Seven subjects (DTG + 3TC: 4; DTG + TDF/FTC: 3) reported a total of 7 cardiovascular events (Data Source: 204861 Week 48 CSR Listing 60; 205543 Week 48 CSR Listing 60). Events in the DTG + 3TC group were Grade 2 coronary artery stenosis, Grade 3 transient ischemic attack, Grade 1 tachycardia, and Grade 5 acute myocardial infarction (fatal SAE; Subject [redacted] described in Section 2.1.3). There were 3 events of arrhythmia in the DTG + TDF/FTC group (Grade 1 palpitations, Grade 1 bradycardia, and Grade 2 tachycardia).

Metabolism and Nutrition Disorders

There was a modest difference between the treatment groups in the proportions of subjects reporting AEs from the Metabolism and nutrition disorders SOC (DTG + 3TC: 54 [8%]; DTG + TDF/FTC: 32 [4%]) (Data Source: GEMINI ISS/ISE Table 3.2).

Vitamin D deficiency (2% overall) was the most common adverse event reported from this SOC (DTG + 3TC: 17 [2%]; DTG + TDF/FTC: 8 [1%]). As described in Section 2.1.1, an additional AE of Vitamin D deficiency (Grade 2) was reported in a subject in the DTG +TDF/FTC group; this AE had not been reported by the data cut-off date and was not included in the analyses due to a GCP noncompliance issue at a single study center (updated data for subjects reporting an AE of Vitamin D deficiency would be as follows: DTG + 3TC, 17 [2%]; DTG + TDF/FTC, 9 [1%]).

All other individual preferred terms were reported in ≤1% of subjects overall. Two subjects from the DTG + 3TC group and no subjects from the DTG + TDF/FTC group reported an event of glucose tolerance impaired, which was Grade 1 for one subject and Grade 2 for the other subject (Data Source: 204861 Week 48 CSR Listing 15; 205543 Week 48 CSR Listing 15).

2.2. Narratives

Case narratives for all deaths, other SAEs, and pregnancies received by the company for 204861 and 205543 as of [redacted] are included in 204861 Week 48 CSR Section 13 and 205543 Week 48 CSR Section 13, respectively.

3. CLINICAL LABORATORY EVALUATIONS

3.1. General Clinical Chemistry

Clinical laboratory assessments were collected as a measure of subject safety and drug tolerability, and demonstrated there were no laboratory signals of concern in subjects receiving DTG + 3TC.

Graded emergent clinical toxicities for selected safety laboratory parameters of interest are summarized in Table 14; additional chemistries and related AEs are described in the subsections below. The distribution and number of graded emergent clinical chemistry toxicities was similar between the treatment groups, with the majority of the emergent clinical chemistry toxicities of maximum Grade 1 or Grade 2 intensity.

Table 14 Summary of Maximum Emergent Chemistry Toxicities for Selected Laboratory Parameters for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED	
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=258 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)
Alanine Aminotransferase						
Grade 1	17 (5)	32 (9)	26 (7)	29 (8)	43 (6)	61 (9)
Grade 2	5 (1)	8 (2)	8 (2)	12 (3)	13 (2)	20 (3)
Grade 3	4 (1)	3 (<1)	4 (1)	4 (1)	8 (1)	7 (<1)
Grade 4	5 (1)	5 (1)	5 (1)	6 (2)	10 (1)	11 (2)
Aspartate Aminotransferase						
Grade 1	18 (5)	31 (9)	25 (7)	33 (9)	43 (6)	64 (9)
Grade 2	12 (3)	8 (2)	10 (3)	11 (3)	22 (3)	19 (3)
Grade 3	4 (1)	8 (2)	3 (<1)	9 (3)	7 (<1)	17 (2)
Grade 4	1 (<1)	4 (1)	4 (1)	3 (<1)	5 (<1)	7 (<1)
Bilirubin						
Grade 1	20 (6)	24 (7)	25 (7)	27 (8)	45 (6)	51 (7)
Grade 2	4 (1)	9 (3)	5 (1)	8 (2)	9 (1)	17 (2)
Grade 3	2 (<1)	4 (1)	0	2 (<1)	2 (<1)	6 (<1)
Grade 4	2 (<1)	0	3 (<1)	1 (<1)	5 (<1)	1 (<1)
Creatine Kinase						
Grade 1	18 (5)	12 (3)	27 (8)	20 (6)	45 (6)	32 (4)
Grade 2	11 (3)	10 (3)	15 (4)	11 (3)	26 (4)	21 (3)
Grade 3	8 (2)	11 (3)	9 (3)	6 (2)	17 (2)	17 (2)
Grade 4	5 (1)	7 (2)	10 (3)	11 (3)	15 (2)	18 (3)
Creatinine						
Grade 1	14 (4)	20 (6)	11 (3)	17 (5)	25 (3)	37 (5)
Grade 2	1 (<1)	1 (<1)	3 (<1)	1 (<1)	4 (<1)	2 (<1)
Grade 3	0	1 (<1)	0	1 (<1)	0	2 (<1)
Grade 4	0	0	0	0	0	0
Hyperglycaemia						
Grade 1	36 (10)	37 (10)	44 (12)	36 (10)	80 (11)	73 (10)
Grade 2	20 (6)	11 (3)	28 (8)	18 (5)	48 (7)	29 (4)
Grade 3	3 (<1)	2 (<1)	2 (<1)	2 (<1)	5 (<1)	4 (<1)
Grade 4	0	0	0	1 (<1)	0	1 (<1)
Hypoglycaemia						
Grade 1	6 (2)	10 (3)	9 (3)	9 (3)	15 (2)	19 (3)
Grade 2	5 (1)	2 (<1)	1 (<1)	3 (<1)	6 (<1)	5 (<1)
Grade 3	1 (<1)	0	2 (<1)	0	3 (<1)	0
Grade 4	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Hypophosphataemia (Phosphate)						
Grade 1	21 (6)	16 (4)	22 (6)	18 (5)	43 (6)	34 (5)
Grade 2	18 (5)	28 (8)	29 (8)	29 (8)	47 (7)	57 (8)
Grade 3	1 (<1)	3 (<1)	2 (<1)	4 (1)	3 (<1)	7 (<1)
Grade 4	0	0	0	0	0	0

	204861		205543		POOLED	
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=258 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)
Lipase						
Grade 1	18 (5)	25 (7)	27 (8)	32 (9)	45 (6)	57 (8)
Grade 2	18 (5)	16 (4)	19 (5)	18 (5)	37 (5)	34 (5)
Grade 3	4 (1)	4 (1)	0	9 (3)	4 (<1)	13 (2)
Grade 4	1 (<1)	5 (1)	2 (<1)	1 (<1)	3 (<1)	6 (<1)

Data Source: 204861 Week 48 CSR Table 3.55; 205543 Week 48 CSR Table 3.55; GEMINI ISS/ISE Table 3.55.
Note: Subjects with missing Baseline are assumed to be normal.

3.2. Hepatobiliary Disorders

Over the time period during which 204861 and 205543 were conducted, outbreaks of hepatitis A virus were reported among men who have sex with men in many regions, including many countries in Europe [World Health Organization, 2017]. During the study, there was a larger than expected number of extreme liver enzyme abnormalities, many of which were attributable to acute hepatitis A infection.

In the pooled treatment groups, a small number of subjects met liver event stopping criteria (DTG + 3TC: 13 [2%]; DTG + TDF/FTC: 16 [2%]), with no difference between the treatment groups (Data Source: Table 3.10). Treatment was not restarted in 7/13 subjects in the DTG + 3TC group and 5/16 subjects in the DTG + TDF/FTC group after meeting liver event stopping criteria.

A small number of subjects reported AEs from the Hepatobiliary disorders SOC (DTG + 3TC 9 [1%], DTG + TDF/FTC 14 [2%]). Nine subjects reported events with a maximum Grade 3 intensity (DTG + 3TC: 1; DTG + TDF/FTC: 8 [reporting 9 Grade 3 events]), and all other hepatobiliary events were Grade 1 or 2 (Data Source: 204861 Week 48 CSR Listing 15; 205543 Week 48 CSR Listing 15; GEMINI ISS/ISE Table 3.3). One of the Grade 1 events (hepatotoxicity, Subject [redacted]) was considered by the investigator to be possible DTG-related DILI.

This possible DILI case and the Grade 3 events are summarized below:

- **Subject [redacted] (Hepatotoxicity [possible DILI]; DTG + 3TC group)** was age 20 to 30 years and reported an event of Grade 1 hepatotoxicity on Study Day 60. The subject was recovering from Hepatitis A at screening and therefore had a positive Hepatitis A antibody result at liver event screening that was not considered relevant by the investigator. The subject experienced an asymptomatic ALT increase (Grade 1) at the Week 4 visit with a Grade 3 elevation at Week 8. Bilirubin was normal. The subject had a past history of hepatitis A and alcohol abuse. The subject was never hospitalized for these events. There were no clinical signs or symptoms of hepatotoxicity. Liver ultrasound was normal, and biopsy was not performed. Study drug was interrupted at Week 8. The subject experienced retroviral syndrome while off study drug, and the degree of liver enzyme elevation precluded study drug restart. The investigator could not exclude possible DILI, as no clear alternative cause could be demonstrated. The subject was using alcohol and had positive anti-smooth muscle antibodies, but neither were considered relevant by the investigator. The subject started FTC/TAF/rilpivirine, and the subject's liver enzymes normalized (per local laboratory results). The event resolved.
- **Subject [redacted] (Hepatitis alcoholic; DTG + 3TC group)** was age 30 to 40 years and experienced Grade 3 hepatitis alcoholic on Study Day 337. The event was not serious and was not related to study drug, and the event resolved. The subject was withdrawn from the study.
- **Subject [redacted] (Cholecystitis acute; DTG + TDF/FTC group)** was age 40 to 50 years and experienced Grade 3 cholecystitis acute on Study Day 394. The event was serious and was not considered related to study drug; the event resolved and the subject remained on study.
- **Subject [redacted] (Cholelithiasis; DTG + TDF/FTC group)** was age 30 to 40 years and experienced Grade 3 cholelithiasis on Study Day 55. The event was serious and was not considered related to study drug; the event resolved and the subject remained on study.
- **Subject [redacted] (Drug-induced liver injury; DTG + TDF/FTC group)** was age 30 to 40 years and experienced Grade 3 drug-induced liver injury (verbatim text: toxic hepatitis caused by drug abuse) on Study Day 114. The event was considered non-serious and was not related to study drug; the event resolved but the subject was withdrawn from the study due to ongoing substance abuse.
- **Subject [redacted] (Hepatitis toxic; DTG + TDF/FTC group)** was age 20 to 30 years and experienced Grade 3 hepatitis toxic on Study Day 91. The event was considered non-serious and was not related to study drug; the subject remained on study at the time. Liver enzymes improved and then became elevated again (meeting liver stopping criteria) and the subject was diagnosed with Hepatitis C (Study Day 172). The subject was abusing alcohol with possible other substance abuse and was withdrawn from the study. The event was not resolved.

- **Subject [redacted] (Biliary colic and Cholelithiasis; DTG + TDF/FTC group)** was age 30 to 40 years and experienced Grade 3 biliary colic (non-serious, related to study drug) and Grade 3 cholelithiasis (serious, related to study drug) on Study Day 98. Both events resolved and the subject remained on study. See Section 2.1.4.1 for additional details.
- **Subject [redacted] (Cholecystitis acute; DTG + TDF/FTC group)** was age 30 to 40 years and experienced Grade 3 cholecystitis acute on Study Day 158. The event was serious and was not considered related to study drug; the event resolved and the subject remained on study.
- **Subject [redacted] (Alcoholic liver disease; DTG + TDF/FTC group)** was age 40 to 50 years and experienced Grade 3 alcoholic liver disease on Study Day 1. The event was non-serious and was not considered related to study drug; the event resolved and the subject remained on study.
- **Subject [redacted] (Hepatitis alcoholic; DTG + TDF/FTC group)** was age 20 to 30 years and experienced Grade 3 hepatitis alcoholic on Study Day 106. The event was not serious and was not related to study drug, and the event resolved. The subject was withdrawn from the study.

Proportions of subjects meeting hepatobiliary criteria (subcategories of subjects with ALT ≥3xULN) are summarized in Table 15.

Table 15 Summary of Subjects with ALT >=3 x ULN for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

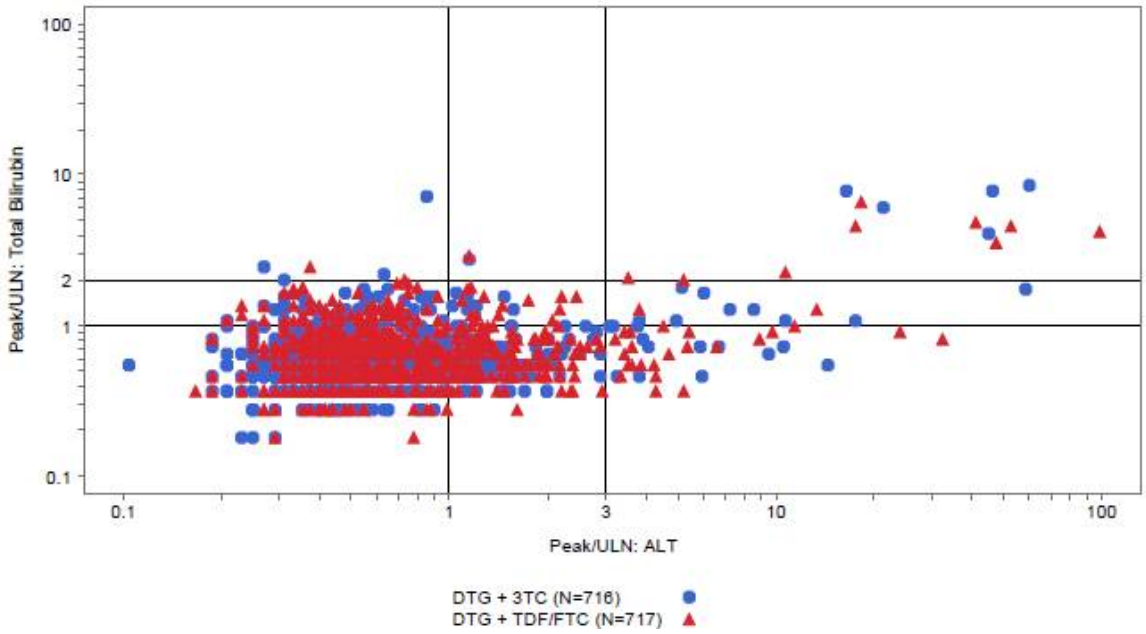
	204861		205543		POOLED	
Hepatobiliary Criteria	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=258 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)
ALT ≥3 x ULN	13 (4)	16 (4)	14 (4)	18 (5)	27 (4)	34 (5)
ALT ≥3 x ULN - <5 x ULN	4 (1)	8 (2)	5 (1)	8 (2)	9 (1)	16 (2)
ALT ≥5 x ULN - <10 x ULN	4 (1)	3 (<1)	4 (1)	4 (1)	8 (1)	7 (<1)
ALT ≥10 x ULN - <20 x ULN	3 (<1)	1 (<1)	2 (<1)	4 (1)	5 (<1)	5 (<1)
ALT≥20 x ULN	2 (<1)	4 (1)	3 (<1)	2 (<1)	5 (<1)	6 (<1)

Data Source: 204861 Week 48 CSR Table 3.81; 205543 Week 48 CSR Table 3.81; GEMINI ISS/ISE Table 3.81.
Note: For ALT ≥3 x ULN - <5 x ULN, ≥5 x ULN - <10 x ULN, ≥10 x ULN - <20 x ULN, ≥20 x ULN, subjects are summarized based on the maximum value post baseline.

The eDISH plot of maximum bilirubin versus maximum ALT is provided for the pooled analysis as Figure 2. There were a small number of subjects with bilirubin ≥2 x ULN in either treatment group. There were 14 subjects with a maximum ALT elevation ≥3 x ULN and a maximum bilirubin elevation ≥2 x ULN at any time on study. Twelve of these 14 subjects had a bilirubin elevation ≥2 x ULN within 28 days after having an ALT elevation ≥3 x ULN; these are the 12 cases appearing well into the upper right quadrant (above the bilirubin 2 x ULN line). The 12 cases were due to hepatitis A infection (n=11; 1 of these had a combined HCV and hepatitis A infection) and acute HCV infection (n=1). In Figure 2, there are 2 subjects where the bilirubin values appear directly on the

2 x ULN line (Subject [redacted] and Subject [redacted]); these subjects had a maximum bilirubin value and maximum ALT value >28 days apart.
Subject [redacted] experienced a transient Grade 3 ALT elevation at Week 8 considered related to either EBV infection or antibiotic therapy. The subject had elevated bilirubin prior to treatment and through most study visits, with a maximum elevation of 2 x ULN at Week 48; the elevated bilirubin was considered unrelated to the study drug.
Subject [redacted] experienced a transient Grade 2 ALT elevation at Week 8 and bilirubin elevation of 2 x ULN at Week 60, both considered related to gallstones.

Figure 2 Maximum Total Bilirubin versus Maximum ALT (eDISH Plot) for Pooled (204861 ad 205543) Data (Safety Population)



Data Source: GEMINI ISS/ISE Figure 3.3.
Note: Reference lines for Total Bilirubin represent 2 x ULN and for ALT 3 x ULN.

ALT >3 x ULN with Total Bilirubin ≥2 x ULN and ALP <2 x ULN within 28 Days of the ALT Elevation

There were 4 (<1%) subjects in the DTG + 3TC group and 3 (<1%) subjects in the DTG + TDF/FTC group that had a combination of ALT >3 x ULN with ALP <2 x ULN and total bilirubin ≥2 x ULN (Data Source: GEMINI ISS/ISE Table 3.81). All subjects had hepatitis A infection; 1 was also co-infected with HCV. The co-infected subject withdrew from the study to start HCV treatment. One subject in the DTG + TDF/FTC group was approved to restart drug but was lost to follow-up, and another subject in the DTG + TDF/FTC group was withdrawn from the study as the investigator wished to restart ART prior to liver enzyme elevations meeting re-start criteria. The remaining 4 subjects successfully restarted study drug.

Maximum ALT ≥10 x ULN

There were 21 subjects that had ALT values ≥10 x ULN (DTG + 3TC: 10 [1%]; DTG + TDF/FTC: 11 [2%]) (Data Source: GEMINI ISS/ISE Table 3.81). Each of these cases is summarized in (Table 16). Of these 21 cases, 20 had hepatitis virus infection (hepatitis A, B, or C) and the other case was attributed to a concomitant medication.

Table 16 Subjects with Maximum ALT >=10 x ULN in Studies 204861 and 205543 (Safety Population)

Subject ID	Treatment Group	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No, Reason
[redacted]	DTG + 3TC	14.48	0.55	Considered most likely related to benznidazole treatment. Subject withdrawn as investigator wished to restart ART prior to liver enzyme elevations resolving sufficiently to permit study drug restart.	Yes, Physician decision -
[redacted]	DTG + 3TC	44.96	4.09	Acute HAV. Restarted on study drug.	No
[redacted]	DTG + 3TC	21.33	6	Acute HAV. Restarted on study drug.	No
[redacted]	DTG + 3TC	17.54	1.09	Acute HAV, withdrawn from study as PI wished to resume ART prior to liver function tests returning to levels permitting study drug restart.	Yes, Adverse Event - Hepatitis A
[redacted]	DTG + 3TC	16.54	7.82	Acute HCV and HAV infection, subject withdrawn from study for HCV treatment.	Yes, Subject reached protocol defined liver chemistry stopping criteria – Acute Hepatitis C
[redacted]	DTG + 3TC	46.04	7.91	Acute HAV. Restarted on study drug.	No

Subject ID	Treatment Group	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No, Reason
[redacted]	DTG + 3TC	10.54	0.73	Acute HCV. Restarted study drug.	No
[redacted]	DTG + 3TC	10.77	1.09	Acute HCV infection. Restarted study drug and met liver stopping criteria again for second (different genotype) acute HCV infection.	No
[redacted]	DTG + 3TC	60	8.45	Acute HAV. Restarted on study drug.	No
[redacted]	DTG + 3TC	58.4	1.73	Acute HBV progressing to chronic HBV infection	Yes
[redacted]	DTG + TDF/FTC	23.92	0.91	Acute HCV. Restarted on study drug.	No
[redacted]	DTG + TDF/FTC	52.83	4.64	Acute HAV. Restarted on study drug.	No
[redacted]	DTG + TDF/FTC	47.33	3.55	Acute HAV. Restarted on study drug.	No
[redacted]	DTG + TDF/FTC	99.06	4.18	Acute HAV. Restarted on study drug.	No
[redacted]	DTG + TDF/FTC	13.4	1.27	Viral syndrome followed by acute HCV. Had second liver stopping event with elevated HCV viral load considered by investigator to be due to ongoing substance abuse; therefore, was withdrawn from study.	Yes, Adverse Event - Drug-induced liver injury (verbatim text: toxic hepatitis caused by drug abuse; per the subject narrative, acute hepatitis C due to IV drug [methadone] use)
[redacted]	DTG + TDF/FTC	17.67	4.55	Acute HAV. Restarted study drug.	No

Subject ID	Treatment Group	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No, Reason
[redacted]	DTG + TDF/FTC	18.21	6.64	Acute HCV. Restarted study drug but met liver stopping criteria again, withdrawn from study to allow treatment for HCV.	Yes
[redacted]	DTG + TDF/FTC	41.02	4.82	Acute HAV. Withdrawn from study as PI wished to resume ART prior to liver function tests returning to levels permitting study drug restart.	Yes, Withdrawal by subject
[redacted]	DTG + TDF/FTC	32.42	0.82	Acute HAV. Restarted on study drug.	No
[redacted]	DTG + TDF/FTC	10.77	2.27	Acute HAV. Study drug restart was approved but subject was lost to follow up.	Yes, Lost to follow-up
[redacted]	DTG + TDF/FTC	11.46	1	Acute HCV. Restarted study drug and met liver stopping criteria again considered due to alcoholic hepatitis, withdrawn from study.	Yes, Subject reached protocol defined liver chemistry stopping criteria [Adverse Event: Alcoholic hepatitis]

Data Source:
204861 Week 48 CSR Listing 70, Listing 63, Listing 5, Listing 39;
205543 Week 48 CSR Listing 70, Listing 63, Listing 5, Listing 39.

Increases in ALT ≥5 x ULN but <10 x ULN

There were 15 subjects that had ALT ≥5 x ULN but <10 x ULN (DTG + 3TC 8 [1%]; DTG + TDF/FTC 7 [<1%]) (Data Source: GEMINI ISS/ISE Table 3.81). Each of these cases is summarized in Table 17.

Table 17 Subjects with Maximum ALT >=5 x ULN but <10 x ULN in Studies 204861 and 205543 (Safety Population)

Subject ID	Treatment Group	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No, Reason
[redacted]	DTG + 3TC	5.88	0.73	Acute HCV.	No
[redacted]	DTG + 3TC	7.21	1.27	Chronic HCV.	No
[redacted]	DTG + 3TC	5.92	0.45	Chronic HCV.	No
[redacted]	DTG + 3TC	6.04	1.64	Elevation of ALT at Week 60 with suspected alcohol abuse; the repeat ALT 4 weeks later was normal.	No
[redacted]	DTG + 3TC	5.17	1.82	Acute HAV, restarted study drug.	No
[redacted]	DTG + 3TC	9.54	0.64	Possible DILI (narrative in Section 3.2).	Yes, Adverse Event - Liver Toxicity
[redacted]	DTG + 3TC	6.67	0.73	Grade 3 elevation at week 48. Subject reported heavy alcohol use and had positive treponemal antibody test and recent unprotected sex suggesting syphilis. Subject received penicillin IM, liver enzyme elevations markedly improved.	No
[redacted]	DTG + 3TC	8.63	1.27	Alcoholic hepatitis, drug restart therefore prohibited.	Yes

Subject ID	Treatment Group	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No, Reason
[redacted]	DTG + TDF/FTC	6.58	0.73	Chronic HCV, restarted study drug but met liver stopping criteria again, withdrawn from study. The investigator did not consider this as an adverse event as the degree of liver enzyme elevations, while crossing stopping thresholds, was not significantly different from the subject's baseline/pre-study levels.	Yes, Subject reached protocol-defined liver chemistry stopping criteria
[redacted]	DTG + TDF/FTC	9.77	0.91	Acute HCV, study drug not restarted as PI withdrew subject due to non-compliance.	Yes, Subject reached protocol defined liver chemistry stopping criteria – Hepatitis C
[redacted]	DTG + TDF/FTC	5.19	2	Recent EBV infection and subject received levofloxacin and amoxicillin-clavulanate. PI considered liver enzyme elevations to be due to EBV and/or antibiotic use.	No
[redacted]	DTG + TDF/FTC	8.88	0.82	Chronic HCV. Restarted study drug.	No
[redacted]	DTG + TDF/FTC	5.42	0.91	Acute cholecystitis. Restarted study drug.	No
[redacted]	DTG + TDF/FTC	5.35	0.73	Chronic HCV.	No
[redacted]	DTG + TDF/FTC	5.23	0.36	Chronic HCV.	No

Data Source:
204861 Week 48 CSR Listing 70, Listing 63, Listing 5, Listing 39;
205543 Week 48 CSR Listing 70, Listing 63, Listing 5, Listing 39.

Increases in ALT ≥3 x ULN but <5 x ULN

There were 25 subjects that had ALT ≥3 x ULN but <5 x ULN (DTG + 3TC 9 [1%]; DTG + TDF/FTC 16 [2%]) (Data Source: GEMINI ISS/ISE Table 3.81). Each of these cases is summarized in Table 18.

Table 18 Subjects with Maximum ALT >=3 x ULN but <5 x ULN in Studies 204861 and 205543 (Safety Population)

Subject ID	Treatment Group	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No, Reason
[redacted]	DTG + 3TC	4.08	0.73	Grade 2 elevation at Baseline, no significant change on study, no cause identified.	No
[redacted]	DTG + 3TC	3.75	1	Transient Grade 2 elevation at Week 24, no cause identified; subject had taken a course of amoxycillin and ciprofloxacin one month prior to ALT elevation.	No
[redacted]	DTG + 3TC	3.81	0.45	Chronic HCV.	No
[redacted]	DTG + 3TC	3.94	0.82	Likely NASH suggested by recent weight increase and hepatic ultrasound. Liver enzyme elevations resolving following diet and exercise regimen.	No
[redacted]	DTG + 3TC	3.25	0.45	Transient Grade 2 elevation at Week 8, no cause identified.	No
[redacted]	DTG + 3TC	3.83	1.09	Grade 1 elevation at Baseline, no significant change on study, no further action required unless elevations increase.	No
[redacted]	DTG + 3TC	3.08	1	Transient Grade 2 elevation at Week 4 related to myopathy following heavy exercise.	No

Subject ID	Treatment Group	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No, Reason
[redacted]	DTG + 3TC	4.96	1.09	Considered related to ingestion of food containing toxins, treated with toxin binders and antibiotics.	No
[redacted]	DTG + 3TC	3.17	1	Asymptomatic ALT elevation at week 72 from heavy alcohol use	No
[redacted]	DTG + TDF/FTC	4.31	0.45	Sustained Grade 2 elevation starting from Week 12, considered due to hepatic steatosis (visible on liver ultrasound scan).	No
[redacted]	DTG + TDF/FTC	3.56	0.91	Transient Grade 2 elevation at week 4, no cause identified.	No
[redacted]	DTG + TDF/FTC	3.44	0.91	Grade 2 elevation at week 12, alcohol related.	Yes, Withdrawal by subject (subject was incarcerated)
[redacted]	DTG + TDF/FTC	3.54	2.09	Transient Grade 2 elevation at week 8, no cause identified.	No
[redacted]	DTG + TDF/FTC	3.35	0.45	Grade 1 elevation from Week 4, ALT >5x ULN at Week 60 visit, returned to Grade 1 elevation at Week 72. Etiology unknown, remains under investigation.	No
[redacted]	DTG + TDF/FTC	3.54	0.55	Grade 2 elevation at Week 24 considered related to either herpes zoster or treatment with paracetamol and acyclovir.	Yes, Lack of efficacy – Virologic failure
[redacted]	DTG + TDF/FTC	3.63	0.55	Chronic HCV.	Yes, Lost to follow-up
[redacted]	DTG + TDF/FTC	3.46	0.64	Asymptomatic ALT elevation at Week 72, alcohol related.	No

Subject ID	Treatment Group	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No, Reason
[redacted]	DTG + TDF/FTC	3.79	1.27	Grade 1 elevation at Baseline, no significant change on study, considered related to alcohol.	No
[redacted]	DTG + TDF/FTC	4.29	0.36	Grade 2 elevations at Week 8 and Week 24 considered related to alcohol.	No
[redacted]	DTG + TDF/FTC	4.73	0.64	Transient Grade 2 elevation at Week 8, no cause identified.	No
[redacted]	DTG + TDF/FTC	3.63	0.73	Non-alcoholic steatohepatitis.	No
[redacted]	DTG + TDF/FTC	4.23	0.55	Grade 2 elevation at Week 24 due to hypothyroidism; ALT elevations resolved after increasing thyroid hormone replacement dose.	No
[redacted]	DTG + TDF/FTC	4.52	1	Grade 1 elevation at Baseline, no significant change on study, considered related to alcohol.	No
[redacted]	DTG + TDF/FTC	3.88	0.55	Transient Grade 2 ALT elevation at Week 12, no cause identified.	No
[redacted]	DTG + TDF/FTC	3.23	0.82	Subject with baseline obesity and weight gain on study with suspected non-alcoholic steatohepatitis, awaiting ultrasound scan	No

Data Source:
204861 Week 48 CSR Listing 70, Listing 63, Listing 5, Listing 39;
205543 Week 48 CSR Listing 70, Listing 63, Listing 5, Listing 39.

3.3. Renal Results

Overall, there were no laboratory or clinical findings suggesting a significant adverse effect on renal function for the DTG +3TC group at the Week 48 analysis.

Since DTG is known to inhibit OCT-2, mild serum creatinine elevations are expected to occur in both treatment groups.

A total of 29 subjects in the DTG + 3TC group had emergent creatinine elevations with a maximum of Grade 1 (25 [3%]) or Grade 2 (4 [<1%]) intensity, and there were no Grade 3 or Grade 4 elevations in creatinine (Data Source: GEMINI ISS/ISE Table 3.55).

A total of 41 subjects in the DTG + TDF/FTC group had emergent creatinine elevations with a maximum of Grade 1 (37 [5%]), Grade 2 (2 [<1%]), or Grade 3 (2 [<1%]) intensity, and there were no Grade 4 elevations in creatinine.

A small number of subjects reported AEs from the Renal and urinary disorders SOC, with no difference between the treatment groups in the proportions of subjects reporting AEs from this SOC (DTG + 3TC: 27 [4%]; DTG + TDF/FTC: 27 [4%]) (Data Source: GEMINI ISS/ISE Table 3.2). From the Renal and urinary disorders SOC, all renal events in the DTG + 3TC group were Grade 1 or Grade 2; in the DTG + TDF/FTC group, 1 subject reported a single Grade 3 event (renal impairment), and all other events in the DTG + TDF/FTC group were Grade 1 or 2.

Additionally, from the Investigations SOC, 6 subjects reported AEs of creatinine renal clearance decreased (DTG + 3TC: 1 [Grade 3]; DTG + TDF/FTC: 5 [1 was Grade 1, 2 were Grade 2, and 2 were Grade 3]), 1 subject reported an AE of blood creatinine increased (DTG + 3TC group, Grade 2), and 1 subject reported an AE of glomerular filtration rate decreased (DTG + TDF/FTC group, Grade 3).

Thus, a total of 5 subject reported a Grade 3 renal AE. Three of the 5 subjects with Grade 3 renal events met renal toxicity stopping criteria (eGFR <50 mL/min/1.73 m^2) and were withdrawn from study (Subject [redacted], Subject [redacted], and Subject [redacted]). The Grade 3 event of creatinine renal clearance decreased in the DTG + 3TC group (Subject [redacted]) was not serious, was not related to study drug (the event was considered related to acute respiratory infection), and did not lead to discontinuation. The Grade 3 renal events that were considered drug-related or that led to withdrawal are summarized as follows (Data Source: GEMINI ISS/ISE Table 3.3, 204861 Week 48 CSR Listing 15, 205543 Week 48 CSR Listing 15):

- **Subject [redacted] (Renal impairment; DTG + TDF/FTC group)** was age 30 to 40 years and reported a Grade 3 event of renal impairment on Study Day 27. The event was not serious, did not lead to withdrawal, was considered related to study drug, and was not resolved. On Study Day 89, the subject was diagnosed with left renal cell carcinoma, a serious event, and underwent left radical nephrectomy on Study Day 105. The eGFR subsequently declined to <50 mL/min/1.73 m^2, and the subject withdrew from the study.

- **Subject [redacted] (Creatinine renal clearance decreased; DTG + TDF/FTC group)** was age 60 to 70 years and experienced a Grade 3 drug-related adverse event of creatinine renal clearance decreased on Study Day 29. The subject had a past history of nephrectomy (for adrenal tumor). The subject had current hypercholesterolemia, hyperlipidemia, and vascular disorders at Baseline. The subject had an eGFR at Baseline of 63 mL/min/1.73 m^2. At Study Day 85, the subject's eGFR decreased to 48 mL/min/1.73 m^2; an eGFR of 48 mL/min was confirmed at Study Day 112. Compared to Baseline, there was an elevation of urine protein/creatinine ratio at Week 16 (10.4 at Baseline, 22.7 at Week 16) and there was also trace protein by urine dipstick (which was negative at Baseline). There were no clinical signs or symptoms. The subject withdrew on Study Day 122 and had an eGFR of 46 mL/min/1.73 m^2 (nadir). The event was considered related to study drug and was not resolved. At a follow-up visit (Study Day 150), the eGFR was 53 mL/min/1.73 m^2.
- **Subject [redacted] (Glomerular filtration rate decreased; DTG + TDF/FTC group)** was age 60 to 70 years and experienced a Grade 3 drug-related AE of glomerular filtration rate decreased reported on Study Day 322. The subject had a Grade 2 eGFR (64 mL/min/1.73 m^2) at Baseline with normal creatinine (107 μmol/L). The subject had a Grade 3 decreased eGFR from Week 4 (53 mL/min/1.73 m^2) to Week 48. Creatinine became elevated at Week 24 (137.9 μmol/L) and eGFR was 47 mL/min/1.73 m^2; at retest to confirm whether the subject met renal stopping criteria, repeat eGFR had improved slightly to 50 mL/min/1.73 m^2, and therefore the subject continued on study. However, the eGFR was below 50 mL/min/1.73 m^2 at the Week 36 and Week 48 visits, and the subject was withdrawn from the study. It is not known which ART was selected after discontinuing study treatment, but eGFR was 60 mL/min/1.73 m^2 1 month after study discontinuation and was 53 mL/min/1.73 m^2 2 months after study discontinuation.
- **Subject [redacted] (Creatinine renal clearance decreased; DTG + TDF/FTC group)** was age 50 to 60 years and experienced a Grade 3 drug-related AE of creatinine renal clearance decreased on Study Day 57 (GFR 59 mL/min). The subject's Baseline GFR was 80 mL/min (Grade 2). There were no clinical signs or symptoms and no findings of proteinuria. The event was considered related to study drug. The event resolved, and the subject remained on study.

In addition to the 3 subjects noted above with Grade 3 renal events who met renal toxicity stopping criteria, 3 other subjects also met renal toxicity stopping criteria (eGFR <50 mL/min/1.73 m^2):

- **Subject [redacted] (DTG + 3TC group)** was age 60 to 70 years, had a Grade 2 eGFR (68 mL/min/1.73 m^2) at Baseline, had a past history of angina, and had current type II diabetes mellitus, hyperlipidaemia, and hypertension with pre-existing diabetic nephropathy at Baseline. The subject had poor glucose control throughout the study. On Study Day 85, Grade 2 renal impairment was reported for the subject, and the investigator decided to withdraw the subject from the study. The event was not serious, not related to study drug, and was considered to be due to poor control of diabetes.

- **Subject [redacted] (DTG + TDF/FTC group)** was age 50 to 60 years and had a Grade 2 eGFR at Baseline (60 mL/min/1.73 m^2). At Week 4, the eGFR declined below 50 mL/min/1.73 m^2, which was confirmed at the Week 8 visit. The subject withdrew from the study. The investigator attributed the elevated serum creatinine to a high protein diet. The eGFR returned to baseline after study treatment was discontinued. The investigator did not consider the serum creatinine elevation as an adverse event.
- **Subject [redacted] (DTG + TDF/FTC group)** was age 40 to50 years and had a Grade 2 eGFR at Baseline (69 mL/min/1.73 m^2) that declined to <50 mL/min/1.73 m^2 at the Week 8 visit. The subject withdrew from the study. The investigator attributed the elevated creatinine to recent ingestion of nonsteroidal analgesics. The eGFR returned to baseline at the withdrawal visit.

Finally, 1 subject was withdrawn at the discretion of the investigator due to proteinuria:

- **Subject [redacted] (withdrawn due to proteinuria; DTG + TDF/FTC group)** was age 40 to 50 years and had Grade 3 proteinuria, which was present at Baseline and persisted on study for which a diagnosis of hypertensive nephropathy was considered most likely. The subject withdrew at Week 28 due to investigator discretion, due to the possibility that the subject's blinded study treatment included TDF, which the investigator felt could worsen the subject's pre-existing proteinuria.

In the pooled analysis, subjects in both groups had mean increases in serum creatinine at Week 48. Consistent with this, the mean change from Baseline in estimated GFR using creatinine-adjusted CKD-EPI equation showed a small decrease in both groups (Table 19). In contrast to the results using creatinine, there was a slight decrease from Baseline in serum cystatin with an associated slight increase in CKD-EPI GFR using cystatin C for both the DTG + 3TC group and DTG + TDF/FTC group.

Table 19 Mean (SD) Change from Baseline in Creatinine, Cystatin C, and Estimated Glomerular Filtration Rate for Pooled (204861 and 205543) Data (Safety Population)

	POOLED	
	DTG + 3TC N=716 Mean (SD)	DTG + TDF/FTC N=717 Mean (SD)
Serum Creatinine (μmol/L)		
Baseline[a] (DTG + 3TC n= 713, DTG + TDF/FTC n= 715)	75.31 (13.955)	75.25 (13.514)
Week 48 (DTG + 3TC n= 661, DTG + TDF/FTC n= 672)	10.30 (9.783)	13.60 (9.592)
Serum GFR Using Creatinine Adjusted CKD-EPI Equation (mL/min per 1.73 m^2)		
Baseline[a] (DTG + 3TC n= 713, DTG + TDF/FTC n= 715)	111.7 (16.56)	111.1 (16.13)
Week 48 (DTG + 3TC n= 661, DTG + TDF/FTC n= 672)	-12.1 (11.66)	-15.5 (11.09)
Serum Cystatin C (mg/L)		
Baseline[a] (DTG + 3TC n= 713, DTG + TDF/FTC n= 714)	0.82 (0.311)	0.83 (0.155)
Week 48 (DTG + 3TC n= 659, DTG + TDF/FTC n= 668)	-0.06 (0.306)	-0.04 (0.121)
Serum GFR Using Cystatin C Adjusted CKD-EPI Equation (mL/min per 1.73 m^2)		
Baseline[a] (DTG + 3TC n= 713, DTG + TDF/FTC n= 714)	110.9 (21.22)	108.8 (19.15)
Week 48 (DTG + 3TC n= 659, DTG + TDF/FTC n= 668)	5.7 (16.17)	4.3 (13.71)

Data Source: GEMINI ISS/ISE Table 3.461.

a. Baseline values are actual values.

Statistical analyses of changes from Baseline in estimated GFR demonstrated that there was a statistically significant greater decrease in estimated GFR using creatinine-adjusted CKD-EPI equation in the DTG + TDF/FTC group compared with the DTG + 3TC group. For estimated GFR using cystatin C-adjusted CKD-EPI equation, there was a statistically significant greater increase in the DTG + 3TC group compared with the DTG + TDF/FTC group (Table 20).

Table 20 Statistical Analysis of Change from Baseline in Creatinine, Cystatin C, and Estimated Glomerular Filtration at Week 48 for Pooled (204861 and 205543) Data - Multiple Imputed Dataset, MAR (Safety Population)

Treatment	n	Adjusted Mean (S.E.)[a]	Difference[b]	95% CI for Difference	P-value
Serum Creatinine (µmol/L)					
DTG + 3TC (N=716)	716	10.36 (0.357)	-3.17	(-4.16, -2.18)	<0.001
DTG + TDF/FTC (N=717)	717	13.53 (0.356)			
Serum GFR Using Creatinine Adjusted CKD-EPI Equation (mL/min per 1.73 m^2)					
DTG + 3TC (N=716)	716	-12.1 (0.42)	3.4	(2.2, 4.5)	<0.001
DTG + TDF/FTC (N=717)	717	-15.5 (0.41)			
Serum Cystatin C (mg/L)					
DTG + 3TC (N=716)	716	-0.07 (0.004)	-0.03	(-0.04, -0.02)	<0.001
DTG + TDF/FTC (N=717)	717	-0.04 (0.004)			
Estimated Serum GFR Using Cystatin C Adjusted CKD-EPI Equation (mL/min per 1.73 m^2)					
DTG + 3TC (N=716)	716	6.3 (0.44)	2.2	(1.0, 3.4)	<0.001
DTG + TDF/FTC (N=717)	717	4.1 (0.44)			

Data Source: GEMINI ISS/ISE Table 3.521.

a. Adjusted mean is the estimated mean change from baseline at Week 48 in each arm calculated from ANCOVA model adjusting for the following covariates/factors: Study (204861 vs. 205543), treatment, baseline plasma HIV-1 RNA (factor), baseline CD4+ cell count (factor), age, sex (factor), race (factor), presence of diabetes mellitus (factor), presence of hypertension (factor) and baseline biomarker value.

b. Differences: DTG + 3TC - DTG + TDF/FTC.

Findings from sensitivity analyses using Mixed Model Repeated Measures analysis (Data Source: GEMINI ISS/ISE Table 3.541) were consistent with those observed using the Multiple Imputed Dataset (MAR) method.

3.3.1. Urine Concentration Changes

Changes in renal function – including renal failure, renal impairment, elevated creatinine, hypophosphatemia, and proximal tubulopathy (including Fanconi syndrome) – have been reported with the use of TDF in clinical practice. Therefore, evaluations of ratios for urine albumin/creatinine, protein/creatinine, beta-2 microglobulin/creatinine, and retinol binding protein/creatinine were also performed to more comprehensively assess for any impact of study treatment on renal function, as these measurements include markers of possible renal tubular dysfunction.

A single subject (DTG + TDF/FTC group) experienced an event of urine albumin/creatinine ratio increased, which was Grade 2, non-serious, not considered

related to study drug, and did not lead to withdrawal (Data Source: 204861 Week 48 CSR Listing 15, 205543 Week 48 CSR Listing 15). There were no reported AEs of urine protein/creatinine ratio increased.

Data for the change from Baseline urine albumin/creatinine and protein/creatinine ratios are displayed in GEMINI ISS/ISE Table 3.38, and data for the change from Baseline in urine beta-2 microglobulin/creatinine and retinol binding protein/creatinine ratios are displayed in GEMINI ISS/ISE Table 3.462.

Results of statistical analyses for the differences between treatment groups for the change from Baseline in renal biomarkers at Week 48 are shown in Table 21. For the change from Baseline in urine protein/creatinine, beta-2 microglobulin/creatinine, and retinol binding protein/creatinine Week 48/Baseline ratios, there was a modest reduction in the DTG + 3TC group (indicating improvement) and a minimal increase in the DTG + TDF/FTC group, which resulted in the difference between treatments being statistically significant.

Table 21 Statistical Analysis of Change from Baseline in Renal Biomarkers at Week 48 for Pooled (204861 and 205543) Data – Log Transformed Data, Multiple Imputed Dataset, MAR (Safety Population)

Treatment	n	Week 48/ Baseline Ratio[a]	95% CI for Ratio	Treatment Ratio[b]	95% CI for Treatment Ratio	P-value
Urine Albumin/Creatinine Ratio (g/mol)[a]						
DTG + 3TC (N=716)	716	0.914	(0.863, 0.969)	0.917	(0.848,0.993)	0.032
DTG + TDF/FTC (N=717)	717	0.996	(0.942, 1.054)			
Urine Protein/Creatinine Ratio (g/mol)[a]						
DTG + 3TC (N=716)	716	0.869	(0.838, 0.901)	0.845	(0.803,0.888)	<0.001
DTG + TDF/FTC (N=717)	717	1.029	(0.993, 1.066)			
Urine Beta-2 Microglobulin/Creatinine Ratio (mg/mol)						
DTG + 3TC (N=716)	716	0.923	(0.845, 1.007)	0.704	(0.621, 0.797)	<0.001
DTG + TDF/FTC (N=717)	717	1.312	(1.187, 1.450)			
Urine Retinol Binding Protein 4/Creatinine Ratio (µg/mol)						
DTG + 3TC (N=716)	716	0.926	(0.871, 0.984)	0.831	(0.762, 0.906)	<0.001
DTG + TDF/FTC (N=717)	717	1.114	(1.048, 1.184)			

Data Source: GEMINI ISS/ISE Table 3.522.

a. Represents the estimated ratio of geometric means (Week 48 over Baseline) calculated from an ANCOVA model applied to loge transformed data adjusting for the following covariates/factors: Study (204861 vs. 205543), treatment, Baseline plasma HIV-1 RNA (factor), Baseline CD4+ cell count (factor), age, sex (factor), race (factor), presence of diabetes mellitus (factor), presence of hypertension (factor) and loge transformed Baseline biomarker value.

b. Represents the ratio of estimates obtained per treatment group (DTG + 3TC / DTG + TDF/FTC).

3.4. Creatine Phosphokinase Elevations

A total of 103 (14%) subjects in the DTG + 3TC group and 88 (12%) subjects in the DTG + TDF/FTC group experienced emergent elevated creatine kinase levels (Table 14; Data Source: GEMINI ISS/ISE Table 3.55). The majority of these events were attributed to exercise or heavy physical exertion.

Four AEs of blood creatine phosphokinase increased were reported (2 in each treatment group; all were grade 1 and not related to study drug).

Of note, one subject (DTG + TDF/FTC group) reported Grade 3 rhabdomyolysis with CK elevation of 11732 u/L on local laboratory testing (Subject [redacted]; see Section 2.1.4.1).

3.5. Lipid Parameters

In both studies, a small proportion of subjects in each treatment group experienced adverse changes in lipid parameters. The total cholesterol/HDL cholesterol ratios were comparable between treatment groups at Week 48.

Not all subjects were included in the analyses of lipid parameters; subject data for individuals on lipid lowering agents at Baseline were excluded, as were any subject data collected after starting lipid lowering agents post baseline. A small and similar proportion of subjects in each pooled treatment group was using lipid modifying agents at Baseline (DTG + 3TC: 29 [4%]; DTG + TDF/FTC: 23 [3%]) (Data Source: GEMINI ISS/ISE Table 1.28). A small and similar proportion of subjects began receiving lipid modifying agents after entering the study (DTG + 3TC: 23 [3%]; DTG + TDF/FTC: 13 [2%]) (Data Source: GEMINI ISS/ISE Table 1.29).

Only fasting lipid data were summarized. Across both studies, a small proportion of subjects in both treatment groups had emergent cholesterol and triglycerides toxicities of Grade 2 or higher at Week 48 (Table 22).

Table 22 Summary of Maximum Emergent Clinical Chemistry Toxicities for Selected Lipid Parameters for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED	
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=258 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)
Cholesterol						
Grade 1	36 (10)	18 (5)	59 (16)	21 (6)	95 (13)	39 (5)
Grade 2	19 (5)	9 (3)	11 (3)	5 (1)	30 (4)	14 (2)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
LDL Cholesterol[a]						
Grade 1	27 (8)	15 (4)	34 (9)	17 (5)	61 (9)	32 (4)
Grade 2	9 (3)	7 (2)	11 (3)	5 (1)	20 (3)	12 (2)
Grade 3	5 (1)	3 (<1)	3 (<1)	0	8 (1)	3 (<1)
Grade 4	0	0	0	0	0	0
Triglycerides						
Grade 1	45 (13)	34 (9)	47 (13)	45 (13)	92 (13)	79 (11)
Grade 2	5 (1)	7 (2)	8 (2)	6 (2)	13 (2)	13 (2)
Grade 3	5 (1)	2 (<1)	3 (<1)	1 (<1)	8 (1)	3 (<1)
Grade 4	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)

Data Source: 204861 Week 48 CSR Table 3.55; 205543 Week 48 CSR Table 3.55; GEMINI ISS/ISE Table 3.55.
Note: Fasting data is shown for lipids.
Note: Subjects with missing Baseline are assumed to be normal.
a. Generally, LDL was calculated; however, direct measurements were taken when triglycerides were very high or very low.

Pooled statistical analysis of change from Baseline in fasting lipids at Week 48 showed that subjects treated with DTG + 3TC had a mean increase in LDL and HDL values at Week 48 compared with Baseline, whereas subjects in the DTG + TDF/FTC group had a mean decrease for LDL cholesterol and a small mean increase in HDL cholesterol at Week 48 compared with Baseline (Data Source: GEMINI ISS/ISE Table 3.34). The adjusted differences between treatment groups in LDL and HDL were statistically significant (both $p < 0.001$). However, both treatment groups showed an overall reduction in the mean total cholesterol/HDL ratio, with a greater reduction in the DTG + TDF/FTC group ($p = 0.018$). Subjects treated with DTG + 3TC showed a small mean increase in triglycerides compared with a small mean decrease in subjects treated with DTG + TDF/FTC; the difference between treatment groups was statistically significant ($p = 0.046$).

The statistical analysis of maximum emergent Grade 2 or higher laboratory abnormalities in fasting LDL cholesterol was assessed as a secondary endpoint. In the pooled analysis, a small number of subjects in each treatment group experienced LDL cholesterol toxicities ≥ Grade 2, with fewer subjects in the DTG + TDF/FTC group. The difference between the 2 treatment groups was statistically significant (Table 23).

Table 23 Statistical Analysis of Maximum Emergent Grade 2 or Greater Fasting LDL Cholesterol Abnormalities by Week 48 for Pooled Data (204861 and 205543) (Safety Population)

	DTG + 3TC	DTG + TDF/FTC	Difference in Percentage (95% CI)	Fisher's exact P-value[a]
Fasting LDL cholesterol (calculated or direct) Grade >=2	28/642 (4%)	15/652 (2%)	2.1 (0.1, 4.0)	0.044

Data Source: GEMINI ISS/ISE Table 3.40.
Note: Division of AIDS (DAIDS) version 2.0, November 2014 was used for severity grading.
Note: Subjects without any fasting LDL cholesterol value prior to Week 48 or subjects who had baseline lipids-lowering agents were not included. Lipids LOCF dataset was used.
a. Fisher's Exact P-value was based on a test that has been stratified for Study (204861 vs. 205543).

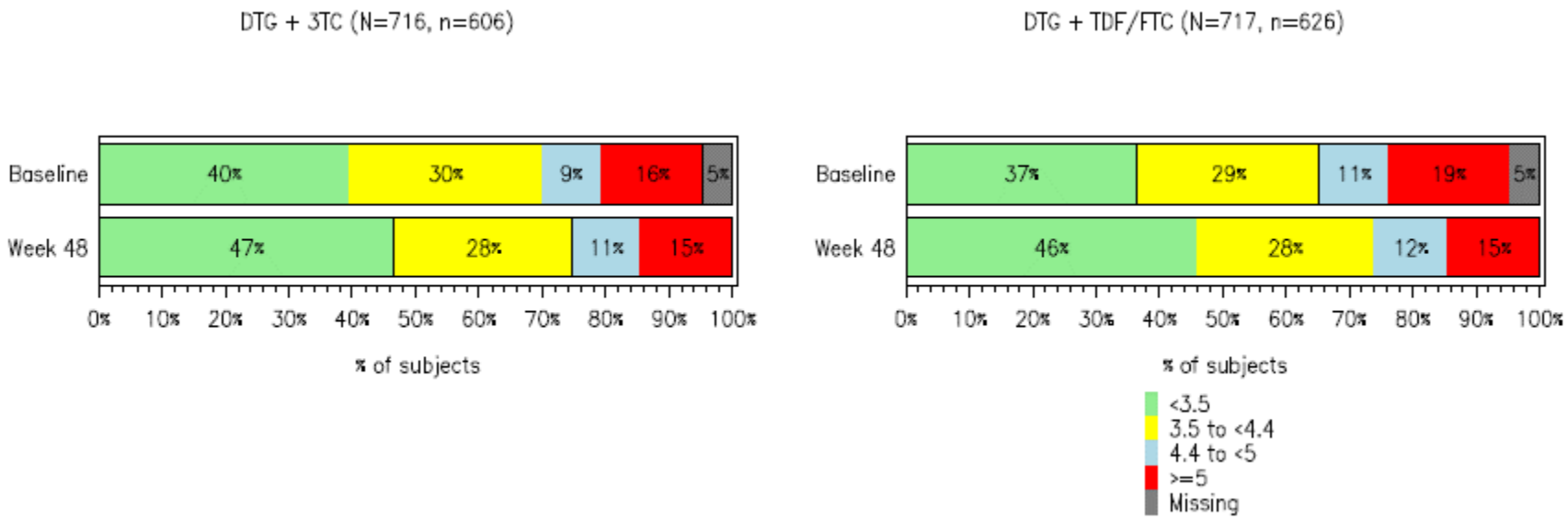
3.5.1. NCEP Categories

NCEP categories for Baseline versus maximum emergent total cholesterol or LDL cholesterol, or Baseline versus minimum emergent HDL cholesterol were evaluated (Data Source: GEMINI ISS/ISE Table 3.41, GEMINI ISS/ISE Table 3.42). These assessments showed that a small number of subjects in the DTG + 3TC group had shifts to a less favorable risk category for total cholesterol and LDL cholesterol, but had shifts to more favorable risk categories for HDL cholesterol. Subjects in the DTG + TDF/FTC group had shifts to more favorable risk categories for LDL cholesterol, but minimal changes in risk categories for total cholesterol and HDL.

3.5.2. Total Cholesterol/HDL Cholesterol Ratio

Figure 3 shows the proportions of subjects at Baseline and Week 48 for categories of total cholesterol/HDL cholesterol ratio. For both pooled treatment groups, the overall profiles were generally improved from Baseline, and the proportions of subjects showing favorable improvements in total cholesterol/HDL cholesterol ratio were similar between the 2 treatment groups.

Figure 3 Bar Chart of Total Cholesterol/HDL Ratio Category at Week 48 versus Baseline for Pooled Data (204861 and 205543) (Safety Population)



Data Source: GEMINI ISS/ISE Figure 3.9.

3.6. Lipase

Emergent chemistry toxicities of lipase elevations were similar between the treatment groups (DTG + 3TC: 89 [12%]; DTG + TDF/FTC: 110 [15%]) (Table 14; Data Source: GEMINI ISS/ISE Table 3.55). Although there were increases in lipase up to Grade 4, none of these were symptomatic.

Across both studies, there was a single case of acute pancreatitis reported in the DTG + 3TC group (Grade 2 event occurring at Study Day 234 that was non-serious and was not related to study drug).

3.7. Hematology

Overall, there were few emergent toxicities (i.e., decreased values) in hematology parameters. The maximum intensity of emergent hematology toxicities was comparable across treatment groups in both studies and in the pooled analysis (Table 24).

Table 24 Summary of Maximum Emergent Hematology Toxicities for Individual Studies (204861 and 205543) and Pooled Data (Safety Population)

	204861		205543		POOLED	
	DTG + 3TC N=356 n (%)	DTG + TDF/FTC N=258 n (%)	DTG + 3TC N=360 n (%)	DTG + TDF/FTC N=359 n (%)	DTG + 3TC N=716 n (%)	DTG + TDF/FTC N=717 n (%)
Hemoglobin						
Grade 1	6 (2)	4 (1)	3 (<1)	3 (<1)	9 (1)	7 (<1)
Grade 2	1 (<1)	1 (<1)	3 (<1)	3 (<1)	4 (<1)	4 (<1)
Grade 3	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Grade 4	0	0	1 (<1)	0	1 (<1)	0
Leukocytes						
Grade 1	3 (<1)	1 (<1)	3 (<1)	3 (<1)	6 (<1)	4 (<1)
Grade 2	2 (<1)	2 (<1)	1 (<1)	0	3 (<1)	2 (<1)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Neutrophils						
Grade 1	6 (2)	7 (2)	10 (3)	4 (1)	16 (2)	11 (2)
Grade 2	7 (2)	3 (<1)	3 (<1)	1 (<1)	10 (1)	4 (<1)
Grade 3	2 (<1)	2 (<1)	1 (<1)	1 (<1)	3 (<1)	3 (<1)
Grade 4	1 (<1)	0	0	0	1 (<1)	0
Platelets						
Grade 1	6 (2)	5 (1)	6 (2)	4 (1)	12 (2)	9 (1)
Grade 2	3 (<1)	3 (<1)	5 (1)	5 (1)	8 (1)	8 (1)
Grade 3	0	1 (<1)	0	0	0	1 (<1)
Grade 4	0	0	0	0	0	0

Data Source: 204861 Week 48 CSR Table 3.56; 205543 Week 48 CSR Table 3.56; GEMINI ISS/ISE Table 3.56.
Note: Subjects with missing Baseline are assumed to be normal.

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

4.1. Electrocardiograms

A 12-lead ECG was performed at the Screening visit in each of the studies to provide a Baseline assessment. No additional ECGs were required per either protocol, but could be performed if indicated. There were no clinically significant ECG findings post-Screening (Data Source: 204861 Week 48 CSR Listing 61, 205543 Week 48 CSR Listing 61).

4.2. Vital Sign Measurements

In both studies, vital signs measurements were recorded at Baseline only. There were no findings to report with regard to vital signs.

4.3. Biomarkers

4.3.1. Renal Biomarkers

At 48 weeks for the pooled analysis, DTG + 3TC treatment was associated with a significantly greater increase in the estimated GFR using cystatin C-adjusted CKD-EPI equation compared with DTG + TDF/FTC treatment (Section 3.3). While the change from Baseline at Week 48 in urine protein/creatinine ratio was modest, the ratio was significantly decreased (indicating improvement) in the DTG + 3TC group compared with the DTG + TDF/FTC group (Section 3.3.1).

4.3.2. Bone Biomarkers

HIV infection is associated with BMD loss. The initiation of ART is also associated with some BMD loss, and the risk is higher with some ARV drugs. The bone-specific biomarkers used in the study are markers of bone turnover, which is associated with increased loss of BMD. Lower rates of biomarkers suggest less bone turnover.

Vitamin D is not a biomarker for bone turnover. However, adequate levels are required for maintenance of BMD. As some antiretroviral drugs have been possibly associated with changes in Vitamin D levels, changes in Vitamin D were measured in these studies along with bone biomarkers.

At Week 48 in the pooled analysis, all markers of bone turnover assessed increased from Baseline in both treatment groups. Larger increases in bone turnover markers were observed in the DTG + TDF/FTC group (Table 25). This difference between the treatment groups was statistically significant for each of the bone biomarkers evaluated, in favor of the DTG + 3TC group (Table 26).

Vitamin D levels declined slightly at Week 48 in the DTG + 3TC group and increased slightly in the DTG + TDF/FTC group. Although the difference between groups reached statistical significance, the magnitude of the changes was small overall. Concomitant use

of Vitamin D was reported in 4% of the total pooled population, with a slightly higher number of subjects reporting use in the DTG + TDF/FTC group compared with the DTG + 3TC group (DTG + 3TC: 24 [3%]; DTG + TDF/FTC: 31 [4%]) (Data Source: GEMINI ISS/ISE Table 1.25).

Findings from sensitivity analyses using Mixed Model Repeated Measures analysis (Data Source: 204861 Week 48 CSR Table 3.51, 205543 Week 48 CSR Table 3.51) were consistent with the analyses presented here using the Multiple Imputed Dataset (MAR) method.

Table 25 Summary of Changes from Baseline in Bone Biomarkers for Pooled (204861 and 205543) Data (Safety Population)

	POOLED					
	DTG + 3TC N=716			DTG + TDF/FTC N=717		
	n	Mean (SD)	Median	n	Mean (SD)	Median
Serum Bone Specific Alkaline Phosphatase (µg/L)						
Baseline[a]	711	12.45 (3.930)	12.00	713	12.85 (3.908)	12.30
Week 48	656	1.24 (3.583)	0.90	668	4.01 (4.713)	3.30
Serum Osteocalcin (µg/L)						
Baseline[a]	711	19.90 (7.412)	18.90	716	20.67 (7.840)	20.00
Week 48	658	0.66 (6.305)	0.90	666	6.10 (7.638)	5.40
Serum Procollagen 1 N-Terminal Propeptide (µg/L)						
Baseline[a]	712	51.2 (23.27)	47.0	716	52.5 (23.28)	48.0
Week 48	657	0.8 (19.59)	1.0	671	12.7 (21.16)	13.0
Serum Type 1 Collagen C-Telopeptide (µg/L)						
Baseline[a]	710	0.4198 (0.23430)	0.3755	708	0.4423 (0.25568)	0.3900
Week 48	656	0.1386 (0.26325)	0.1170	664	0.3335 (0.35314)	0.2890
Serum Vitamin D (nmol/L)						
Baseline[a]	713	54.2 (34.79)	50.0	714	54.0 (23.91)	53.0
Week 48	659	-1.8 (23.31)	-2.0	668	2.1 (21.52)	0.0

Data Source: GEMINI ISS/ISE Table 3.43.

a. Baseline values are actual values.

Table 26 Statistical Analysis of Change from Baseline in Bone Biomarkers at Week 48 for Pooled (204861 and 205543) Data – Multiple Imputed Dataset, MAR (Safety Population)

Treatment	n	Adjusted Mean[a] (SE)	Difference[b]	95% CI for Difference	P-value
Serum Bone Specific Alkaline Phosphatase (µg/L)					
DTG + 3TC (N=716)	716	1.22 (0.159)	-2.86	(-3.30, -2.41)	<0.001
DTG + TDF/FTC (N=717)	717	4.07 (0.160)			
Serum Osteocalcin (µg/L)					
DTG + 3TC (N=716)	716	0.60 (0.251)	-5.56	(-6.26, -4.86)	<0.001
DTG + TDF/FTC (N=717)	717	6.17 (0.253)			
Serum Procollagen 1 N-Terminal Propeptide (µg/L)					
DTG + 3TC (N=716)	716	0.4 (0.63)	-12.7	(-14.4, -10.9)	<0.001
DTG + TDF/FTC (N=717)	717	13.1 (0.63)			
Serum Type 1 Collagen C-Telopeptide (µg/L)					
DTG + 3TC (N=716)	716	0.1361 (0.01174)	-0.1985	(-0.2314, -0.1657)	<0.001
DTG + TDF/FTC (N=717)	717	0.3346 (0.01192)			
Serum Vitamin D (nmol/L)					
DTG + 3TC (N=716)	716	-1.4 (0.70)	-3.2	(-5.1, -1.2)	0.001
DTG + TDF/FTC (N=717)	717	1.7 (0.70)			

Data Source: GEMINI ISS/ISE Table 3.49.

a. Adjusted mean is the estimated mean change from Baseline at Week 48 in each arm calculated from ANCOVA model adjusting for the following covariates/factors: Study (204861 vs. 205543), treatment, Baseline plasma HIV-1 RNA (factor), Baseline CD4+ cell count (factor), age, sex (factor), race (factor), BMI (factor), smoking status (factor), current Vitamin D use (factor) and Baseline biomarker value.

b. Differences: DTG + 3TC - DTG + TDF/FTC.

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1. Intrinsic Factors

5.1.1. Gender, Age, and Race

Data from studies with DTG and 3TC do not suggest any effect of age, gender, or race on the safety profile of either component.

The safety of DTG + 3TC as a 2-drug regimen has not been evaluated in clinical studies enrolling adolescent subjects. However, a summary of the existing safety data in adolescents or pediatric subjects from the single-entity components and other FDCs containing DTG and/or 3TC is presented in the Adolescent Extrapolation Report (see GSK Document Number 2018N363795_00 and m2.7.2 Section 3.3.4) included with the submission. Collectively, these data support the safety of the DTG + 3TC as a 2-drug regimen in adolescent patients.

In the 204861 and 205543 pooled analysis, a smaller proportion of female subjects compared with male subjects reported AEs (Table 27); the difference was primarily due to differences in reporting rates of Grade 1 events.

Table 27 Summary of Adverse Events by Maximum Grade and Gender for Pooled Data (204861 and 205543) (Safety Population)

	Pooled					
	DTG + 3TC n (%)		DTG + TDF/FTC n (%)		Total n (%)	
	Female N=113	Male N=603	Female N=98	Male N=619	Female N=211	Male N=1222
Any event	82 (73)	461 (76)	68 (69)	511 (83)	150 (71)	972 (80)
Grade 1	15 (13)	124 (21)	15 (15)	139 (22)	30 (14)	263 (22)
Grade 2	58 (51)	298 (49)	47 (48)	322 (52)	105 (50)	620 (51)
Grade 3	8 (7)	30 (5)	5 (5)	46 (7)	13 (6)	76 (6)
Grade 4	1 (<1)	7 (1)	1 (1)	4 (<1)	2 (<1)	11 (<1)
Grade 5	0	2 (<1)	0	0	0	2 (<1)

Data Source: GEMINI ISS/ISE Table 3.11.

Proportions of subjects reporting any adverse event for individuals age <35 years (DTG + 3TC 312/420 [74%], DTG + TDF/FTC 326/408 [80%]) and age 35 to <50 years (DTG + 3TC 186/231 [81%], DTG + TDF/FTC 186/229 [81%]) were similar between the treatment groups (Data Source: GEMINI ISS/ISE Table 3.11). A lower proportion of older subjects (≥50 years) reported AEs in the DTG + 3TC group compared with the DTG + TDF/FTC group (DTG + 3TC 45/65 [69%], DTG + TDF/FTC 67/80 [84%]); however, findings for this subgroup should be interpreted with caution given the smaller number of subjects in this age subgroup.

Some differences were observed in the proportions of subject reporting AEs between races in both treatment groups (Table 28); however, the majority of subjects were white and there were relatively small numbers in the other groups. AE reporting was comparable between the treatment groups for Asian subjects; for each of the other race subgroups, subjects reported AEs at a lower frequency for the DTG + 3TC group compared with the DTG + TDF/FTC group.

Table 28 Summary of Adverse Event Incidence by Race for Pooled Data (204861 and 205543) (Safety Population)

	POOLED		
Race	DTG + 3TC n/N (%)	DTG + TDF/FTC n/N (%)	Total n/N (%)
African American /African Heritage	78/99 (79)	65/76 (86)	143/175 (82)
Asian	57/71 (80)	58/72 (81)	115/143 (80)
White	352/480 (73)	390/497 (78)	742/977 (76)
Other	56/66 (85)	66/72 (92)	122/138 (88)

Data Source: GEMINI ISS/ISE Table 3.11.

5.1.2. Hepatitis B and/or C Virus Co-Infection

In studies with DTG, a higher incidence of liver chemistry elevations has been observed in patients co-infected with HBV and/or HCV.

In 204861 and 205543, subjects were excluded if they had evidence of HBV infection at screening, had an anticipated need for hepatitis C therapy during the first 48 weeks of the study, or for use of interferon therapy. Based on screening criteria, there were no HBV-infected subjects in this study.

New data in HCV co-infected subjects are available from these studies from the small number of subjects positive for HCV at Baseline (Table 29). In the pooled treatment groups, there were greater proportions of subjects with elevations of transaminases in HCV co-infected subjects compared with HCV-negative subjects for both treatment groups.

Table 29 Summary of Maximum Emergent Clinical Chemistry Toxicities by Baseline Hepatitis C Status for Selected Laboratory Parameters for Pooled Data (204861 and 205543) (Safety Population)

	POOLED			
	DTG + 3TC		DTG + TDF/FTC	
	HCV-Positive N=39 n (%)	HCV-Negative N=676 n (%)	HCV-Positive N=49 n (%)	HCV-Negative N=668 n (%)
Alanine Aminotransferase				
Grade 1	3 (8)	40 (6)	9 (18)	52 (8)
Grade 2	3 (8)	10 (1)	2 (4)	18 (3)
Grade 3	4 (10)	4 (<1)	4 (8)	3 (<1)
Grade 4	1 (3)	9 (1)	1 (2)	10 (1)
Aspartate Aminotransferase				
Grade 1	3 (8)	40 (6)	8 (16)	56 (8)
Grade 2	6 (15)	16 (2)	2 (4)	17 (3)
Grade 3	1 (3)	6 (<1)	4 (8)	13 (2)
Grade 4	0	5 (<1)	0	7 (1)
Bilirubin				
Grade 1	5 (13)	40 (6)	6 (12)	45 (7)
Grade 2	1 (3)	8 (1)	0	17 (3)
Grade 3	0	2 (<1)	0	6 (<1)
Grade 4	0	5 (<1)	0	1 (<1)

Data Source: GEMINI ISS/ISE Table 3.71.
Note: Borderline hepatitis C is included in hepatitis C.

5.1.3. Hepatic Impairment

Subjects with severe hepatic impairment (Child-Pugh Grade C) were excluded from studies 204861 and 205543. There are therefore no clinical data on the use of DTG + 3TC as a 2-drug regimen in HIV-infected subjects with severe hepatic impairment.

As described in m2.7.2 Section 3.1.5, DTG PK are similar between healthy subjects and subjects with moderate hepatic impairment (Child-Pugh Grade B); no DTG dose adjustment is needed in subjects with mild to moderate hepatic impairment (Child-Pugh Grade A or B). The use of DTG in severe hepatic impairment has also not been studied.

As described in m2.7.2 Section 3.2.5, the use of 3TC in subjects with moderate or severe hepatic impairment was evaluated in study NUCB1002. Hepatic impairment did not impact significantly on 3TC clearance, so no dose modification is required for patients taking 3TC with moderate or severe hepatic impairment (unless accompanied by renal impairment where CrCl <50 mL/min).

Based on current labeling for the single entities, DTG/3TC FDC may be administered without dose adjustment in patients with mild or moderate hepatic impairment (Child-Pugh Grades A & B). DTG/3TC FDC is not recommended for use in patients with severe hepatic impairment.

5.1.4. Renal Impairment

As described in m2.7.2 Section 3.1.5, there is no clinically relevant difference in DTG PK in subjects with mild/moderate renal impairment or severe renal impairment (CrCL <30 mL/min). No DTG dosage adjustment is needed for subjects with mild, moderate, and severe (CrCL<30 mL /min, not on dialysis) renal impairment. No studies have been conducted by the MAH to evaluate DTG PK in subjects on hemodialysis; however, no effect of hemodialysis on DTG PK is expected due to high protein binding of DTG in plasma.

As described in m2.7.2 Section 3.2.5, two studies (NUCB1003, NUCA1004) demonstrated that there was a linear relationship between 3TC clearance and renal function (assessed as CrCl), where a reduction in renal function produced a higher exposure to 3TC. Therefore, dose modification of 3TC is required in patients where CrCl falls below 50 mL/min.

Based on current labeling for the single entities, DTG/3TC FDC is not recommended for use in patients with CrCl less than 50 mL/min.

5.2. Extrinsic Factors

5.2.1. Food Effect

Food effect was evaluated in 204994. Key findings for the [redacted] formulation (selected for development) in the fasted and fed state are summarized as follows.

- Administration of the [redacted] FDC tablet with a high fat meal resulted in higher plasma DTG $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and Cmax, lower plasma 3TC Cmax, and no difference in 3TC AUC parameters. The magnitude of the food effect on DTG and 3TC was no greater than that observed in prior studies with the single entities and is not considered clinically significant. These results support the recommendation that the FDC tablet can be given without regard to meals.

- The DTG/3TC FDC may be taken with or without food. This is consistent with the prescribing information for the DTG and 3TC single entities and is supported by the food effect results for the [redacted] FDC tablet.

Detailed information on the effect of food on DTG/3TC FDC bioavailability is provided in m2.7.1 Section 2.4.

5.3. Drug Interactions

No clinically significant drug interactions are expected between DTG and 3TC.Refer to m2.7.2 Section 3.1.6.2 and m2.7.2 Section 3.2.6.1 for a discussion of drug interactions for DTG and 3TC, respectively.

Refer to m2.7.2 Section 3.3.2 for a summary of the management of drug-drug interactions for the DTG/3TC FDC.

5.4. Use in Pregnancy and Lactation

Women who were pregnant or breastfeeding were excluded from enrollment in 204861 and 205543.

Up to the data cut-off date for the Week 48 analysis, 3 subjects in 204861 (DTG +3TC 1; DTG + TDF/FTC 2) and 1 subject in 205543 (DTG + 3TC group) were discontinued from the study due to pregnancy (see 204861 Week 48 CSR Section 7.7 and 205543 Week 48 CSR Section 7.7, respectively).

Of the 4 subjects who became pregnant, 2 subjects had an elective abortion (1 in each treatment group) and 2 subjects had a spontaneous abortion (1 in each treatment group), all within the first trimester. The sites reported there were no congenital anomalies evident for 1 of the cases of spontaneous abortion (DTG +TDF/FTC group) and 1 of the cases of elective abortion (DTG + 3TC group); the sites did not provide any information for the other 2 cases with regard to the presence of absence of congenital anomalies.

One additional pregnancy has been reported since the Week 48 data cut-off date, in 204861; the pregnancy is currently ongoing.

Full narratives for these pregnancies are provided in 204861 Week 48 CSR Section 13 and 205543 Week 48 CSR Section 13.

In a preliminary analysis of an ongoing birth outcome surveillance study in Botswana, there have been 4 cases (as of May 2018) of neural tube defects reported in 426 infants born to mothers who were exposed to DTG-containing regimens from the time of conception. This is further described in Section 6.1.

5.4.1. Nonclinical Data (Reprotox Studies)

No nonclinical reprotoxicity studies have been conducted with DTG + 3TC. For a complete discussion of the effects of DTG and 3TC single-entity components on reproductive and developmental toxicity see m2.4.

5.5. Safety in Clinical Pharmacology Studies Conducted for the DTG/3TC FDC Program

5.5.1. Relative Bioavailability Study (204993)

204993 was a randomized, open label, three-way crossover study to evaluate the relative bioavailability of 2 experimental FDC formulations of DTG/3TC. Each subject was to receive the reference Treatment A, DTG 50 mg and 3TC 300 mg, administered as single-entity tablets, and 2 experimental [redacted] DTG/3TC FDC tablets (Treatment B and C); under a fasted state over 3 treatment periods in 6 sequences in a randomized fashion. The reference and test formulations were administered to subjects after at least a 10-hour fast. There was a washout period of 7 days between dosing periods.

A total of 30 subjects were enrolled and analyzed in the study. Twenty-nine subjects completed the study, and 1 subject withdrew consent in Treatment Period 1.

A total of 7 subjects (23%) reported 8 AEs during the study (Data Source: 204993 CSR Section 6.1). None of the AEs were reported in more than 1 subject and none were considered related to study drug. There was 1 event with a maximum intensity of moderate (catheter site inflammation), and all other events were mild (Data Source: 204993 Listing 12). There were no deaths or SAEs. There were no AEs that lead to discontinuation of the study drug or withdrawal from the study. There were no laboratory abnormalities reported as an AE.

Further information on 204993 can be found in m.2.7.1 Section 2.3.1.1.

5.5.2. Bioequivalence Study (204994)

204994 was a Phase I open-label, randomized, single-dose, crossover, bioequivalence study of two FDC tablets of DTG/3TC versus DTG + 3TC single entities and food effect assessment in healthy volunteers.

Two formulations were investigated: 1) a [redacted] formulation manufactured using the same quantitative composition used in exploratory RBA study 204993 and 2) a [redacted].

A total of 154 subjects were randomized in this study (78 in Part 1 and 76 in Part 2), and 147 subjects completed the study.

In total, 18 subjects (24%) had AEs with FDC [redacted] (this tablet was not selected for further development); 12 subjects (16%) with FDC [redacted] as compared with 29 subjects (19%) with the reference tablets DTG 50 mg plus EPIVIR 300 mg. Of these, 5 subjects (7%) had drug-related AEs with FDC [redacted] and 5 subjects (7%) with FDC [redacted] compared with 8 (5%) subjects with the reference tablets DTG 50 mg + 3TC 300 mg. No drug related AE was reported in more than 1% of subjects except for headache (4 subjects [5%] in FDC [redacted], 2 subjects [3%] in FDC [redacted] and 3 subjects [2%] in reference tablets DTG 50 mg + 3TC 300 mg). There were no deaths and serious adverse events in both Part 1 and Part 2 of the study.

Further information on 204994 can be found in m2.7.1 Section 2.1.1.1 (bioequivalence) and m2.7.1 Section 2.4.1.1 (effect of food).

5.6. Historical DTG and 3TC Safety Data Supporting the DTG/3TC FDC

As detailed in m2.7.1 Section 2.1.1.1, the bioequivalence study (204994) showed that in fasted state, the proposed commercial formulation of DTG 50 mg and 3TC 300 mg was bioequivalent for DTG AUC(0-∞), AUC(0-72), and Cmax and for 3TC AUC(0-∞) and AUC(0-t). The [redacted] FDC DTG AUC(0-t) was ~16% higher compared to the reference DTG although a sensitivity analysis showed bioequivalence. In addition, the 3TC Cmax was ~32% higher than that of the reference EPIVIR. This section summarizes additional historical DTG and 3TC safety data supporting the use of the proposed commercial DTG/3TC [redacted] FDC formulation.

5.6.1. DTG Component

In addition to the approved dosing of DTG 50 mg once daily, DTG 50 mg is also approved for twice daily administration (for use in patients when certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance are present). In a registrational Phase 3 study of DTG (ING112574), substantially higher steady state AUC values were obtained with 50 mg twice daily doses compared with once daily doses without additional safety concerns. Treatment-emergent adverse reactions in ING112574 were generally similar compared with observations with the 50-mg once-daily dose in Phase 3 trials [Tivicay Product Information, 2017]. Based on the data available from twice daily dosing, the ~16% higher AUC(0-t) is not clinically significant.

5.6.2. 3TC Component

Clinical safety data from registrational studies of 3TC demonstrate that the observed ~32% increase in 3TC Cmax exposure does not impact patient safety. Several previously-submitted dose-ranging, pivotal and open-label studies have demonstrated no dose-related increase in the overall incidence of AEs and no significant safety differences between the standard 3TC 300 mg/day dose and the higher 3TC 600 mg/day dose. The sample sizes from several studies that investigated safety in HIV-infected participants receiving 3TC doses of 300 mg BID or higher (i.e., twice the approved 3TC total daily dose) are shown in Table 30. A short summary of the study design, population, treatment

details and key safety findings from the clinical study reports for the supportive studies identified in Table 30 are provided in Appendix Table 1.

Table 30 Sample Size of Key Registrational Studies of Lamivudine Evaluating Approved or Higher Doses

Study Number	3TC 150 mg BID (300 mg/day) N	3TC 300 mg BID (600 mg/day) N
NUCA3001 (registrational)	92	181
NUCB3001[a] (registrational)		65
NUCA3002 (registrational)	84	84
NUCB3002 (registrational)	75	75
NUCA2001[b] (dose ranging)		48[b]
NUCB2001[b] (dose ranging)		44[b]
NUCA3004[c] (expanded access)	16345	7884
NUCB3004[c] (expanded access)		722
All participants	16596	9103

a. NUCB3001 study did not have a 3TC 150 mg BID arm
b. In the dose ranging studies the number of participants who received a received a 3TC 600 mg/day dose was estimated as follows: per protocol, all participants who weighed ≥70 kg (median weight for NUCA2001 was 72.5 and NUCB2001 was 70 kg) and were randomized to the 8 mg/kg/day group would have received at least 600 mg 3TC/day. Therefore, all participants who received ≥ 8 mg /day (i.e. the 8, 12 or 20 mg/kg/day) may considered to be at a dose of 3TC ≥600 mg/day.
c. The expanded access programs also enrolled paediatric study participants. Only study participants with case report forms are included from these two studies.

5.6.2.1. 3TC Dose Ranging Studies Supporting Safety of Higher 3TC Cmax

In two dose-ranging studies (NUCA2001 and NUCB2001), 201 HIV-infected participants received 3TC monotherapy at doses from ~35 mg/day (0.5 mg/kg/day) to ~1400 mg/day (20 mg/kg/day) for at least 24 weeks. In these studies, the Cmax following repeated 560-mg, 840-mg, and 1400-mg total daily doses were similar to or greater than the predicted steady-state 3TC Cmax for the [redacted] FDC (see m2.7.2 Section 3.3.2.1).

Ninety-two subjects received doses ≥560 mg/day, of whom 62 received 840 mg/day or 1400 mg/day. These studies demonstrated no dose-related increase in the overall incidence of AEs or the overall incidence of study drug related AEs over 24 weeks.

In NUCA2001, at the 20 mg/kg/day (1400 mg/day) dose level, hematologic laboratory abnormalities were noted in some subjects. Sustained Grade 3/Grade 4 neutropenia was seen in 4 of 15 subjects and led to withdrawal in 1 subject. There was an increased incidence of decreased red blood cell counts (in 8 of 15) at the 20 mg/kg/day dose level. However, there was no dose-related increase in the incidence of either hemoglobin declines nor was there a dose-related increase in the incidence of clinically significant anemia. The increased incidence of hematologic laboratory abnormalities was not seen at the lower dose levels.

In NUCB2001, the laboratory data revealed no major toxicities related to 3TC treatment and there was no obvious dose-response. While an increased incidence of hematologic laboratory abnormalities was seen at 1400 mg/day in NUCA2001, this was not seen with the 1400 mg/day in NUCB2001. These studies show that 3TC at doses of up to 840 mg/day were generally well-tolerated, with no dose associated increase in the incidence of clinical AEs or laboratory toxicities. The predicted 3TC steady-state Cmax for the [redacted] DTG/3TC FDC (the formulation chosen for development) in fasted state (which represents the highest exposure) is similar to the observed range of steady-state Cmax values from 840 mg/day (see m2.7.2 Section 3.3.2.1).

Given the evaluated data to date, the observed higher 3TC Cmax seen with the [redacted] FDC does not confer a significant safety risk because:

1. There is no dose-related increase in toxicities up to and including a dose level of 840 mg/day.
2. There is an overlap in steady-state 3TC Cmax between the [redacted] FDC (fasted and fed) and dose ranges of 300 mg/day to 840 mg/day.
3. Although some hematologic laboratory abnormalities were seen in the 1400 mg/day level, the predicted steady-state 3TC Cmax and AUC of the [redacted] FDC is lower than that seen with the 1400 mg/day dose.

5.6.2.2. 3TC Phase 3 Registrational Studies Supporting Higher 3TC Cmax

Across the 3 randomized, controlled studies (NUCA3001, NUCA3002, and NUCB3002), study participants received 3TC for at least 24 weeks as either 600 mg/day monotherapy (in NUCA3001), 600 mg/day + ZDV, or 300 mg/day + ZDV. A fourth study, NUCB3001, examined the safety of 3TC 600 mg/day + ZDV in comparison with ZDV monotherapy. These studies showed no significant safety differences between the 3TC 300 mg total daily dose and the 3TC 600 mg total daily dose. The overall differences at the individual study level between treatment groups were small and statistically non-significant when comparing the frequencies of AEs, drug-related AEs, serious AEs, Grade 3/4 clinical and laboratory abnormalities, and withdrawals due to AEs over the ≥24-week treatment period (Table 31). These studies also demonstrated that at 300 mg/day and 600 mg/day, 3TC had comparable clinical efficacy.

Table 31 Randomized, Controlled Studies with 3TC 300 mg BID: AEs, SAEs, Grade 3/4 AEs, and Grade 3/4 Lab Abnormalities

Study ID	Population	Treatment Regimens (N)	AEs n (%)	Non-fatal SAEs n (%)	Fatal SAEs n (%)	Grade 3/4 AEs[a] n (%)	Grade 3/4 Lab AEs[a] n (%)
NUCA3001	HIV+; ≥12 years Entry CD4: 200-500 cells/mm^3 NA: 1993-1994	3TC 150 mg BID +ZDV (92)	86 (93)	11 (12)	0	7 (8)	24 (26)
		3TC 300 mg BID (87)	80 (92)	5 (6)	1 (1)	5 (6)	13 (15)
		3TC 300 mg BID +ZDV (94)	91 (97)	9 (10)	0	8 (9)	20 (21)
		ZDV (93)	91 (98)	11 (12)	2 (2)	10 (11)	21 (23)
NUCB3001	HIV+ ≥18 Entry CD4: 100-400 cells/mm^3 EU: 1993-1994	3TC 300 mg BID +ZDV (65)	55 (85)	7 (11)	0	9 (14)	17 (26)
		ZDV (64)	61 (95)	2 (3)	0	5 (8)	13 (20)
NUCA3002	HIV+ ≥18 Entry CD4: 100-300 cells/mm^3 NA: 1993-1994	3TC 150 mg BID+ZDV (84)	80 (95)	11 (13)	0	4 (5)	22 (26)
		3TC 300 mg BID +ZDV (84)	81 (96)	21 (25)	0	13 (15)	29 (35)
		ZDV + ddC (86)	83 (97)	15 (17)	0	8 (9)	28 (33)
NUCB3002	HIV+ ≥18 Entry CD4: 100-400 cells/mm^3 EU: 1993-1994	3TC 150 mg BID +ZDV (75)	62 (83)	4 (5)	0	2 (3)	9 (12)
		3TC 300 mg BID +ZDV (75)	59 (79)	10 (13)	0	0	16 (21)
		ZDV (73)	56 (77)	6 (8)	0	0	12 (16)

NOTE: All comparison of treatment groups had summary p values >0.05

a. ACTG grading was used for grading of toxicity and labs as specified in the protocol.

The study treatment-related AEs and SAEs reported in the NUCA3001, NUCB3001, NUCA3002 and NUCB3002 are summarized in Table 32. There were no statistically significant differences by treatment groups within each study in the frequency of treatment-related AEs.

Table 32 Randomized, Controlled Studies with 3TC 300 mg BID: Treatment-Related AEs and SAEs

Study ID	Population	Treatment Regimens	AEs n (%) considered drug related[a]	Non-fatal SAEs n considered drug related[a]	Fatal SAEs n considered drug related[a]
NUCA3001	HIV+; ≥12 years Entry CD4: 200-500 cells/mm^3 NA: 1993-1994	3TC 150 mg BID +ZDV (N=92)	64 (70)	1	0
		3TC 300 mg BID (N=87)	63 (67)	3	0
		3TC 300 mg BID +ZDV (N=94)	48 (55)	0	0
		ZDV (N=93)	59 (63)	2	0
NUCB3001	HIV+ ≥18 Entry CD4: 100-400 cells/mm^3 EU: 1993-1994	3TC 300 mg BID +ZDV (N=65)	40 (62)	5	0
		ZDV (N=64)	40 (63)	1	0
NUCA3002	HIV+ ≥18 Entry CD4: 100-300 cells/mm^3 NA: 1993-1994	3TC 150 mg BID+ZDV (N=84)	55 (65)	6	0
		3TC 300 mg BID +ZDV (N=84)	50 (60)	10	0
		ZDV + ddC (N=86)	63 (73)	8	0
NUCB3002	HIV+ ≥18 Entry CD4: 100-400 cells/mm^3 EU: 1993-1994	3TC 150 mg BID +ZDV (N=75)	30 (40)	1	0
		3TC 300 mg BID +ZDV (N=75)	34 (45)	3	0
		ZDV (N=73)	35 (48)	3	0

NOTE: All comparison of treatment groups had summary p values >0.05

a. Drug-related AEs were defined as events with possibly, probably, or almost certainly related to treatment by the investigator or for which the investigator's opinion of the AE's relationship to study medication was unknown or missing.

In addition, AE data from these studies through 24 weeks on treatment were summarized in the 3TC Integrated Summary of Safety (ISS, 1995). The results of the combined analysis of these pivotal studies observed a comparable safety profile in treatment groups that received 3TC 600 mg/day (300 mg BID) to groups that received 3TC 300 mg/day (150 mg BID) (Table 33).

Some individual AEs and laboratory abnormalities (including abdominal pain, diarrhea, anemia, musculoskeletal pain, decreases in hemoglobin, hematocrit, and platelets) were reported with slightly higher frequency for participants who received 3TC 600 mg/day + ZDV compared to those who received 3TC 300 mg/day + ZDV or 3TC 600 mg/day monotherapy, but in most instances, these were not cause for withdrawal from the study. Similarly, there were certain AEs, including headache, neuropathy, dizziness, temperature regulation disturbances, and various infections/viral infections, that were reported more frequently in the 3TC 300 mg/day compared to the 3TC 600 mg/day groups. However, relative differences for these AEs were small (ranging from <1% up to 4%). In addition, review of SAEs, grouped by body system, identified <1% reporting frequency in both arms for the majority of SAEs. Over half of the SAEs were not considered drug-related.

The Phase I/IIa dose-ranging studies suggested neutrophil and erythrocyte toxicity at the highest 3TC dose level tested (1400 mg/day). The significance of this finding is uncertain as it was only seen in 1 out of 2 studies. Notably, in the 4 registrational studies, hematologic toxicities were noted in the 3TC + ZDV arms, but were rarely seen in the arms that contained 3TC 600 mg/day alone. Specifically, Grade 3 or 4 neutropenia was reported in 0% of patients in the 3TC 600 mg arm, and Grade 3 or 4 decreased hemoglobin was reported in 1% of patients in the 3TC 600 mg arm. In comparison, 11 to 13% of patients in the ZDV-containing arms had Grade 3 or 4 neutropenia while 4 to 11% of the patients in the ZDV-containing arms had Grade 3 or 4 decreased hemoglobin.

Overall, the 3TC ISS reported low frequencies of SAEs, drug related SAEs, and treatment-limiting (S)AEs. There were comparable frequencies of these events in participants who received 3TC 600 mg/day + ZDV 200 mg three times daily (TID) compared to those who received 3TC 300 mg/day + ZDV 200 mg TID.

Table 33 Integrated Summary of 3TC 150 mg BID (+ZDV) and 3TC 300 mg BID (+ZDV 200 mg TID) Safety Data from the 3TC Registrational Studies

	3TC[a] 150 mg BID + ZDV N=251	3TC[b] 300 mg BID + ZDV N=318
Participants with at least one AE (%)	228 (91)	286 (90)
Subgroup of Participants with at least one AE with onset <24 weeks	n=60 49 (82)	n=79 70 (89)
Subgroup of Participants with at least one AE with onset >24 weeks (%)	n=191 105 (55)	n=239 114 (48)
Participants with at least one SAE (%)	25 (10)	46 (14)
Participants with at least one study-drug-related SAE (%)	8 (3)	21 (7)
No. of drug-related SAEs	8	29
Participants that W/D due to AE and SAEs (%)	17 (7)	34 (11)
Participants that W/D due to study drug related AE; includes SAEs (%)	16 (6)	30 (9)
Participants with at least one G3/4 laboratory toxicity (%)	55 (22)	85 (27)
Deaths	0	0

Data Source: 3TC ISS [1995] Vol 98; Vol 100 Table 6.1, Table 6.5, Table 6.6, Table 6.14, Table 6.15, Table 8.1; Vol 101 Table 16.1, Table 16.2; Vol 101.

a. Data are from NUCA3001, NUCA3002 and NUCB3002.
b. Data are from NUCA3001, NUCB3001, NUCA3002 and NUCB3002.

The current 3TC labeling contains a list of adverse reactions which have been reported with 3TC over the last 22 years. These were chosen based on their seriousness, frequency of reporting or potential causal relationship to 3TC. As these are reported voluntarily from a population of unknown size, it is not possible to estimate frequency or establish a causal relationship to drug exposure. Table 34 describes the reporting frequencies in NUCA3001, NUCA3002, NUCB3001 and NUCB3002 for these specific

adverse reactions that have been identified through the post-marketing experience listed in the 3TC product labeling.

Table 34 Frequency of Adverse Reactions Identified through the EPIVIR Post-Marketing Experience in Section 6.2 of the EPIVIR USPI as Reported in the 3TC Registrational Studies Combined Analysis Comparing 3TC 150 mg BID and ZDV vs 3TC 300 mg BID and ZDV-treated Participants

AEs as defined in the USPI Section 6.2	3TC[a] 150 mg BID + ZDV N=251	3TC[b] 300 mg BID + ZDV N=318
No of Participants having at least one event (%)	**228 (91)**	**286 (90)**
Body as a Whole	NA	NA
Redistribution/accumulation of body fat	NA	NA
Endocrine and Metabolic	48 (19)	45 (14)
Hyperglycemia	3 (1)	0
General	2 (1%)	6(2%)
Weakness	NA	NA
Hemic and Lymphatic (Blood and Lymphatic System Disorders)	43 (17)	53 (17)
Anemia	10 (4)	16 (5)
Hepatic and Pancreatic (Hepatobiliary Tract and Pancreas)[c]	9 (4)	25 (8)
Lactic Acidosis[c]	NA	NA
Severe Hepatomegaly with Hepatic Steatosis	0	2
Hypersensitivity	NA	NA
Anaphylaxis	NA	NA
Utricaria (as part of Skin SOC)	3 (1)	3 (<1)
Musculoskeletal	67 (27)	78 (25)
Muscle weakness (muscle atrophy weakness and tiredness)	6 (2)	3 (<1)
CPK elevations from baseline to worst value	72 (30)	86 (28)
Rhabdomyolysis[c]	NA	NA
Skin	100 (40)	97 (31)
Alopecia	1 (<1)	4 (1)
Pruritus	8 (3)	10 (3)

Source data: are from the EPIVIR ISS Volume 100 Table 6.1 and Volume 98 Section 7.1.1; the relationship between investigator terms and group terms are detailed in Vol 104, Appendix 2A

a. Data are from NUCA3001, NUCA3002 and NUCB3002
b. Data are from NUCA3001, NUCB3001, NUCA3002 and NUCB3002
c. The frequencies for the terms “lactic acidosis” and “rhabdomyolysis” were included based on 3TC USPI Section 6.2 Post marketing Experience but are not listed in the EPIVIR ISS; “hepatobiliary signs” is an AE term from the EPIVIR ISS.

As noted, the safety findings in these studies, in which approximately half of the subjects received 600 mg/day, are consistent with the safety profile of 3TC, established over 22 years. The data from two large rollover open-label studies - NUCA3004 and NUCB3004 [Glaxo Report Number RM1996/00334/00 and Glaxo Report Number GIO/95/002, respectively] - also reported similar safety findings for participants receiving 3TC 300 mg

BID and 3TC 150 mg BID. These studies included more than 9,000 study participants who received 3TC 300 mg BID.

In summary, the safety outcomes were comparable for study participants randomized to the 3TC 300 mg/day (150 mg BID) vs the 3TC 600 mg/day (300 mg BID) regimens in the described 3TC registrational studies. Data from the 3TC dose-ranging studies and the open-label studies demonstrated no dose-related increase in overall incidence of AEs or the overall incidence of study drug-related AEs.

There are a number of limitations of these data, including that the studies were conducted during the 1990s at a time when patients generally had lower CD4 cell counts and more severe HIV disease stage at study entry. Furthermore, there was a different treatment paradigm with use of less potent mono- and dual therapy and a limited selection of other ARTs, which led in many instances to less than optimal control of HIV disease. Thus, in these studies, many AEs and SAEs were attributable to the underlying HIV disease. In addition, ZDV used concomitantly in many treatment arms, is associated with higher rates of nucleoside-related AEs and laboratory toxicities than 3TC, most notably some reversible, low grade hematologic changes, which occurred when 3TC was dosed with ZDV. Nonetheless, we consider that the controlled, randomized and double-blind design of the registrational studies still enables a fair comparison of the overall safety and efficacy of 3TC 300 mg/day vs 3TC 600 mg/day. Also, the large number of study participants in the open-label rollover trials provide a valuable supportive data set for understanding the longer-term safety profile of a 3TC 600 mg/day.

In conclusion, safety data from 3TC historical studies demonstrate no clinically significant safety findings at exposures that are comparable to those expected with the [redacted] FDC. These data support the progression of a FDC tablet of DTG/3TC with a higher Cmax value of 3TC.

5.6.2.3. Conclusions of Clinical Studies Supporting Safety at Higher 3TC Cmax

Several previously submitted registrational pivotal Phase II/III studies (NUCA3001, NUCA3002, and NUCB3002) showed no significant safety and efficacy differences between the 3TC 300 mg/day and the 3TC 600 mg/day. The overall differences at the individual study level between treatment groups were small and statistically nonsignificant when comparing the frequencies of AEs, drug-related AEs, SAEs, Grade 3/4 clinical and laboratory abnormalities and withdrawals due to AEs over the ≥24-week treatment period. Results from the NUCB3001 study, which examined a comparison of 3TC 300 mg BID in combination with ZDV in comparison with ZDV monotherapy, also support the overall safety of the 3TC 600 mg/day.

The data from two large roll-over, open-label studies, NUCA3004 and NUCB3004, also reported comparable safety findings for participants receiving 3TC 300 mg BID (in NUCA3004 versus those receiving 3TC 150 mg BID). While there may be small differences at individual AE levels, overall the safety profiles are comparable for these studies, which included more than 16,000 participants who received 3TC 300 mg/day and more than 9,000 participants who received 3TC 600 mg/day.

5.6.2.4. Additional Information from Post-Marketing Experience Supporting Safety of Higher 3TC Exposure

The 3TC single-entity product information and the extensive post-marketing experience also support the conclusions above (Section 5.6.2.3) that no clinically significant safety findings would be expected at exposures that are comparable to the [redacted] FDC. There are situations related to drug-drug interactions or mild renal impairment where 3TC, used within its licensed indication, would lead to a sustained increase in the extent of absorption (AUC). As the increase in AUC in these situations is not associated with clinically significant safety findings, an increase in the rate of absorption leading to a higher (but transient) Cmax is therefore not expected to impact patient safety. Lamivudine (alone or in combination with other antiretrovirals) has over 7 million years patient exposure. Over 23 years of post-marketing surveillance, no safety signal has been attributed to higher exposure to 3TC.

The co-administration of 3TC with trimethoprim/sulphamethoxazole 160 mg/800 mg (co-trimoxazole) increases 3TC AUC exposure by 40% because the trimethoprim component inhibits the renal elimination of 3TC. However, in the approved labels, unless the patient has renal impairment, no dosage adjustment of EPIVIR is necessary. The use of co-trimoxazole with 3TC would be expected to be relatively frequent given the prophylactic use of co-trimoxazole in advanced HIV disease and its use in the treatment of the HIV-associated conditions of *Pneumocystis jiroveci* pneumonia and toxoplasmosis. To date, no safety issues relating to co-administration of 3TC and co-trimoxazole have been identified in the post-marketing phase.

Lamivudine undergoes predominantly renal clearance (greater than 70%) and therefore plasma concentrations (AUC) are increased in patients with renal dysfunction due to decreased clearance. Dose adjustment is required at a creatinine clearance <50 mL/min. However, patients with creatinine clearance in the 50-80 mL/min range are expected to have higher 3TC AUC exposures than those with normal renal function based on the linear relationship between renal function as measured by CrCL and 3TC apparent oral clearance (m2.7.2). Similarly, the extensive post-marketing experience and absence of safety issues in subjects with impaired (but above 50 mL/min) creatinine clearance further supports that clinically significant safety issues are unlikely to be observed at exposures seen with the [redacted] FDC.

5.7. Overdose

There is limited experience of overdose with DTG + 3TC. Across 204861 and 205543, 1 event of overdose (Grade 4 event in which Subject [redacted] took 30 tablets each of DTG and 3TC; associated with events of Grade 3 depression and Grade 4 suicide attempt) was reported among the 1433 participants. The subject had emergency treatment with gastric lavage and activated charcoal 30 minutes after the overdose. During subsequent follow-up, the subject was asymptomatic and did not develop any laboratory abnormalities.

5.8. Drug Abuse

No studies have been performed to investigate the potential for drug abuse with DTG/3TC FDC. There are not safety data to report regarding the potential for drug abuse from 204861 and 205543. However, the Sponsor does not consider there is a potential for misuse of DTG/3TC FDC for illegal purposes.

5.9. Withdrawal and Rebound

No studies have been performed to investigate the potential for withdrawal and rebound effects with DTG/3TC FDC. There are no safety data to report regarding the potential for withdrawal or rebound from 204861 and 205543. However, the Sponsor does not consider that there is a potential for this type of effect with DTG/3TC FDC.

5.10. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

There are no safety data from either 204861 or 205543 suggestive of any potential effects of DTG + 3TC on the ability to drive or operate machinery or the impairment of mental ability.

Drug-related adverse events were reported in 204861 and 205543 that may influence a patient's ability to drive or operate machinery, or that may impact upon mental ability (e.g., headache, dizziness, somnolence), however, findings were consistent with product labelling for the single-entity components.

Across the studies, there were 2 road traffic accidents reported among the 1433 participants; neither event was drug-related.

6. POST-MARKETING DATA

Both single entities (TIVICAY and 3TC) have well-characterized safety data from extensive post-marketing experience. TIVICAY has over 560,000 patient years' exposure based on prescribing data as of [redacted] (Intercontinental Medical Statistics [IMS] Health data). 3TC alone or in combination with other antiretroviral medicinal products as KIVEXA, COMBIVIR, TRIZIVIR, or TRIUMEQ has over 7 million patient years' exposure as of [redacted]. The components of DTG/3TC have been used together in combination with ABC as TRIUMEQ, with over 445,000 patient years' experience as of [redacted]. Data from the single entities will be used to inform the adverse reaction section of the proposed product labeling.

DTG is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-infected adults, adolescents, and children above 6 years of age weighing at least 15 kg. DTG was approved in the US on 12 August 2013 and in the EU on 20 January 2014. As of January 2018, DTG has been approved in the US, all EU member states, and Japan, as well as over 90 further countries.

3TC was first approved for HIV infection in 1995 in the US and is available in over 70 countries. It is also available as part of two backbone FDC products; ZDV/3TC (COMBIVIR) is approved in over 60 countries and ABC/3TC (EPZICOM/KIVEXA) is approved in over 50 countries.

The components of DTG + 3TC have been used together in combination with ABC as TRIUMEQ. The MAH received its first approval of the DTG/ABC/3TC (TRIUMEQ) FDC tablet on 22 August 2014 in the US for treatment of HIV-1 infection at dose(s) of DTG/ABC/3TC (50 mg/600 mg/300 mg). DTG/ABC/3TC is also currently approved in the EU and Japan as well as over 50 further countries.

Depression and suicidal behaviors were upgraded from an important potential risk to an important identified risk and added to the DTG GDS/RSI as a labelled adverse reaction in [redacted]. The following non-serious events were also added to the DTG GDS/RSI as labelled adverse reactions – myalgia and arthralgia in [redacted], anxiety ([redacted]), and weight increased ([redacted]). Based on review of post-marketing cases, the event of acute hepatic failure was added to the DTG GDS/RSI in [redacted].

A safety signal has been identified relating to neural tube defects in 4/426 infants born to women who were taking DTG at the time of conception from a preliminary analysis of an ongoing birth outcome surveillance study in Botswana (described in Section 6.1). No other significant safety concerns or risks have been identified from marketing experience through to April 2018 for DTG.

Section 6.2 provides an overview of literature describing the use of DTG and 3TC together, and Section 6.3 describe post-marketing reports from the Global Safety databases that report the use of DTG and 3TC together.

6.1. Neural Tube Defects

6.1.1. Source of Signal and Data

In May 2018, ViiV was notified of the results of an unscheduled analysis performed by investigators in a study of birth outcomes in Botswana. A full evaluation of the safety of DTG in pregnancy was conducted with a data-lock point of [redacted]; a summary of the evaluation is provided below.

Preliminary findings from this unscheduled analysis of a birth outcomes surveillance study show a higher than expected number of neural tube defects (NTDs) among newborns whose mothers were exposed to DTG-based ART at the time of conception.

The findings are part of the Tsepamo study, an NIH/NICHD-funded birth outcomes surveillance study conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana. The two primary aims of the study are (1) to evaluate adverse birth outcomes by HIV-status and ART regimen, and (2) to determine if there is an increased risk of NTDs among infants exposed to EFV from conception. The study is powered to detect at least a two-fold increase in the risk of NTDs following EFV exposure, with an anticipated surveillance of ~95,000 births over 4 years (August 2014-August 2018).

Initial information provided to the MAH by the investigator on [redacted] indicated that among infants born to women on DTG-based ART from conception, 4/385 had a neural tube defect (1.04%; 95% CI: 0.4%, 2.6%) compared with 14/11,173 (0.13%; 95% CI: 0.08%, 0.22%) infants born to women on any non-DTG ART from conception. The absolute risk difference between DTG-based and non-DTG-based ART from pre-conception, was 0.91 (95% CI: 0.27%, 2.5%). Neural tube defects occurred among 3/5747 (0.05%; 95% CI: 0.02%, 0.15%) infants born to women on EFV from conception and 58/65,477 (0.09%, 95% CI: 0.07%, 0.12%) infants born to HIV-uninfected women. No infant born to a woman who started DTG during pregnancy had a NTD (N=0/2749, 0.00%; 95% CI: 0.0%, 0.14%).

Since the initial findings, further information on pregnancy outcomes have been communicated to the MAH by the investigator and published [Zash 2018]. As of [redacted], 4 cases of NTDs (of 426 pregnancies: 4/426) with pre-conception exposure to DTG had been reported, a prevalence of about 0.9%. In women who started DTG during pregnancy (N = 2812, updated data) there continue to be no NTDs. It should be noted that as this is an ongoing study, the total numbers of pregnancies and neural tube defects are subject to change.

From the data currently available on the 4 cases of NTD born to women on DTG, there are no obvious confounders. However, some relevant information is missing; for example, it is not known if there was any family history of NTDs, or previous pregnancy outcomes in these 4 cases. None of the 4 women received Vitamin B12 or folic acid supplementation during the initial weeks of pregnancy; however, this is not routine practice in Botswana and there is no reason to suggest that there would be any differences between treatment groups with respect to supplementation that might explain the observed difference in risk.

Following receipt of this information, the MAH notified the relevant Regulatory Agencies (including the EMA and the FDA), and consulted with relevant Agencies to agree appropriate action. The WHO, FDA, and EMA issued statements on their websites on 18 May 2018 to highlight this potential risk and to provide interim recommendations regarding the use of DTG in women of childbearing potential while assessment of this issue is ongoing [WHO, 2018; FDA, 2018; EMA, 2018].

Prior to the alerts issued by the WHO, EMA, and FDA about this issue on 18 May 2018, only one other case of a NTD had been reported with DTG; this was a poorly-documented spontaneous report from Namibia. Since then (to [redacted]), the MAH has been notified about 2 additional spontaneous reports describing NTDs from the US (cases of anencephaly and sacromeningocele) in patients taking DTG prior to conception. Both women had risk factors for the development of NTDs (obesity and history of seizures and spontaneous abortions), though some relevant information was missing. There have been two additional reports of neuronal migration disorders in patients taking DTG prior to conception (one from the US and one from the UK), however, these are not NTDs and are not typically drug induced.

6.1.2. Incidence of NTD and Known Risk Factors

Although the background rates vary with geography, neural tube defects have been reported to occur in 0.5-1.0 in 1,000 pregnancies in the US [Shaer, 2007], and this is the background rate included in the SmPC for EFV in the EU [Sustiva SmPC 2018]. The exact causes of NTDs are not known, but environmental and genetic factors are known to play a part. Risk factors include: folate and Vitamin B12 deficiency, obesity, diabetes, certain medicines such as some anti-epileptic medications (e,g., sodium valproate, carbamazepine), maternal age, and hyperthermia/febrile illness [Wilde, 2014]. There is no evidence that neural tube defects occur more commonly in women living with HIV [Ford, 2011].

6.1.3. Sources of Information Reviewed in the Evaluation

6.1.3.1. MAH Data

As of 20 April 2018, a total of 75 pregnancies occurred in patients receiving DTG or DTG/ABC/3TC therapy as part of the DTG MAH-sponsored clinical development program. One congenital anomaly relating to a cardiac condition was reported.

A total of 499 pregnancies with 501 infants were reported for DTG or DTG/ABC/3TC from post- marketing sources. Of the 153 pregnancy outcomes where trimester of exposure was known, 78 related to use of DTG prior to conception and a further 37 reported use of DTG in the first trimester (but did not specify use prior to conception).

Across the clinical trials and spontaneous data, a total of 29 cases reporting a congenital anomaly have been identified. The most common organ systems affected were renal and cardiac. Three cases report polydactyly and/or syndactyly, but there was no pattern with regard to the other anomalies reported, with events spread over several body systems, likely reflective of background incidence. Twenty-three of the 29 cases reported trimester of exposure; 12 cases were exposed to DTG prior to conception (of which 2 congenital anomalies related to the nervous system, 1 neural tube defect from Namibia, and a case reporting abnormality of the auditory pathway); 7 cases had other first trimester exposure; and second or third trimester exposure was reported in 4 cases.

6.1.3.2. Other (non-MAH) Pregnancy Cohorts

In addition to the Tsepamo study, 10 additional cohorts were identified and reviewed that reported use of DTG pre-conception or in the first trimester. The largest sources of information were from the antiretroviral pregnancy registry (APR, discussed below, with 274 subjects exposed to DTG during pregnancy up to 31 January 2018) and the Tsepamo cohort published in 2017 [Zash, 2017] (845 subjects exposed to DTG *during* pregnancy, with 116 patients exposed during the first trimester); none of the 116 patients exposed to DTG during the first trimester reported a congenital anomaly.

6.1.3.3. APR Data

The APR is an international registry that monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. Clinicians register pregnant women with prenatal exposures to any antiretroviral therapy before the outcome of pregnancy is known, report data on exposure throughout pregnancy, and provide birth outcome data. Registration is voluntary and confidential. Defects are reviewed by a teratologist, and all data are reviewed semi-annually by an independent Advisory Committee. Exposure is classified and analyzed by the earliest trimester of exposure to each individual antiretroviral medication. The APR has provided the MAH with a preliminary unpublished analysis from the registry covering the period up to 31 January 2018

As of 31 January 2018, a total of 274 pregnancies with exposure to DTG have been prospectively reported to the APR; 178 were exposed in the first trimester (with 133 pre-conception exposures), and 96 were first exposed during the second/third trimesters. Of the 274 pregnancies, 255 (93%) resulted in live births (121 with pre-conception exposure), there were 2 stillbirths (both with second/third trimester DTG exposure), 11 spontaneous abortions (7 with DTG exposure at conception), and 6 induced abortions (5 with DTG exposure at conception). Seven of the 255 (2.7%) reported birth defects; 3 were associated with DTG exposure pre-conception (bilateral polydactyly, ectopic kidney, and a cardiac endocardial abnormality), 2 occurred in infants exposed to DTG after conception but during the first trimester (1 case reporting polydactyly and syndactyly and 1 case reporting talipes equinovarus), and the other 2 occurred following second/third trimester exposure (hypoglossia-hypodactyly syndrome and Down's syndrome). No neural tube defects have been reported.

Across the registry, the number of live births associated with birth defects following exposure to DTG (7/255, 2.8%) was comparable to that observed with exposure to elvitegravir (5/232, 2.2%) or raltegravir (21/569, 3.7%). While the number of DTG exposures are still too small to draw definitive conclusions, these data do not suggest that DTG is associated with an increased risk of congenital anomalies above the population expected rates (2.72-4.17/100 live births), or the rates observed with all antiretroviral therapy or other INSTIs.

In total, data for over 3000 patients exposed to DTG during pregnancy are available from these non-MAH cohorts, including 723 (426 from Tsepamo study and 297 from other sources) with exposure prior to conception. No particular patterns of congenital anomalies could be identified and events appeared consistent with background rates.

6.1.3.4. Nonclinical Data

Since learning of the potential relationship between DTG treatment and neural tube defects, the MAH has carefully reviewed existing nonclinical reproductive toxicology data to ensure that there are no signals that should be reconsidered based on the preliminary data from the Tsepamo study in Botswana. The review did not identify any evidence of adverse effects on neural tube formation or embryonic toxicity, nor did this review suggest a plausible mechanism for the emerging safety signal.

6.1.4. Actions Taken by the MAH

The following actions have been taken:

- Direct Health Care Professional Communications have been issued that provide recommendations regarding use of effective contraception in women of child bearing potential taking DTG and its avoidance in those actively seeking to become pregnant.
- Communication to study investigators to ensure awareness of this issue. Study 200336, which enrolled women on DTG/ABC/3TC who became pregnant while in Study 117172 (a study evaluating DTG/ABC/3TC versus ritonavir-boosted atazanavir + TDF/FTC), was placed on hold to new enrollment. The protocols for the remaining MAH-sponsored studies do not allow pregnant women or women who want to become pregnant to enroll and participate in the study. In addition, protocols require that women of child bearing potential use effective contraception while on study treatment. Women are screened for pregnancy at every study visit. Women who become pregnant are withdrawn from the study. All pregnancies are followed until conclusion of the pregnancy and both maternal and fetal outcomes are documented.
- Updating the product information, including the prescribing information, Investigator's Brochure, informed consent form, and protocols to incorporate relevant information on this potential risk in these documents.
- Updates to the risk management plan to add neural tube defects as an important potential risk are in progress.
- A targeted follow up questionnaire for cases reporting NTDs is being created for all DTG-containing products to ensure the collection of consistent detailed information on these events and the pregnancy exposure.
- There are ongoing activities relating to this potential risk, including consultation with external experts to further understand the nature of the neural tube defects reported.

6.1.5. Conclusions for Neural Tube Defects Signal

Combining the available data from all sources and including the data from the Tsepamo study, over 3000 women have taken DTG during pregnancy, including over 700 with exposure to DTG at conception. There has been no evidence of any other safety issue related to the use of DTG during pregnancy. The data from the Tsepamo study are of concern, but currently there is insufficient evidence to demonstrate causality. More data needs to be collected to understand this issue further. Surveillance is ongoing for additional pregnant women in the Tsepamo study who were exposed to DTG at time of conception. Their deliveries will be monitored closely over the next 9 months (May 2018 to March 2019), and results for women who became pregnant on DTG before the warnings were issued in May 2018 are expected to be known soon thereafter. The Tsepamo study team are also in the process of expanding the study to additional sites in Botswana to capture more pregnancies. With this expanded surveillance, it is estimated that data on 1226 births with exposure to DTG at the time of conception may be available by the end of March 2019, when the next formal analysis is planned. These data will

provide more information about the safety of DTG for women of childbearing age. The MAH is also exploring options for additional data generation from other sources as well as conducting additional non-clinical studies.

6.2. Literature

Review of the literature identified a number of conference abstracts, posters, and papers that describe the use of DTG and 3TC as dual therapy in antiretroviral treatment-naïve and -experienced populations. DTG + 3TC safety information was assessed to determine whether the safety profile in the literature was consistent with the established safety profile of the individual components and the safety profile of DTG + 3TC in the pivotal trials. In addition, DTG + 3TC drug resistance mutations leading to virologic failure were also reviewed since this is an important potential risk in the DTG/3TC FDC EU RMP. A summary of these studies is provided below and individual studies are detailed in Table 35.

6.2.1. DTG + 3TC Dual Therapy Studies in Antiretroviral Treatment-Naïve Populations

The PADDLE study [Cahn, 2017; Figueroa, 2017] and ACTG A5353 [Taiwo, 2018] provide information on a total of 140 subjects who have used DTG and 3TC as dual therapy. The subjects in these prospective clinical studies are antiretroviral therapy-naïve patients that were initiated on DTG + 3TC with HIV-1 RNA viral load cap ≤100,000 c/mL in the PADDLE study and <500,000 c/mL in ACTG A5353 with negative HbsAg, which is similar to those enrolled in the two Phase III clinical trials (204861 and 205543). Review of this information has not identified any new risks or adverse drug reactions from those observed in the Phase III clinical trials of DTG + 3TC. Where AEs were reported, these were consistent with the established safety profile for DTG and 3TC. Furthermore, a high level of virologic success was observed, and the number of AEs reported across the studies was low, suggesting that the use of DTG + 3TC as a dual therapy is both efficacious and well tolerated.

6.2.2. DTG + 3TC Dual Therapy Studies in Antiretroviral Treatment-Experienced Populations with Pre-Existing 3TC Resistance Mutations

Six studies [Borghetti, 2016; Borghetti, 2018; Reynes, 2017; Charpentier, 2017; Gagliardini, 2018; Baldin, 2016] provide additional information on the use of DTG + 3TC as dual therapy in treatment-experienced patients, including patients with pre-existing 3TC resistance mutations at the time of switch to DTG + 3TC. Review of this information has not identified any new risks or adverse drug reactions from those observed in the 2 Phase III clinical trials of DTG + 3TC conducted in treatment-naïve patients (204861 and 205543). Where AEs were reported, these were consistent with the established safety profile for DTG and 3TC. Drug resistance is an important potential risk in the DTG/3TC FDC EU RMP. However, across these studies, DTG + 3TC was considered effective in maintaining viral suppression in treatment-experienced patients, including those with pre-existing 3TC drug resistance mutations.

Table 35 Summary of Articles Reporting Use of DTG and 3TC as Dual Therapy

Article	Study design	Number on DTG + 3TC Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Cahn et al [Cahn, 2017] PADDLE study Full article	Single arm, prospective proof-of-concept study	20 patients on DTG + 3TC ART-naive adults with HIV-1 RNA ≤100,000 copies/mL and negative HBsAg.	Up to 48 weeks 18 patients completed 48 weeks	At week 48, 90% (18/20) reached the primary endpoint of a plasma viral load (pVL) <50 copies/mL. One virologic failure at week 36, Patient was discontinued and followed off-study until week 48; pVL obtained at that time was below 50 copies/mL, without any change to ARV regimen.	No resistance mutations identified in one subject with virologic failure.	1 completed suicide in context of severe stress and trauma with history of psychiatric disturbances which was not disclosed by the patient during his clinical visits. Eight drug-related AEs reported in six patients: headache (3), somnolence (1), epigastric pain (1), diarrhoea (1) and nausea (2) (grade 1 to 2). DTG + 3TC was well tolerated. No AEs led to discontinuation of the study drug.	Grade 2 to 3 laboratory abnormalities (3 events in 3 patients) were proteinuria (grade 3, since baseline), creatinine phosphokinase (grade 3, only at baseline) and haematuria (grade 3, at week 48).

Article	Study design	Number on DTG + 3TC Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Figueroa et al. [Figueroa, 2017] PADDLE study Poster/abstract	Single arm, prospective proof-of-concept study	20 patients on DTG + 3TC ART-naive adults with HIV-1 RNA ≤100,000 copies/mL and negative HBsAg.	Extension phase up to 96 weeks. 15 patients completed 96 weeks	100% maintained plasma HIV-1 RNA below 50 c/mL.	-	Two grade 3 laboratory abnormalities were reported (high cholesterol, and proteinuria) but considered unrelated to study drug.	-
Taiwo et al. [Taiwo, 2018] ACTG A5353 study Full article and private communication with lead author	Single arm, open-label, Phase II, prospective pilot study	120 patients on DTG + 3TC ART-naive adults with screening HIV-1 RNA ≥1000 and <500000 copies/mL. Approximately one-third of participants had study entry HIV-1 RNA >100,000 copies/mL.	Up to 144 weeks 100 patients completed study per protocol	Virologic efficacy at week 48 was 102/120 (85%, CI [77%, 91%]), with similar results for >100000 copies/mL and ≤100000 copies/mL. Three participants with VF had undetected plasma DTG at ≥1 time point.	One subject with virologic failure and undetectable plasma DTG at ≥1 time point acquired the M184V and R263R/K mutations	Sixteen (13.3%) participants reported grade 3 or 4 adverse events, 6 events were considered possibly related to DTG + 3TC including change in creatinine clearance (2), angioedema (1), paresthesia (1), palpitations (1), and suicidal ideation (1) Two cases of grade 2 allergic rash noted. No participant discontinued study treatment due to adverse events.	-

Article	Study design	Number on DTG + 3TC Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Borghetti et al. [Borghetti, 2016] Full article	Retrospective, observational study	36 patients on DTG + 3TC ART-experienced patients; hepatitis B surface antigen-negative participants on stable cART, with undetectable HIV-RNA (<50 copies/mL) and no previous failures with integrase inhibitors. 3 of 20 participants M184V resistance mutation	187.5 person-months of follow-up	No virologic failures or viral blips including the 3 participants with prior detection of M184V. The estimated probability of remaining on DTG + 3TC at week 24 was 91.2% (95% CI 81.6%–100%).	-	3 participants discontinued treatment (2 for gastrointestinal toxicity; 1 headache) A small, but significant, increase in mean ALT levels was detected. Two participants had a worsening of 1 DAIDS grade in ALT levels, resulting in one participant (3%) with grade 2 ALT elevation and none with grade 3–4.	Significant decreases in total cholesterol, the total cholesterol/HDL cholesterol ratio and triglycerides and an increase in the HDL cholesterol/LDL cholesterol ratio.

Article	Study design	Number on DTG + 3TC Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Borghetti et al. [Borghetti, 2018] Full article	Multicentre cohort, retrospective	206 patients on DTG + 3TC ART-experienced patients Patients with comorbidities, previous M184V detection, previous VF and coinfections with hepatic viruses were not excluded	Up to 48 weeks	Estimated probability of maintaining virological suppression at 48 and 96 weeks was 98.2% and 95.1%, respectively. The estimated probability of remaining on 3TC plus DTG was 86.7% and 80.5% at week 48 and 96, respectively.	5 VFs in total. Two cases were explained by lack of adherence; 1 patient carried the M184V mutation in the historical genotype. In all cases, viral control was subsequently achieved (in one case with the same regimen)	Treatment discontinuations were mainly attributable to toxicity of mild/moderate severity (13 of 206; 6.3%; with 7 neuropsychiatric adverse events). Neuropsychiatric type events were the most frequent event.	A decrease in the ratio of total cholesterol (TC) to high-density lipoprotein (HDL) cholesterol (TC:HDL) and triglycerides was found at week 48 and was associated with higher baseline values, but not with the previous regimen type.
Reynes et al. [Reynes, 2017] DOLULAM study Conference abstract/poster	Prospective cohort study	27 patients on DTG + 3TC ART-experienced with HIV RNA <50 copies/ml for >12 months, with problems of tolerability and without resistance to integrase inhibitors. Ten (37%) patients had a history of genotypic test prior switch with M184V mutation.	Up to 96 weeks	No patient experienced virologic failure (defined as confirmed VL > 50 copies/mL). Two patients experienced a viral blip (52 and 66 copies/mL at week 12 and 36).	-	No severe clinical or laboratory adverse event reported. Two patients discontinued DTG + 3TC due to fatigue.	Small decrease from baseline in estimated glomerular filtration rate at first on-treatment assessment but remained stable over the 96-week follow-up.

Article	Study design	Number on DTG + 3TC Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Charpentier et al. [Charpentier, 2017] DOLULAM virologic substudy Full article	Virologic substudy	Among the 27 patients enrolled in the DOLULAM study, historical HIV DNA and RNA Sanger sequences were available in 14 and 18 patients, respectively	Next-generation sequencing data on HIV DNA was at initiation of the DOLULAM study	-	45% and 21% of patients harbored minority resistant variants in reverse transcriptase and integrase, respectively. M184I/V was observed in 17 of 27 (63%) of patients.	-	-
Gagliardini et al. [Gagliardini, 2018] Full article	Retrospective observational study performed using the Antiviral Response Cohort Analysis (ARCA) database	126 patients on DTG + 3TC. Of these 21 had pre-existing M184V mutation (M184V+) and 105 had no pre-existing M184V mutation (M184V-). ART-experienced patients with HIV-RNA ≤50 copies/mL	693 person-years of follow-up	2 virologic failures on DTG + 3TC in the M184V- group Previous selection of the M184V mutation had no major impact on the virologic efficacy with DTG + 3TC	-	Causes of treatment discontinuation were toxicity (55 in the M184V- group and 10 in the M184V+ group)	-

Article	Study design	Number on DTG + 3TC Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Baldin et al. [Baldin, 2016] Conference abstract/poster	Retrospective analysis, 4 Italian centres	105 patients on DTG + 3TC 13 were HCV-coinfected; 2 were HBsAg-positive; 24 had prior AIDS; 8 had M184V mutation	495.4 persons-month of follow-up	The estimated probability of continuing 3TC-DTG at 48 weeks was 76.1%, whereas the 48 weeks probability of remaining free from VF was 89.6%. 2 virological failures.	-	10 discontinuations due to: VF (2), gastrointestinal (3), liver (1), neurological (1), drug interaction with DTG (1), unspecified (2). A worsening of ALT or AST levels at DAIDS grade 2 was observed in 1 patient	CD4 absolute count and percentage and renal function remained stable over time, whereas total cholesterol and triglycerides decreased

6.3. Post-Marketing Cases of DTG + 3TC Two-Drug Therapy

The GSK Global Clinical Safety database was searched for spontaneous or post-marketing cases reporting use of DTG + 3TC two-drug therapy using a datalock point of [redacted]. There was a single case reporting virologic failure in a 2[redacted]-year-old female subject. This case was identified from a report from a physician providing limited details about a cohort of 69 patients treated with DTG + RPV and reasons for discontinuation of therapy (the results from this cohort have not yet been published). This female subject had 5 years of ART comprising 4 different regimens before switching to DTG + RPV. The most recent previous regimen was reported to be DTG + 3TC, where virologic failure was reported after 2 months of treatment with a viral load of 130 c/mL (no resistance data available). Treatment was switched to DTG + RPV and failed after 1 month with a viral load of 170 c/mL, at which point resistance to NNRTIs was reported. The patient was switched back to DTG + 3TC, and viral load was undetectable at 1 month and was <40 c/mL at 3 months.

SAFETY CONCLUSIONS

Pivotal studies 204861 (GEMINI-1) and 205543 (GEMINI-2) evaluated the safety and efficacy of a new 2-drug regimen of DTG + 3TC for the treatment of HIV-1 infection in adults who are naïve to ART therapy and without known or suspected resistance to either antiretroviral component. The goal of the DTG/3TC FDC program is to develop a FDC tablet of this 2-drug regimen. The 48-week data from studies 204861 and 205543 support the proposition that DTG + 3TC is an effective and well tolerated regimen for the treatment of HIV-1 infection.

Week 48 safety data from the identical Phase III studies 204861 and 205543 were generally consistent with one another. Data from these pivotal studies, the pooled analysis of these studies, and other safety data presented herein support the following conclusions:

- Over 48 weeks, the safety data from these randomized, double-blind Phase III studies comparing DTG + 3TC to a standard-of-care regimen of DTG + TDF/FTC is consistent with the known safety profile for the individual products.
- In each treatment group, there was a small number of AEs leading to withdrawal of study drug; few were considered drug-related.
- Fewer drug-related AEs were reported in the DTG + 3TC group (18%) compared with the DTG + TDF/FTC group (24%). This was driven primarily by larger numbers of subjects reporting drug-related Grade 1 events, notably nausea, in the DTG + TDF/FTC group. This could reflect the contribution of a dual NRTI backbone of TDF/FTC versus a backbone of 3TC.
- The frequency of SAEs was similar between the treatment groups. There were few drug-related SAEs reported during the study, with <1% incidence observed for both treatment groups and no discernible patterns of related events.

- Two fatalities were reported up to the Week 48 analysis cut-off (both in the DTG + 3TC group); neither death was related to study drug.
- Serious rash was not observed in this study, including no reports of Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis, or erythema multiforme.
- Across both DTG-containing treatment groups, the psychiatric AE profile was comparable to the known safety profile for DTG. Psychiatric AEs leading to withdrawal occurred in <1% of subjects. Suicidal ideation occurred in 1% of subjects in each treatment group, compared with DTG single-entity studies reporting rate of <1%. Because this rate crossed the 1% threshold, this small numeric change will lead to a new frequency category within the DTG + 3TC prescribing information.
- Clinical laboratory assessments demonstrated there were no newly identified laboratory signals of concern in subjects receiving DTG + 3TC or DTG + TDF/FTC.
- The hepatic safety profile of DTG + 3TC was consistent with the known profile for the individual single-entity components.
- DTG + 3TC was associated with lower impact on renal safety parameters compared with DTG + TDF/FTC FDC. At 48 weeks, there were more favorable changes from Baseline in GFR (cystatin C) and urine protein/creatinine ratio in the DTG + 3TC group, suggesting that renal function in the DTG + 3TC group was better preserved relative to the DTG + TDF/FTC group. Withdrawals from study for renal function-related AEs or for meeting predefined renal toxicity criteria were more frequently observed in subjects in the DTG + TDF/FTC group compared with the DTG + 3TC group.
- Few subjects experienced changes in lipid profile. A small number of subjects in each treatment group experienced LDL cholesterol toxicities ≥Grade 2, with fewer subjects in the DTG + TDF/FTC group; the difference between the 2 treatment groups was statistically significant. However, the total cholesterol/HDL ratio category, often used to estimate long-term cardiovascular risk, was generally improved from Baseline for both treatment groups.
- Biomarkers for bone formation and bone resorption showed a significantly smaller increase from Baseline in the DTG + 3TC group, indicating less bone turnover in that group.
- Together with the bioequivalence data from module 2.7.1 and module 2.7.2, safety data presented here support the use of the DTG + 3TC FDC for the treatment of HIV-1 infection in treatment-naïve adults and adolescents.

7. APPENDIX

7.1. Tabular Summaries of Pivotal and Supportive Studies

Appendix Table 1 Summary of Completed Safety Studies that were Previously Submitted as Part of the TIVICAY or EPIVIR Registration and are Considered "Supportive" Single-Entity Studies for the Safety Assessment of the DTG/3TC FDC Submission (Reports Available Upon Request)

Study No. (Component) Status	Short Description of Study	Conclusion(s)
ING111762 (SAILING) (DTG) Status: Complete	A Phase III Randomized, Double-blind Study of the Safety and Efficacy of DTG 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered with an Investigator-selected Background Regimen Over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults	The safety profile for DTG was similar to RAL, with similar rates of occurrence in both arms for the most common AEs and low rates of discontinuation due to AEs for both DTG and RAL.
ING112276 (SPRING-1) (DTG) Status: Complete	Phase IIb randomized, multicenter, parallel group, dose-ranging study in HIV-1-infected, ART-naïve adults Subjects received: DTG 10 mg QD + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; DTG 25 mg QD + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; DTG 50 mg QD + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; or EFV 600 mg QD + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg At Week 96, subjects in the DTG arms were switched to open-label DTG 50 mg (dosed as two DTG 25 mg tablets); subjects in the EFV arm were discontinued.	Safety results of this study support selection of DTG 50 mg once daily for Phase III INSTI-naïve subjects. The tolerability profile for DTG was better than EFV and the safety profile for DTG was comparable to EFV, with some noted improvement to be further evaluated in Phase III.

Study No. (Component) Status	Short Description of Study	Conclusion(s)
ING113086 (SPRING-2) (DTG) Status: Complete	Phase III, randomized, double blind safety and efficacy study	DTG demonstrated a safety and tolerability profile that was similar to that of RAL over 96 weeks. Compared with RAL, there is no evidence of increased risk for DTG of renal or hepatic toxicity, psychiatric disorders, or serious hypersensitivity events. Mild to moderate general GI intolerance (mainly diarrhea and nausea) is associated with DTG treatment in a small proportion of subjects; however nonclinical findings for GI erosions did not translate into significant clinical findings. There is no evidence for increased risk of torsades de pointes with DTG. Other serious conditions that are labeled for RAL, such as serious rash (e.g., Stevens Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme) and rhabdomyolysis have not been observed in this study.
ING114467 (SINGLE) (DTG) Status: Complete	Phase III, randomized, double blind safety and efficacy study in HIV-1-infected, ART-naive adults Subjects received: DTG 50 mg + ABC/3TC 600 mg/300 mg; or EFV/TFD/FTC (Atripla)	DTG + ABC/3TC demonstrated a safety and tolerability profile that was generally favorable to that of Atripla over 144 weeks. Compared with Atripla, there appears to be no increased risk for DTG + ABC/3TC of hepatic toxicity, renal toxicity, or rash with or without systemic symptoms. Nervous system and psychiatric disorders were more frequent with Atripla, with the exception of insomnia, which was more frequent with DTG + ABC/3TC. Data from this study suggests that insomnia was a short term mild tolerability issue for the DTG + ABC/3TC combination, occurring early in treatment. Non-clinical evidence for GI toxicity (ulceration events) with DTG use did not translate into significant clinical findings for DTG. There is no evidence from this study for increased risk of torsades de pointes with DTG. There was no untoward effect on the overall lipid profile in either treatment group.

Study No. (Component) **Status**	**Short Description of Study**	**Conclusion(s)**
ING114915 (FLAMINGO) (DTG) Status: Complete	Phase IIIb, randomized, open-label safety and efficacy study in HIV-1-infected, ART-naive adults Subjects received: DTG 50 mg + either ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; once daily; or DRV 800 mg + RTV 100 mg + either ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; once daily with food; once daily	DTG demonstrated a safety and tolerability profile that was generally comparable to that of DRV + RTV over 96 weeks. Compared to DRV + RTV based on Week 96 data, there is no increased risk for DTG of renal toxicity, hepatic toxicity rash with or without systemic symptoms. Serious rash (e.g., Stevens Johnson syndrome, toxic epidermal necrolysis or erythema multiforme) was not observed in this study. No cases suggestive of hypersensitivity reaction to DTG were reported. Non-clinical findings for GI erosions did not translate into significant clinical findings. The psychiatric AE profile for DTG was comparable to prior studies. There is no evidence from this study for increased risk of torsades de pointes with DTG. The changes in lipid profile through Week 96 were favorable for DTG compared with DRV + RTV.
ING112574 (VIKING-3) (DTG) Status: Complete	A Phase III Study to Demonstrate the Antiviral Activity and Safety of Dolutegravir in HIV-1 Infected Adult Subjects with Treatment Failure on an Integrase Inhibitor Containing Regimen	DTG 50 mg BID was well tolerated in this ART-experienced INI-resistant population, despite additional confounding factors such as receipt of multiple concurrent medications and advanced HIV disease status. The safety profile observed for DTG 50 mg BID in these subjects was similar to that described for DTG 50 mg once daily from 48 week data in ART-naive subjects.
ING116529 (VIKING-4) (DTG) Status: Complete	A Phase III Randomized, Double-Blind Study to Demonstrate the Antiviral Activity of Dolutegravir (DTG) 50 mg Twice Daily Versus Placebo Both Co-Administered with a Failing Antiretroviral Regimen over Seven Days, Followed by an Open Label Phase with All Subjects Receiving DTG 50 mg Twice Daily Co-Administered with an Optimized Background Regimen (OBR) in HIV-1 Infected, Integrase Inhibitor Therapy-Experienced and Resistant, Adults:	DTG 50 mg BID was well tolerated in this ART-experienced, INI- resistant population, despite additional confounding factors such as the advanced stage of disease, multiple concomitant medications, and a wide variety of concurrent antiretrovirals taken as OBR. Safety and tolerability data represented a median follow-up time of 55 weeks, and were consistent with those from previous studies investigating DTG across treatment indications, and specifically in ART-experienced (INI- resistant) subjects, with no new concerns highlighted.

Study No. (Component) **Status**	**Short Description of Study**	**Conclusion(s)**
ING116070 (DTG) Status: Complete	Single-arm study of the safety, efficacy and central nervous system and plasma PK of DTG 50 mg QD in combination with ABC/3TC FDC over 96 weeks in HIV-1-infected ART-naive adults	DTG concentrations observed in CSF at both Week 2 and Week 16 exceed the in vitro IC_{50} against wild-type viruses (0.2 ng/mL) for all subjects suggesting that DTG is able to achieve therapeutic concentrations in the CSF. DTG concentrations were similar to the unbound DTG concentrations in plasma, with statistically significant correlations between DTG CSF and plasma, (both total and unbound) concentrations. A regimen of DTG + ABC/3TC was effective in decreasing CSF HIV-1 RNA levels.
ING112578 (P1093 pediatric study) (DTG) Status: Ongoing, Week 24 CSR Complete	Phase I/II, multi-center, open-label pharmacokinetic, safety, tolerability and antiviral activity of DTG (weight based dose of approximately 1 mg/kg once daily, with a maximum daily dose of 50 mg) in combination regimens in HIV-1-infected pediatric subjects (infants, children and adolescents)	No major safety issues were identified. Overall, in this small population of adolescent subjects, DTG dosed at 35mg and/or 50mg once daily was safe and well tolerated when administered with optimized background therapy. Clinical AEs were reported by 90% of the subjects and many were related to common childhood illnesses (e.g., impetigo, ear congestion) or pre-existing secondary Baseline diagnoses. There were no discontinuations due to an AE, no AEs reported as related to DTG, or Grade 3 or Grade 4 clinical AEs over 24 weeks of treatment.

Study No. (Component) **Status**	**Short Description of Study**	**Conclusion(s)**
NUCA2002 (3TC) Status: Complete	Randomized, double-blind study in HIV-1 infected adults who were ZDV-experienced with CD4 counts of 100-300 cells/mm^3 Subjects received: 3TC 150 mg BID+ZDV (n=84 median exposure 346 days); 3TC 300 mg BID+ZDV (n=84; median exposure 389 days); ZDV + ddC (n=86)	There was no statistically significant difference between the treatment groups in the frequency of AEs, drug related AEs, SAEs, Grade 3/4 clinical and laboratory toxicities and withdrawal (W/D) due to AEs (all summary p values >0.05). At 24 weeks in secondary comparisons of 3TC 150 mg BID + ZDV vs 3TC 300 mg BID + ZDV treatment groups, as reported in the NUCA3002 study for the DAVGT analysis there were no statistically significant differences between treatment groups for absolute CD4 cell counts and log_{10} HIV RNA PCR (p =0.978 and p=0.292 respectively). There was a slightly higher incidence of some AEs and laboratory abnormalities in the 3TC 300 gm BID + ZDV group and the ZDV+ ddC group than the 3TC 150 mg BID + ZDV group, but the differences were not statistically significant. The 3TC 300 mg BID and 3TC 150 mg BID with ZDV combination therapies produced similar and sustained virologic and immunologic responses.
NUCA3001 (3TC) Status: Complete	A randomized double-blind multicenter trial to compare the safety and efficacy of 3TC monotherapy versus ZDV monotherapy versus 3TC administered concurrently with ZDV in the treatment of HIV-1 infected study participants who are ZDV naïve (≤4 weeks) with CD4 cell counts of 200-500 cells/mm^3 Subjects received: 3TC 150 mg BID +ZDV (n=92; median exposure 355.5 days); 3TC 300 mg BID (n=87; median exposure 364 days); 3TC 300 mg BID +ZDV (n=94; median exposure 320 days); ZDV (n=93, median exposure 337 days)	There were no statistically significant differences between the treatment groups in the frequency of adverse event (AE), drug-related AEs, serious adverse event (SAE), Grade 3/4 clinical and laboratory toxicities and withdrawals due to AE events reported (all summary p values >0.05). There was a decrease in viral load and sustained increase in CD4 cell counts over 24 weeks which was not statistically significant different between the two combination therapy groups which differed only by the 3TC dose (150 mg BID vs 300 mg BID) for CD4 cell counts (p=0.764) and HIV viral load (p=0.450).

Study No. (Component) **Status**	**Short Description of Study**	**Conclusion(s)**
NUCB3001 (3TC) Status: Complete	Controlled 3TC double-blinded trial to compare the safety and efficacy of 3TC (300 mg BID) in combination with ZDV versus ZDV monotherapy in treating HIV-1 infected study participants who are ZDV therapy naïve with a CD4 cell count between 100-400 cells/mm^3 Subjects received: 3TC 300 mg BID+ZDV (n=65); ZDV (n=64).	Over 24 weeks, there were no statistically significant differences between the treatment groups in the frequency of AEs, drug-related AEs, SAEs, Grade 3/4 clinical and laboratory toxicities (all summary p values >0.05). The combination was well tolerated, with no differences reported in the nature or incidence of laboratory or clinical AEs between the two groups over 24 weeks of treatment. Note: After 24 weeks, study participants were eligible to enter NUCB3001C, a rollover trial.
NUCB3001C (3TC) Status: Complete	Continuation Phase (Week 24 to Week 48) of NUCB3001 Subjects received 3TC 300 mg BID with ZDV (n=110)	Over 48 weeks, the 3TC 300 mg BID+ZDV combination continued to be well tolerated and the majority of AEs were related to the underlying disease, associated infections or recognized side effects of ZDV. Viral load suppression was sustained and all participants showed sustained rise in CD4 cell counts above baseline through 48 weeks.
NUCA3002 (3TC) Status: Complete	A randomized 3TC, ddC double-blind (ZDV open-labeled) multicenter trial to evaluate the safety and efficacy of 3TC (150 mg low dose) administered concurrently with ZDV versus 3TC (300 mg high dose) administered concurrently with ZDV versus dideoxycytidine (ddC) administered concurrently with ZDV in the treatment of HIV-1 infected ZDV-experienced (≥24 weeks) study participants with CD4 cell counts of 100-300 cells/mm^3	The incidence of all AEs was comparable across all treatment groups. Many of the events appeared to be related to the patients' underlying disease. The incidence of drug-related AEs in this study was higher in the ZDV+ddC (0.75mg) group (73%) than in the ZDV+3TC (150mg) group (65%) and the ZDV+3TC (300mg) group (60%). Overall, ZDV and 3TC combination therapy was well tolerated. There were no deaths. The majority of the SAEs were related to the progression of the disease or associated infections. The number of patients who withdrew from the study due to an AD was lower in the ZDV+3TC (150mg) group (11%) than in the ZDV+3TC (300mg) group (21%) and in the ZDV+ddC (0.75mg) group (17%).

Study No. (Component) **Status**	**Short Description of Study**	**Conclusion(s)**
NUCB3002 (3TC) Status: Complete	A randomized, controlled, Lamivudine (3TC) double-blinded trial to compare the safety and efficacy of ZDV monotherapy versus Lamivudine plus ZDV in combination in treating HIV-1 infected patients who are ZDV Therapy-experienced with a CD4+ cell count between 100 cells/mm^3 to 400 cells/^{mm3} Subjects received: 3TC 150 mg BID +ZDV (n=75); 3TC 300 mg BID +ZDV (n=75); ZDV (n=73)	Over 24 weeks, there was no statistically significant difference between the treatment groups in the frequency of AEs, SAEs, Grade 3/4 clinical and laboratory toxicities (all summary p values >0.05; statistical testing was not done on withdrawals (W/D) due to AEs). There were also no differences between the 150 mg BID or 300 mg BID dose 3TC combination treatment groups. Upon comparison between the 3TC 150 mg BID + ZDV group and the 3TC 300 mg BID + ZDV group at 24 weeks, there were no statistically significant differences between treatment groups in absolute CD4 cell counts and log_{10} HIV RNA PCR (p =0.840 and p <0.260 respectively).
NUCA3004 (3TC) Status: Complete	Open-label program for 3TC in HIV-infected pediatric and adult patients Subjects received: 3TC 150 mg BID (n=9665); 3TC 300 mg BID (n=7884); 3TC 150 mg BID + ZDV (n=6680)	Treatment with either 3TC 150 mg BID, or 300 mg BID (or 3TC 150 mg BID + ZDV) was generally well tolerated by the 24,229 study participants with confirmed HIV infection. Clinical event frequency remained constant with increasing doses of 3TC with low incidence of clinical abnormalities. These results are similar to the observations from the 3TC randomized trials comparing 150 mg and 300 mg 3TC BID
NUCB3004 (3TC) Status: Complete	Open-label program for 3TC in HIV-infected pediatric and adult patients Subjects received 3TC 300 mg BID (n=722)	Of the 722 participants as reported in the interim safety CSR, the pattern and incidence of AEs and laboratory abnormalities were consistent with the safety profile of 3TC plus ZDV in the adult comparative studies where the patient population had less advanced HIV disease

Note: Supportive studies are tabulated briefly in this safety summary; reports will be made available upon request for the convenience of the reviewer.

Appendix Table 2 Description of Pivotal Efficacy and Safety Studies

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date[a]; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age, (Range, years)	Primary Endpoint(s)
GEMINI-1 204861	87 centers; Argentina, Australia, Belgium, Canada, France, Germany, Italy, Republic of Korea, Mexico, The Netherlands, Portugal, Romania, Russia, South Africa, Spain, Taiwan, UK, US	FSFV 21JUL2016; Ongoing; W48/W52 LSLV: 29MAR2018, 719/700	To demonstrate the non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks	Phase III, randomized, double-blind, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1-infected, ART-naïve adults	DTG 50 mg; tablet; oral; once daily + 3TC 300 mg; tablet; oral; once daily; 148 weeks DTG 50 mg; tablet; oral; once daily + FDC of TDF/FTC 300 mg/200 mg; tablet oral; once daily; 148 weeks	ITT-E Population: DTG + 3TC: 356/320 ongoing DTG + TDF/FTC: 358/330 ongoing	DTG + 3TC: 297/59; 34, (1[redacted]-6[redacted]) DTG + TDF/FTC: 306/52; 35, (1[redacted]-6[redacted])	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm) in ITT-E Population

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date[a]; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age, (Range, years)	Primary Endpoint(s)
GEMINI-2 205543	104 centers; Argentina, Australia, Belgium, Canada, France, Germany, Italy, Mexico, Peru, Poland, Portugal, Romania, Russia, Spain, Switzerland, Taiwan, UK, US	FSFV 18JUL2016; Ongoing; W48 LSLV: [redacted], W52 LSLV 04APR2018; 722/700	To demonstrate the non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks	Phase III, randomized, double-blind, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1-infected, ART-naïve adults	DTG 50 mg; tablet; oral; once daily + 3TC 300 mg; tablet; oral; once daily; 148 weeks DTG 50 mg; tablet; oral; once daily + FDC of TDF/FTC 300 mg/200 mg; tablet oral; once daily; 148 weeks	ITT-E Population: DTG + 3TC: 360/330 ongoing DTG + TDF/FTC: 359/335 ongoing	DTG + 3TC: 306/54; 34.6, (1[redacted]-7[redacted]) DTG + TDF/FTC: 313/46; 34.4, (1[redacted]-7[redacted])	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm) in ITT-E Population

a. A confirmatory viral load measurement is performed at Week 52 for subjects presenting with HIV-1 RNA ≥50 c/mL at Week 48.

7.2. Definition of an Adverse Event

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (Overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae.) • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that

leads to the procedure is an AE.

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

7.3. Definition of a Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc.).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> impaired liver function defined as: • ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** • ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

2.7.5. References

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2.7.6 Synopses of Individual Studies

Table 1 Tabular Listing of All Clinical Studies

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
Biopharmaceutic Studies						
Comparative Bioavailability and Bioequivalence Study Reports for DTG + 3TC						
204993	To evaluate the relative BA of a single dose of DTG 50 mg and 3TC 300 mg when administered together in each of 2 FDC tablet formulations compared to the co-administration of a single dose of the single-entity DTG and 3TC products	R, OL, 3-way crossover	Healthy adult subjects	Two FDC tablet formulations of DTG 50 mg and 3TC 300 mg; oral; single dose DTG 50 mg + 3TC 300 mg single entity; oral; single dose	30 randomized/ 29 completed	Completed Full CPSR 5.3.1.2
204994	To evaluate the BE of FDC tablet formulations of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg and 3TC 300 mg, in the fasted state	R, OL, single-center, 2-part	Healthy adult subjects	Two FDC tablet formulations of DTG 50 mg and 3TC 300 mg; oral; single dose DTG 50 mg + 3TC 300 mg single entity; oral; single dose	Part 1: [redacted] 78 randomized/ 74 completed Part 2: [redacted] 76 randomized/ 74 completed	Completed Full CPSR 5.3.1.2

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
Efficacy and Safety Studies						
Controlled Clinical Studies Pertinent to the Claimed Indication for DTG + 3TC						
204861 GEMINI-1 Week 24 CSR 204861 GEMINI-1 Week 48 CSR	To demonstrate the non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks	Phase III, randomized, double-blind, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1-infected, ART-naïve adults	DTG 50 mg; tablet; oral; once daily + 3TC 300 mg; tablet; oral; once daily; 148 weeks DTG 50 mg; tablet; oral; once daily + FDC of TDF/FTC 300 mg/200 mg; tablet; oral; once daily; 148 weeks	DTG + 3TC: 359 Randomized/ 0 Completed (320 Ongoing) DTG + TDF/FTC: 360 Randomized/ 0 Completed (330 Ongoing)	Ongoing Week 24: Full CSR Week 48: Full CSR 5.3.5.1
205543 GEMINI-2 Week 24 CSR 205543 GEMINI-2 Week 48 CSR	To demonstrate the non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks	Phase III, randomized, double-blind, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1-infected, ART-naïve adults	DTG 50 mg; tablet; oral; once daily + 3TC 300 mg; tablet; oral; once daily; 148 weeks DTG 50 mg; tablet; oral; once daily + FDC of TDF/FTC 300 mg/200 mg; tablet; oral; once daily; 148 weeks	DTG + 3TC: 360 Randomized/ 0 Completed (330 Ongoing) DTG + TDF/FTC: 362 Randomized/ 0 Completed (335 Ongoing)	Ongoing Week 24: Full CSR Week 48: Full CSR 5.3.5.1

3TC = lamivudine
ABC = abacavir
ART = antiretroviral therapy
CSR = clinical study report
DTG = dolutegravir
FDC = fixed dose combination FTC = emtricitabine
HIV-1 = human immunodeficiency virus type 1
OL = open-label
R = randomized
TDF = tenofovir disoproxil fumarate