Module 2.5

Clinical Overview

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir sulfate
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse Event
AESI	Adverse Events of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
c/mL	Copies per milliliter
CI	Confidence Interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVW	Confirmed Virologic Withdrawal
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DRESS	Drug rash with Eosinophilia and System Symptoms
DRV	Darunavir
DTG	Dolutegravir
DTG + 3TC	Dolutegravir 50 mg Single Entity Tablet and Lamivudine 300 mg Single Entity Tablet
DTG/3TC FDC	Dolutegravir 50 mg and Lamivudine 300 mg Fixed Dose Combination Tablet
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
EU	European Union
FDC	Fixed dose combination
FTC	Emtricitabine
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
HCV	Hepatitis C virus
HDPE	High density polyethylene
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus type 1
HLA-B	Major histocompatibility complex, class I, B
HSR	Hypersensitivity Reaction
INI	Integrase Inhibitor
INSTI	Integrase Strand Inhibitor
IRIS	Immune Reconstitution Inflammatory Syndrome
ITT-E	Intent-To-Treat Exposed
LPV	Lopinavir
MAH	Marketing Authorization Holder
mg	milligram
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor

PI	Protease Inhibitor
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development
RBA	Relative Bioavailability
RMP	Risk Management Plan
RTV	Ritonavir
SAE	Serious Adverse Event
SE	Single Entity
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEN	Toxic Epidermal necrolysis
TDF	Tenofovir disoproxil fumarate
TDF/FTC FDC	Tenofovir disoproxil fumarate 300 mg and Emtricitabine 200 mg Fixed Dose Combination Tablet
ULN	Upper Limit of Normal
US	United States of America
VL	Viral load

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1. PRODUCT DEVELOPMENT RATIONALE

DTG + 3TC is a 2-drug regimen intended for the long-term treatment of HIV-1 infected patients. It is the combination of 2 well-established marketed products, DTG and 3TC. The efficacy and clinical safety and tolerability of the treatment regimen of DTG 50 mg + 3TC 300 mg is being evaluated in 2 pivotal, identical, ongoing, randomized, double-blind, parallel group, 148-week, Phase III studies (204861 [GEMINI-1] and 205543 [GEMINI-2]) in ART-naïve adults.

Full CMC development and bioequivalence evaluation for DTG/3TC FDC have been completed. Additional data to support the proposed marketing use (labeling) of DTG/3TC have been obtained in the SE development programs. These include areas of preclinical safety and virology, drug interaction studies, and PK and safety in special populations. Based on the lack of drug interaction between the individual components, these prior studies were not repeated with the DTG/3TC FDC. They will be used as supporting information, and their use in the application has been described in this document.

1.1. Introduction

Current treatment guidelines recommend the lifelong use of 3 drugs to construct a complete regimen for the treatment of HIV, usually a 2-drug NRTI backbone plus a third drug in a non-NRTI class (e.g., INI, PI, or NNRTI) [BHIVA, 2016; DHHS, 2018; EACS, 2017; Günthard, 2016]. Due to the long-term toxicities associated with these regimens, significant interest has emerged in the use of 2-drug regimens that may reduce cumulative drug exposure and associated drug-related toxicities while maintaining the efficacy of current 3-drug regimens and potentially preserve future treatment options. Current therapies and unmet medical need are discussed further in Section 6.1.2.

DTG + 3TC is a streamlined 2-drug regimen of 2 potent, well-characterized and well-tolerated ARVs. DTG + 3TC provides a novel 2-drug regimen that offers effective antiviral suppression while limiting the risk of adverse reactions by having one less ARV in the regimen. The combination of 3TC with DTG, with its high barrier to resistance and ability to confer a rapid decline in HIV-1 RNA, may have a low risk of selecting for resistance that is comparable overall to 3-drug regimens.

DTG is an HIV-1 INSTI with low to moderate intersubject PK variability, a predictable exposure-response relationship, and a 14-hour plasma half-life that supports once-daily dosing without the need for a PK booster. In addition, DTG lacks many of the associated drug interactions, specifically with oral contraceptives, statins, antidepressants, anxiolytics, anticoagulants, and other medications commonly taken by individuals with HIV infection.

3TC is a potent cytidine nucleoside analogue in the NRTI class of drug with a favorable long-term safety profile. Although 3TC monotherapy quickly selects for resistance due to a single point mutation at position M184V, that mutation impacts HIV-1 fitness and confers a half-log lower viral load level in patients [Eron , 1995].

1.2. Summary of Clinical Development Program

ViiV Healthcare is developing a 2-drug regimen of DTG + 3TC. ViiV Healthcare is the Sponsor of the development program; various aspects of the program are being conducted by GSK and [redacted] on behalf of ViiV Healthcare.

The goal of the clinical development program (Table 1) was to develop a DTG/3TC FDC tablet; a 2-drug regimen for the long-term treatment of HIV-1 infection that retains the efficacy of a 3-drug regimen while minimizing the long-term adverse effects from cumulative drug exposure and preserving future treatment options. The pivotal Phase III studies, Study 204861 (GEMINI-1) and Study 205543 (GEMINI-2) are being conducted with the single entities, DTG 50 mg + 3TC 300 mg. After evaluating the relative bioavailability of experimental FDC tablets in Study 204993, the bioequivalence and food effect of the selected FDC was evaluated in Study 204994, in parallel with the Phase III clinical program of DTG + 3TC. The proposed commercial product with this application is the FDC tablet.

Data are provided in this application in support of DTG 50 mg + 3TC 300 mg from Study 204861 (GEMINI-1) and Study 205543 (GEMINI-2). These studies are pivotal, identical, ongoing, randomized, double-blind, parallel group, 148-week, Phase III studies. Week 48 data from Studies 204861 and 205543 presented herein are intended to support the use of DTG 50 mg + 3TC 300 mg for the treatment of HIV-1 infection in ART-naïve adult patients. The BE Study 204994, and data from 3TC historical studies provide an acceptable bridge to the single entities used in the GEMINI-1 and GEMINI-2 Phase III studies and support the proposed submission for the FDC tablet.

Full study data are available in the Study 204861 Week 48 CSR and the Study 205543 Week 48 CSR found in m5.3.5.1.

Table 1 Summary of Clinical Studies

Study	Study Design	Population	Treatment details	Key Conclusions
204861 (GEMINI-1) GSK Document Number 2018N371626_00 Status: Ongoing; Week 48 CSR Complete	Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1-infected, ART-naïve adults	DTG 50 mg tablet + 3TC 300 mg tablet, once daily DTG 50 mg tablet + TDF/FTC FDC 300 mg/200 mg tablet, once daily	The primary analysis demonstrated that DTG + 3TC is non-inferior to DTG + TDF/FTC, with 90% of subjects in the DTG + 3TC group and 93% of subjects in the DTG + TDF/FTC group achieving the primary endpoint of <50 c/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm [adjusted treatment difference and 95% CI: -2.6 (-6.7, 1.5) for the ITT-E Population.
205543 (GEMINI-2) GSK Document Number 2018N371863_00 Status: Ongoing; Week 48 CSR Complete	Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1-infected, ART-naïve adults	DTG 50 mg tablet + 3TC 300 mg tablet, once daily DTG 50 mg tablet + TDF/FTC FDC 300 mg/200 mg tablet, once daily	The primary analysis demonstrated that DTG + 3TC is non-inferior to DTG + TDF/FTC, with 93% of subjects in the DTG + 3TC group and 94% of subjects in the DTG + TDF/FTC group achieving the primary endpoint of <50 c/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm [adjusted treatment difference and 95% CI: -0.7 (-4.3, 2.9) for the ITT-E Population.

Study	Study Design	Population	Treatment details	Key Conclusions
204993 GSK Document Number 2016N291427_00 Status: Complete	Phase I, randomized, open label, crossover study to evaluate the Relative Oral Bioavailability Study of Different Fixed Dose Combinations of Dolutegravir and Lamivudine in Healthy Subjects	Healthy adult subjects	Reference Treatment = DTG 50 mg and 3TC 300 mg once daily administered as single entity tablets Test Treatments = FDC Product Code AA, FDC Product Code AB	Single oral doses of DTG 50 mg and 3TC 300 mg administered as single entity tablets or as 2 experimental FDC tablets, AA and AB, were safe and well tolerated. Plasma exposures (AUC(0-∞) and Cmax) of DTG following FDC formulation AA administration were approximately 12.2% and 14.5% higher than those following the co-administration of DTG 50 mg and EPIVIR 300 mg, respectively. Plasma exposures (AUC(0-∞) and Cmax) of DTG following FDC formulation AB administration 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 that following the co-administration of DTG 50 mg and EPIVIR 300 mg, however 3TC Cmax was 17.8% higher when compared to the reference. Following FDC formulation AB administration, 3TC AUC(0-∞) was similar to that following the co-administration of DTG 50 mg and EPIVIR 300 mg, however 3TC Cmax was 23.1% higher when compared to the reference.
204994 GSK Document Number 2017N342011_00 Status: Complete	Phase 1, randomized, open label, crossover study to evaluate the Bioequivalence of two Fixed Dose Combination Tablets of Dolutegravir and Lamivudine and Food Effect in Healthy Subjects	Healthy adult subjects	**Reference Treatment:** DTG 50 mg tablet (clinical image) plus a single EPIVIR 300 mg tablet **Test Treatments:** DTG/3TC Tablets, 50 mg/300 mg FDC [redacted] formulation Product Code AH DTG/3TC Tablets, 50 mg/300 mg FDC [redacted] formulation Product Code AK	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 sensitivity 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 m2.7.4, 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. Administration of the [redacted] FDC tablet with a high-fat meal resulted in higher plasma DTG AUC(0-∞), AUC(0-t), and Cmax and lower plasma 3TC Cmax.

Study	Study Design	Population	Treatment details	Key Conclusions
				The magnitude of the food effect on DTG and 3TC was similar to that observed in prior studies and is not considered clinically significant. These results support the recommendation that the [redacted] FDC tablet can be given without regard to meals.

1.2.1. Pivotal Efficacy and Safety Studies 204861 (GEMINI-1) and 205543 (GEMINI-2)

Studies 204861 (GEMINI-1) and 205543 (GEMINI-2) are being conducted to provide evidence to support the efficacy, safety, and tolerability of the new 2-drug regimen combining DTG + 3TC for the treatment of HIV-1 infection in ART-naïve adult subjects, with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. The Week 48 data from these studies establish that 2-drug regimen of DTG + 3TC is effective and safe at treating HIV-1 infection and provide important information regarding efficacy, safety, tolerability, and quality of life.

1.2.2. Bioequivalence Study 204994

Study 204994 (Table 1) was conducted to evaluate the bioequivalence of two oral DTG 50 mg/3TC 300 mg FDC tablet formulations, including the DTG/3TC FDC proposed for commercial use, compared with co-administration of the separate tablet formulations of DTG 50 mg (clinical trial material image) and 3TC 300 mg (commercial). This study also assessed the effect of food on the FDC formulations.

1.2.3. Relative Bioavailability Study 204993

Study 204993 (Table 1) was a relative bioavailability study that evaluated the PK of 2 experimental prototype DTG/3TC FDC tablets compared with co-administration of the SE tablets in fasted conditions. This study also served as a guide for pharmaceutical development, and supports the proposed indication.

1.2.4. DTG and 3TC Single Entity Studies

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

- **Key SE Studies**: these studies provide data that may be included in labeling, and were conducted during the individual agent development programs. Key clinical studies are described in module 2.7, 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 on the proposed indication. Supportive studies are briefly tabulated in the module 2.7 summaries, but reports will be made available upon request for the convenience of the reviewer.

All single agent data that are considered not to be relevant to this DTG/3TC FDC application, e.g., efficacy data not related to the indication, will not be provided in this FDC submission.

1.3. Regulatory History

The DTG + 3TC development program has been formally discussed with key regulatory agencies at various milestones throughout development (see m2.2).

Both DTG and 3TC are commercially available products in many markets worldwide. Tivicay (DTG) Tablets, 50 mg are available in over 124 countries, including the US, EU, and Canada. DTG was developed by GSK on behalf of ViiV Healthcare. Epivir (3TC) Tablets, 300 mg were first approved in US in 1995, followed by approval in the EU in 1996.

1.4. Claimed Indication and Dosage

The new formulation being developed is a FDC of DTG/3TC 50 mg/300 mg as a 2-drug regimen for the treatment of HIV-1 infection in patients without known or suspected resistance to either antiretroviral component. The recommended oral dose of DTG/3TC for adults and adolescents ≥12 years (and ≥40 kg) is 1 tablet of DTG 50 mg/3TC 300 mg administered once a day, and is based on already established/approved doses of the single entities of DTG and 3TC.

DTG 50 mg once daily is indicated for the treatment of HIV infection in combination with other antiretroviral agents in adults and adolescents 12 years of age or older and ≥40 kg. Lower strength pediatric tablets are approved in some countries for body weight-based dosing in children 6 years of age and older and weighing ≥15 kg [Tivicay Product Information, 2017]. 3TC 300 mg once daily is approved for use in adults, adolescents, and children ≥25 kg. Scored 150 mg tablets and oral solution are available for weight-based dosing of children <25 kg [Epivir Product Information, 2018].

1.5. Compliance with GCP

All studies were undertaken in accordance with standard operating procedures of ViiV Healthcare and the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authority.

2. OVERVIEW OF BIOPHARMACEUTICS

For detailed information on biopharmaceutic data described in this Section, refer to m2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods).

The bioanalytical methods used to measure concentrations of DTG in human plasma, in the presence of 3TC and 3TC in the presence of DTG were sensitive, accurate and reproducible (m2.7.1 Section 1.4).

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

This application for the DTG/3TC FDC tablet is supported by the BE Study 204994, a 2-part, single dose, 2-way crossover study conducted in healthy volunteers to evaluate the bioequivalence of two ([redacted] and [redacted]) FDC formulations of DTG 50mg and 3TC

300mg compared to co-adminstration of the separate tablet formulations of DTG 50mg and 3TC 300mg in the fasted state, and to evaluate the effect of food, on the bioavailability of the FDC formulations (see m2.7.1, Section 2.4.1.1).

The results of BE Study 204994 showed that the [redacted] DTG/3TC FDC tablet met the bioequivalence criteria for DTG AUC and Cmax and for 3TC AUC; however, the [redacted] had an approximately 32% higher 3TC Cmax than the reference 3TC SE tablet. 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. Therefore, the data from 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. Furthermore, the magnitude of the effect of food on the exposures of DTG and 3TC in the FDC was no greater than that observed in historical data for the SE tablets and is not considered clinically significant. Therefore, the DTG/3TC FDC may be taken with or without food, which is consistent with the prescribing information for the DTG and 3TC single entities.

2.1. DTG/3TC FDC Formulation Development

Formulation development for FDC tablets of DTG 50 mg and 3TC 300 mg included the investigation of [redacted] and [redacted] DTG/3TC tablets.

[redacted] DTG/3TC tablet formulations were dosed in the initial RBA Study 204993. Based on the RBA study results, a [redacted] formulation was developed in parallel to enable both a [redacted] and [redacted] formulation to be tested in BE Study 204994. Complete statements of the components and quantitative composition of the [redacted] and [redacted] DTG/3TC tablets dosed in Studies 204993 and 204994 are presented in m3.2.P.2.2, Section 1.2.1. Based on the pharmacokinetic results of Study 204994, the [redacted] tablet formulation was selected as the commercial formulation.

The proposed commercial formulation for DTG/3TC tablets contains 52.6 mg of DTG sodium, which is equivalent to 50 mg DTG (free acid), and 300 mg of lamivudine. The tablets are oval (approximately 18.5 x 9.5 mm), biconvex, white tablets, debossed with "SV 137" on one face.

The tablets are packaged in HDPE bottles with polypropylene child-resistant closures that include induction seal liners.

2.2. Biopharmaceutics Studies

The key results from the biopharmaceutics studies for consideration in clinical use and detailed in m2.7.1 are as follows:

- In the fasted state, the [redacted] FDC formulation of DTG 50 mg and 3TC 300 mg was bioequivalent for DTG AUC(0-∞), and Cmax, and for 3TC AUC(0-∞) and AUC(0-t) . The [redacted] FDC AUC(0-t) was ~16% higher than the reference DTG. However, a sensitivity analysis showed bioequivalence for this parameter (m2.7.1 Section 2.1.1.1) and historical safety data from registrational Phase 3 studies with DTG 50 mg BID doses showed no additional safety concerns (m2.7.4 Section 5.6).

In addition, 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 (m2.7.4 Section 5.6). Therefore, the PK of the [redacted] FDC provide an acceptable bridge to the co-administration of Tivicay and Epivir tablets in Phase III trials (m2.7.1 Section 2.1.1.1).

- Administration of the [redacted] FDC tablet 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. These results support the recommendation that the [redacted] FDC tablet can be given without regard to meals (m2.7.1 Section 2.4.1.1).

- In summary, results of the bioequivalence and food effect Study 204994 support use and posology of the [redacted] DTG/3TC FDC in the proposed indication (Section 1.4).

3. OVERVIEW OF CLINICAL PHARMACOLOGY

A comprehensive set of clinical pharmacology studies was completed to support the initial marketing application and post-marketing commitments of the individual DTG or 3TC component as Tivicay or Epivir, respectively (see Summary of Clinical Pharmacology m2.7.2, Section 2). The PK (ADME), drug-drug interaction and special population labelling for the SEs will be applied to establish the clinical pharmacology labelling for the DTG/3TC FDC tablet, and conclusions from prior drug-drug interaction, ADME, thorough QT studies, and special population studies, including PK studies in adolescents, can be applied to the DTG/3TC FDC. These studies are described in m2.7.2.

The key characteristics of clinical pharmacology related to the DTG/3TC FDC product are based upon information obtained from the SE development programs for DTG and 3TC, along with the BE and food effect study of the DTG/3TC FDC (Study 204994) (Table 1, m2.7.2 Section 1.2). The BE and food effect Study 204994, together with the 3TC safety data from historical dose-ranging and registrational studies that evaluated higher 3TC doses/exposures provide an acceptable bridge between the DTG/3TC FDC and the DTG + 3TC single entities used in GEMINI-1 and GEMINI-2 studies (m2.7.1 Section 2.1.1.1; m2.7.2 Section 3.3.4; m2.7.4 Section 5.6).

The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC which are adult doses already authorized as individual agents for the treatment of HIV infection in adolescents ≥12 years of age weighing ≥40 kg (DTG) or in pediatric patients weighing ≥25 kg (3TC). Since prior studies have demonstrated that DTG and 3TC PK exposures in adolescents are similar to adults, the efficacy data in adults from the GEMINI studies can be extrapolated to adolescents.

4. OVERVIEW OF EFFICACY

The Week 48 efficacy analysis from pivotal studies 204861 and 205543 demonstrated that DTG + 3TC provided a high level of clinical efficacy that is similar to that of a standard 3-drug regimen, DTG + TDF/FTC. In the individual and pooled analyses,

similar proportions of subjects in each treatment group achieved the primary efficacy endpoint of plasma HIV-1 RNA <50 c/mL by Snapshot at Week 48. Based on a 10% non-inferiority margin, both pivotal studies and the supportive pooled data from the 2 studies demonstrate 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% (Section 4.4.1).

For a full presentation of efficacy results, see the Summary of Clinical Efficacy (m2.7.3).

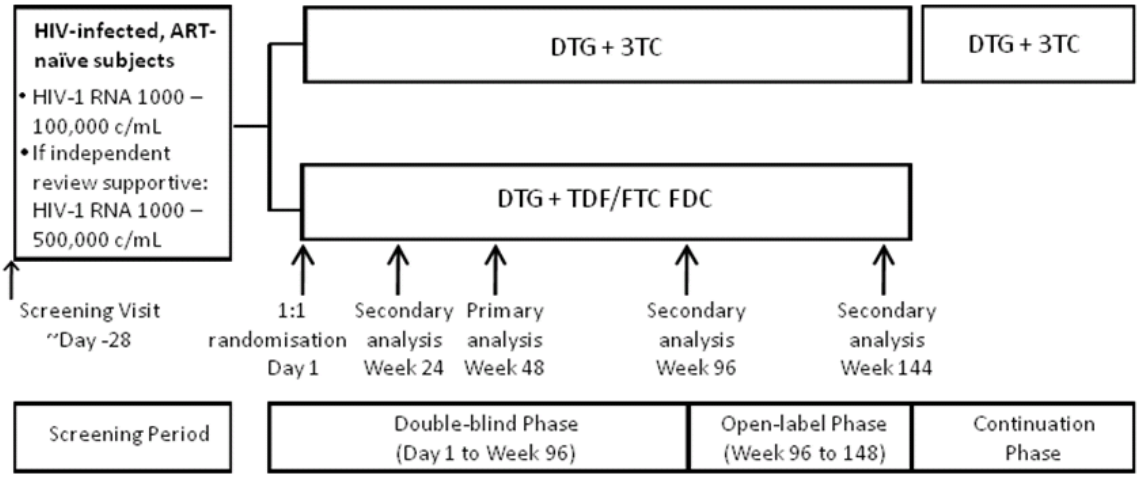
4.1. Clinical Trial Methodology, Design, and Patient Population

The 2 ongoing pivotal efficacy studies, 204861 (GEMINI-1) and 205543 (GEMINI-2), are identical 148-week, Phase III, randomized, double-blind, active-controlled, multicenter, parallel-group, non-inferiority studies. The studies are being conducted in adult 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 (≤200 cells/mm^3 or >200 cells/mm^3). All subjects who successfully complete 96 weeks of randomized, blinded treatment will receive their randomized treatment (DTG + 3TC or DTG + TDF/FTC FDC) in an open-label manner as part of the study through Week 148 (Figure 1).

The primary analysis took place after the last subject completed the Week 48 visit. The Week 24 analysis was a secondary analysis performed for regulatory purposes. Additional analyses will be conducted after the last subject completes the Week 96 visit, and the Week 144 visit. Further data cuts and analyses may be conducted, as necessary, after Week 144 to support regulatory submissions and publications.

The studies include a Screening Phase (up to 35 days), a Double-blind Randomized Phase (Day 1 up 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 these studies.

Figure 1 Study Schematic for 204861 (GEMINI-1) and 205543 (GEMINI-2)



Target enrollment N=700 randomized subjects planned/study. Subjects randomized 1:1 to receive a 2-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).

4.2. Efficacy Endpoints and Statistical Considerations of Efficacy Analyses

The primary population for the Week 48 efficacy analyses was the ITT-E population, which consisted of all randomly assigned subjects who received at least 1 dose of study drug.

4.2.1. Primary and Secondary Efficacy Endpoints

The primary efficacy 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.

Secondary endpoints evaluated at Week 48 are provided in m2.7.3 Section 1.5.

4.2.2. Statistical Considerations

For each study (204861 and 205543), non-inferiority could be concluded if the lower bound of a two-sided 95% CI for the difference in response rates between the 2 treatment groups was greater than -10%. If r_d is the response rate on DTG + 3TC and r_f is the response rate on DTG + 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 treatment group and an 89% response rate for the DTG + TDF/FTC treatment group, a non-inferiority margin of -10%, and a 2.5% one-sided significance level, each study (204861 and 205543) required 347 subjects per treatment group.

4.3. Subject Disposition and Baseline Characteristics

There are no differences in the demographic or Baseline characteristics that would impact the interpretation of the efficacy or safety results (m2.7.3 Section 3.1.2).

In each study, similar proportions of subjects in each treatment group withdrew from the study (m2.7.3 Section 3.1.1). In each study and the pooled analysis, the most common reasons for withdrawal were lost to follow up, withdrawal by subject, and AE (Data Source: GEMINI ISS/ISE Table 1.4).

4.4. Efficacy Results at Week 48

Refer to m2.7.3 Section 3 for a full presentation of the efficacy results.

4.4.1. Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48

The primary endpoint for these studies was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population.

In each study and the pooled analysis, efficacy response rates were high and similar between the DTG + 3TC and DTG + TDF/FTC FDC groups at Week 48 (Table 2) (Data Source Study 204861 CSR Table 2.1, Study 205543 CSR Table 2.1, GEMINI ISS/ISE Table 2.1, and m2.7.3 Section 3.2.1). Based on a 10% non-inferiority margin, the individual studies and the pooled analyses demonstrated that DTG + 3TC is non-inferior to DTG + TDF/FTC FDC 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 (Data Source Study 204861 CSR Table 2.2, Table 2.3, Study 205543 CSR Table 2.2, Table 2.3, GEMINI ISS/ISE Table 2.2, Table 2.3).

Table 2 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 n/N (%)	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 FDC	332/358 (93)		
205543			
DTG + 3TC	335/360 (93)	-0.8 (-4.4, 2.8)	-0.7 (-4.3, 2.9)
DTG + TDF/FTC FDC	337/359 (94)		
Pooled			
DTG + 3TC	655/716 (91)	-1.8 (-4.6, 0.9)	-1.7 (-4.4, 1.1)
DTG + TDF/FTC FDC	669/717 (93)		

Data Source: 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 FDC.

b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factors: Plasma HIV-1 RNA (≤ or >100,000 c/mL) and CD4+ cell count (≤ or >200 cells/mm3). Pooled analysis also stratified by study.

4.4.2. Time to Viral Suppression

Within the individual studies and in the pooled analysis, a rapid and sustained response was observed in both treatment groups. In each study, Kaplan-Meier estimates of the time to viral suppression (<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) (m2.7.3 Section 3.2.3).

4.4.3. Absolute Values and Changes from Baseline in CD4+ Cell Counts at Week 48

Mean and median CD4+ cell counts increased at each visit in both treatment groups from Baseline to Week 48 (m2.7.3 Section 3.2.7). At Week 48, there was no significant difference between treatment groups in the change in CD4+ cell counts from Baseline in either study or in the pooled analysis.

4.4.4. Incidence of HIV-1 Disease Progression (HIV-associated Conditions, AIDS, and Death)

In each study and in the pooled analysis, few subjects (≤1%) progressed to either Stage 3 or death up to Week 48 in the DTG + 3TC and DTG + TDF/FTC FDC groups (m2.7.3 Section 3.2.8). HIV-1 associated conditions are discussed in m2.7.3 Section 3.2.8.

4.4.5. Subgroup analyses at Week 48 based on Baseline Strata

To assess the generalizability of the Week 48 analysis results (proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48), one-way homogeneity across the Baseline HIV-1 RNA (≤or >100,000 c/mL) and Baseline CD4+ cell count subgroups (≤ or >200 cells/mm$^{3)}$ was tested.

In Study 205543, there was statistically significant evidence of heterogeneity (p=0.03), indicating a difference in response rates between treatments across Baseline plasma HIV-1 RNA categories (Data Source: Study 205543 Table 2.7). 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. This finding was not replicated in Study 204861 nor in the pooled analysis (Data Source: Study 204861 Table 2.7, Study 205543 Table 2.7, GEMINI ISS/ISE Table 2.7).

In Study 205543 and the pooled analysis, there was evidence of heterogeneity across Baseline CD4 cell count categories, with a lower response rate in the DTG + 3TC arm in subjects with CD4+ cell count ≤200 cells/mm^3 (tested at 10% level of significance; p=0.03 for Study 205543 and p=0.10 for the pooled analyses). A similar trend was seen in Study 204861, although the test for heterogeneity was not significant (Data Source: Study 204861 Table 2.7). It should be noted that the number of subjects in the ≤200 cells/mm^3 subgroup is small (n=118, 8% of total randomized subjects). The reasons for subjects having Snapshot outcomes that fell into one of the "non-response" categories varied; except for one 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.

Beyond testing for evidence of heterogeneity, a number of subgroups were assessed based on demographic and baseline characteristics. Where subgroups are sufficiently large, subgroup results are supportive of the primary endpoint of the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Data Source: GEMINI ISS/ISE Table 2.12).

4.5. Virology

Overall, the numbers of subjects meeting protocol-defined virological withdrawal criteria in the DTG + 3TC group (n=6) and the DTG + TDF/FTC group (n=4) were low (m2.7.3 Section 3.2.6). All subjects meeting virological withdrawal criteria experienced viral rebound rather than non-response.

4.5.1. Subjects Who Met Confirmed Virologic Withdrawal Criteria

The CVW Population included all subjects in the ITT-E Population who met protocol-defined CVW criteria, as defined in the RAP. No subject meeting CVW

criteria in either group had treatment emergent INSTI or NRTI resistance while on study (m2.7.3 Section 3.2.6).

4.6. Value Evidence and Outcomes

A summary of change from Baseline in health-related quality of life using EQ-5D-5L can be found in m2.7.3 Section 3.4.

In both studies, mean Baseline EQ-5D-5L Utility and Thermometer scores were high in both arms (Data Source: Study 204861 CSR Table 5.2, Table 5.3, Study 205543 CSR Table 5.2, Table 5.3). Similar improvements were observed in the 2 treatment groups in EQ-5D-5L Utility score and Thermometer scores at Week 48.

4.7. Efficacy Conclusions

At Week 48, in both the pooled analysis and in the individual studies, DTG + 3TC was non-inferior to DTG + TDF/FTC. The proportion of subjects with plasma HIV-1 RNA <50 c/mL was similar in each treatment group. At least 90% of subjects in each treatment group had plasma HIV-1 RNA <50 c/mL using the Snapshot algorithm.

There were few subjects meeting CVW criteria by Week 48 in either treatment arm. Drug resistance mutations did not emerge in any subjects meeting CVW criteria in either treatment arm.

The DTG + 3TC 2-drug regimen is effective in the treatment of HIV-1 infection across a diverse spectrum of ART-naïve subjects, including those in both low and high Baseline HIV-1 RNA strata (≤ or >100,000 c/mL), as demonstrated in the subgroup analyses of the primary endpoint. However, in Study 205543 and the pooled analysis, there was evidence of heterogeneity across the Baseline CD4 cell count subgroup, with a lower response rate in the DTG + 3TC arm in subjects with Baseline CD4 cell counts ≤200 cells/mm^3. 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; except for one subject that met protocol-defined CVW in Study 204861, none resulted in treatment-related discontinuation at Week 48. 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.

Based on a 10% non-inferiority margin, a 2-drug regimen of DTG + 3TC is non-inferior to the 3-drug regimen of DTG + TDF/FTC FDC, with no increase in incidence of virologic failure at Week 48. The DTG + 3TC regimen provides effective antiviral suppression over 48 weeks.

Since prior studies demonstrated that DTG and 3TC PK exposures in adolescents are sufficiently similar to those in adults, this efficacy data can be extrapolated to adolescents (m2.7.2 Section 3.3.4).

5. OVERVIEW OF SAFETY

For a full presentation of safety results, see the Summary of Clinical Safety (m2.7.4).

The safety database consists of pooled safety data from 1433 subjects (DTG + 3TC 716; DTG + TDF/FTC FDC 717) from the 2 identical Phase III Studies 204861 and 205543. The safety data presented for each study are cumulative up to the data cut-off for the Week 48 Database Freeze. In this analysis, the safety data obtained in the 204861 and 205543 studies of this regimen of DTG + 3TC are not pooled with safety data previously reported for the individual components.

5.1. Introduction

The methodology and design of clinical studies (Study 204861 and Study 205543) used to support the safety of DTG + 3TC are presented in Section 4.1.

5.1.1. Population Included in Safety Analyses

Safety analyses were conducted based on the pooled Safety Population, defined as all subjects who received at least 1 dose of study drug.

5.1.2. Data Cut-off Dates

This submission contains safety data collected and analyzed up to the data cut-off date for the Week 48 database freeze of [redacted]. Details of individual study cut-off dates are provided in m2.7.4 Section 1.1.6.

5.1.3. Extent of Exposure in Studies 204861 and 205543

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).

5.2. Non-Clinical Data Relevant to Human Safety

The safety of the individual components of DTG and 3TC have been well characterized in a battery of nonclinical studies discussed in m2.4 (Nonclinical Overview), and have previously supported the marketing approval of the individual components. The overall nonclinical safety data support the clinical use of DTG and 3TC as individual agents. There is no known effect on each other's exposure, and no known combined nonclinical safety risk. There are no common target organs identified in respective non-clinical studies. The nonclinical data for the individual agents support the use of DTG + 3TC in the treatment of HIV-1 infection in ART-naïve adult subjects at the recommended dose of DTG 50 mg and 3TC 300 mg once daily.

5.3. Adverse Events

Overall, safety results observed between the 2 treatment groups were comparable. Table 3 provides an overall summary of AEs up to the Week 48 cut-off date.

In both studies and in the pooled analysis, a lower proportion of subjects in the DTG + 3TC group compared with the DTG + TDF/FTC group reported drug-related AEs; most of these were Grade 1 or Grade 2 events (m2.7.4 Section 2.1.2.4).

Table 3 Overall Summary of Adverse Events (Safety Population)

	Study 204861 and Study 205543, Pooled	
	DTG + 3TC N=716 n (%)	DTG + TDF/FTC FDC N=717 n (%)
Any AE	543 (76)	579 (81)
Drug-related AEs	126 (18)	169 (24)
Any Grade 2 to 5 AEs	404 (56)	425 (59)
Any Drug-related Grade 2 to 5 AE	42 (6)	47 (7)
AEs Leading to Withdrawal	15 (2)	16 (2)
Drug-related AEs Leading to Withdrawal	6 (<1)	9 (1)
Any SAE	50 (7)	55 (8)
Drug-related SAEs	4 (<1)	4 (<1)
Fatal SAEs	2 (<1)	0
Drug-related Fatal SAEs	0	0

Data Source: GEMINI ISS/ISE Table 3.2, Table 3.4, Table 3.7, Table 3.9, Table 3.14, Table 3.15, Table 3.16, Table 3.17, Table 3.19, Table 3.76.

5.3.1. Common Adverse Events

The most commonly reported AEs for the DTG + 3TC and DTG + TDF/FTC groups were headache, diarrhea and nasopharyngitis (m2.7.4 Section 2.1.2). Fewer subjects in the DTG + 3TC group compared with the DTG + TDF/FTC group reported nasopharyngitis, insomnia, nausea and diarrhea. There were no other notable differences between the 2 treatment groups when comparing individual preferred terms. The majority of events reported had a maximum intensity of Grade 1 or Grade 2 for both treatment groups (m2.7.4 Section 2.1.2.3).

5.3.1.1. Drug-Related Adverse Events

Overall, for both treatment groups, most drug-related AEs had a maximum intensity of Grade 1 or Grade 2 (m2.7.4 Section 2.1.2.4). A lower proportion of subjects in the DTG + 3TC group (18%) reported at least 1 drug-related AE compared with the DTG + TDF/FTC group (24%), driven primarily by larger numbers of subjects reporting Grade 1 events, notably drug-related nausea in the DTG + TDF/FTC group (Data Source: GEMINI ISS/ISE Table 3.4, Table 3.5).

Other than nausea, the incidence of drug-related AEs by individual preferred term was similar between treatment groups (Data Source: GEMINI ISS/ISE Table 3.4). The most frequently reported Grade 2 to 5 drug-related AE in each treatment group was headache (Data Source: GEMINI ISS/ISE Table 3.9). All other Grade 2 to 5 drug-related AEs were reported in <1% of subjects in each treatment group.

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.

5.3.2. Deaths

Across the 2 studies, 2 subjects experienced fatal events up to the safety cut-off for the Week 48 analysis (m2.7.4 Section 2.1.3). Both subjects were in the DTG + 3TC group of Study 205543. The first subject died due to Burkitt's lymphoma, and the second subject died due to acute myocardial infarction associated with possible drug abuse. Neither fatality was considered related to study drug by the investigator.

5.3.3. Other Serious Adverse Events

In each study and in the pooled analysis, the incidence of subjects reporting any individual SAE or any drug-related SAE was similar between treatment groups (Data Source: Study 204861 Table 3.16, Table 3.17, Study 205543 Table 3.16, Table 3.17, GEMINI ISS/ISE Table 3.16, Table 3.17). All SAE preferred terms were reported in <1% of subjects in any pooled group (m2.7.4 Section 2.1.4, Data Source: GEMINI ISS/ISE Table 3.16).

5.3.3.1. Drug-Related SAEs

Eight subjects (DTG + 3TC, 4; DTG + TDF/FTC, 4) experienced a drug-related non-fatal SAE (Data Source: GEMINI ISS/ISE Table 3.17). In the DTG + 3TC group, the 4 drug-related SAEs were substance-induced psychotic disorder, psychotic disorder, suicidal ideation, and hepatotoxicity (m2.7.4 Section 2.1.4.1). In the DTG + TDF/FTC group, the 4 drug-related SAEs were rhabdomyolysis, cholelithiasis, suicide attempt, and suicidal ideation. Full narratives for all SAEs are presented in the CSR for each study.

5.3.4. Other Significant Adverse Events

5.3.4.1. Adverse Events Leading to Withdrawal

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 (m2.7.4 Section 2.1.5.1). AEs leading to discontinuation were most commonly from the Psychiatric or Infections SOC, and the proportion of subjects with

AEs leading to discontinuation were balanced between treatment groups (Data Source: GEMINI ISS/ISE Table 3.19.)

5.3.5. Adverse Events of Special Interest

AESI have been determined for DTG + 3TC based on: non-clinical and/or clinical safety data for DTG and 3TC, labeling and/or regulatory authority interest for approved INSTIs; and/or regulatory authority requirements. There is no expected or observed additive or synergistic effect on AESIs in subjects taking DTG + 3TC beyond that expected for the SEs. Details on AESIs are available in m2.7.4 Section 2.1.6.

5.3.5.1. Drug Hypersensitivity

There were 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. None of the events recurred, were serious, were considered study drug-related, or led to withdrawal (m2.7.4 Section 2.1.6.1).

5.3.5.2. Severe (Grade 3 or 4) or Serious Rash

No rash-related events were Grade 3 or Grade 4, considered serious, or led to discontinuation from the study (Data Source: GEMINI ISS/ISE Table 3.21). There were no reports of SJS, DRESS, TEN, or erythema multiforme (m2.7.4 Section 2.1.6.2).

5.3.5.3. Psychiatric Disorders Including Suicidal Ideation and Behavior, Depression and Anxiety

Reporting rates of AEs from the Psychiatric disorders SOC were consistent between the treatment groups (DTG + 3TC, 13%; DTG + TDF/FTC, 15%) (Data Source: GEMINI ISS/ISE Table 3.2). Insomnia (5%), anxiety (2%), depression (2%), and suicidal ideation (1%) 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 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). Similar proportions of subjects in each treatment group reported drug-related AEs from the Psychiatric disorders SOC (DTG + 3TC, 5%; DTG + TDF/FTC, 5%); the majority of these drug-related events were Grade 1 (Data Source: GEMINI ISS/ISE Table 3.4, Table 3.5).

Suicidal ideation and behaviors

The reporting rate for AEs relating to suicidal ideation and behavior were similar in both treatment groups [DTG + 3TC, 17 subjects (2%); DTG + TDF/FTC, 12 subjects (2%)] (Data Source: GEMINI ISS/ISE Table 3.63). Across both treatment groups, reporting of these events generally occurred in subjects with past history of psychiatric disorder or previous suicidal ideation or behavior. In addition, these cases generally had additional psychosocial stressors reported at the time of the event. Two subjects in each treatment

group had an event leading to withdrawal. There were 7 subjects reporting suicide attempt or intentional overdose (DTG + 3TC, 5 subjects, DTG + TDF/FTC, 2 subjects). Few subjects reported events considered drug related (DTG + 3TC 3; DTG + TDF 2) (m2.7.4 Section 2.1.6.3). There were no completed suicides.

A slightly higher proportion of subjects treated with DTG + 3TC reported a past medical history of depression (DTG + 3TC 86 (12%), DTG + TDF/FTC 72 (10%). On-treatment suicide-related events were 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. Despite the higher rates of suicidality reporting in this subgroup, the majority of subjects with a past history of depression did not experience an on-treatment suicidality event.

Depression

For AESIs related to depression, there was no difference between the treatment groups in the reporting rates [DTG + 3TC, 22 subjects (3 %); DTG + TDF/FTC, 24 subjects (3%)] (Data Source: GEMINI ISS/ISE Table 3.62). All events were single occurrences in both treatment groups. 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). There were 3 depression events considered drug-related in the DTG + 3TC group and 5 in the DTG + TDF/FTC group. Two Grade 3 events were reported in each treatment group, and all other events had a maximum intensity of Grade 1 or 2. There were 2 withdrawals (1 in each group) for a depression-related AESI. One depression-related AESI was reported as an SAE in the DTG + 3TC group (m2.7.4 Section 2.1.6.3). The majority of subjects with a past history of depression did not experience a recurrence of depression on study by the Week 48 safety cutoff date.

Anxiety

There was no difference between the treatment groups in the reporting rate for AEs related to anxiety [DTG + 3TC, 23 subjects (3%); DTG + TDF/FTC, 18 subjects (3%)] (Data Source: GEMINI ISS/ISE Table 3.61). Two subjects in the DTG + TDF/FTC had a second occurrence, and all other events for both treatment groups were single occurrences. 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). There were 9 subjects with anxiety events considered drug-related in the DTG + 3TC group and 5 in the DTG + TDF/FTC group. Three Grade 3 events were reported (all in the DTG + 3TC group). All other events had a maximum intensity of Grade 1 or 2.

5.3.5.4. Sleep Disorders

The rate of insomnia was slightly higher in the DTG + TDF/FTC group (45 subjects, 6%) compared to the DTG + 3TC group (27 subjects, 4%) (Data Source: GEMINI ISS/ISE Table 3.27). There were 18 subjects (3%) reporting a drug-related event in the DTG + TDF/FTC group and 13 (2%) in the DTG + 3TC group. All events were Grade 1

or Grade 2, and no events were serious (m2.7.4 Section 2.1.6.4). One event of insomnia in a subject in the DTG +3TC group led to withdrawal. 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).

The reporting rate for AEs related to nightmare/abnormal dreams was slightly higher in the DTG + 3TC group (DTG + 3TC, 11 subjects, 2%; DTG + TDF/FTC, 6 subjects, <1%) (Data Source: GEMINI ISS/ISE Table 3.30). There were 9 subjects reporting a drug-related event in the DTG + 3TC group and 3 in the DTG + TDF/FTC group. 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). Two Grade 2 events were reported in the DTG + 3TC group, and all other events had a maximum intensity of Grade 1. No nightmare/abnormal dreams AESIs were serious or led to withdrawal (m2.7.4 Section 2.1.6.4).

5.3.5.5. Immune Reconstitution Inflammatory Syndrome

A small number of IRIS cases, classified by the internal adjudication process as definite or possible IRIS, were reported in each group (2 possible in the DTG + 3TC group and 2 possible in the DTG + TDF/FTC group) (m2.7.4 Section 2.1.6.5).

5.4. Clinical Laboratory Evaluations

Results of the clinical laboratory findings demonstrate that there are no new laboratory signals of concern in subjects receiving DTG + 3TC treatment.

5.4.1. Clinical Chemistry

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 Grade 1 or Grade 2 intensity. (m2.7.4 Section 3.1, GEMINI ISS/ISE Table 3.55).

5.4.1.1. Hepatobiliary

Over the time period during which Study 204861 and Study 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 studies, there were larger than expected numbers of extreme liver enzyme abnormalities, many of which were attributed 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: GEMINI ISS/ISE 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 (DTG + 3TC 1, DTG + TDF/FTC 8) reporting Grade 3 events, and all other hepatobiliary events were Grade 1 or 2 (Data Source: GEMINI ISS/ISE Table 3.3, Study 204861 Listing 15, Study 205543 CSR Listing 15). One of the Grade 1 events (hepatotoxicity) was considered by the investigator to be possible DTG-related DILI (m2.7.4 Section 3.2).

There were 21 subjects that had ALT values ≥10 x ULN [DTG + 3TC, 10 subjects (1%); DTG + TDF/FTC, 11 subjects (2%)] (Table 4, Data Source: GEMINI ISS/ISE Table 3.81). Of these 21 cases, 20 had hepatitis virus infection and the other case was attributed to a concomitant medication. Many subjects who met liver stopping criteria due to viral hepatitis were successfully restarted on study drug (m2.7.4, Section 3.2).

Table 4 Summary of Subjects Meeting Hepatobiliary Abnormality Criteria ALT Greater Than or Equal to 3 x ULN (Safety Population)

Hepatobiliary Criteria	Study 204861 and Study 205543, Pooled	
	DTG + 3TC N=716 n (%)	DTG + TDF/FTC FDC N=717 n (%)
ALT ≥3 x ULN	27 (4)	34 (5)
ALT ≥3 x ULN to <5 x ULN	9 (1)	16 (2)
ALT ≥5 x ULN to <10 x ULN	8 (1)	7 (<1)
ALT ≥10 x ULN to <20 x ULN	5 (<1)	5 (<1)
ALT≥20 x ULN	5 (<1)	6 (<1)

Data Source: GEMINI ISS/ISE Table 3.81
Note: For ALT ≥3 x ULN to <5 x ULN, ≥5 x ULN to <10 x ULN, ≥10 x ULN to <20 x ULN, ≥20 x ULN, subjects are summarized based on the maximum value post Baseline.

5.4.1.2. Renal

Overall, there were no new laboratory or clinical finding suggesting a significant adverse effect on renal function by either treatment regimen at the Week 48 analysis.

Prior studies with DTG have shown that subjects receiving DTG had mean increases from Baseline in serum creatinine evident by Week 2 that remained stable while subjects remained on drug (m2.7.4 Section 3.3).

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. In the DTG + TDF/FTC group, 41 subjects had emergent creatinine elevations, with a maximum of Grade 1 (37 [5%]), Grade 2 (2 [<1%]), or Grade 3 (2 [<1%]) toxicity, and there were no Grade 4 elevations in creatinine (Data Source: GEMINI ISS/ISE Table 3.55).

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 (4% in each treatment group) (Data Source: GEMINI ISS/ISE Table 3.2). For this SOC, all renal events in the DTG + 3TC group

were Grade 1 or Grade 2, and in the DTG + TDF/FTC group, 1 subject reported a single Grade 3 event (renal impairment), and all other events were Grade 1 or 2 (Data Source: GEMINI ISS/ISE Table 3.3). 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) (Data Source: GEMINI ISS/ISE Table 3.3, Study 204861 CSR Listing 15, 205543 CSR Listing 15). Withdrawals from study for renal function-related AEs or for meeting predefined renal toxicity criteria (eGFR <50 ml/min/1.73m2) were observed more frequently in subjects in the DTG + TDF/FTC group (6 subjects) compared with the DTG + 3TC group (1 subject) (m2.7.4 Section 3.3).

In the pooled analysis, subjects in both groups had mean increases in serum creatinine at Week 48 similar to what has been described previously for DTG-containing regimens. Consistent with this, the mean change from Baseline in estimated GFR from the CKD-EPI equation showed a similar small decrease in both groups. In contrast to the results using creatinine at 48 weeks, DTG + 3TC treatment was associated with a significantly greater increase in the estimated GFR from cystatin C adjusted using the CKD-EPI equation compared with DTG + TDF/FTC treatment (Data Source: GEMINI ISS/ISE Table 3.521).

5.4.1.3. CK 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 CPK creatine kinase levels (Data Source: GEMINI ISS/ISE Table 3.55). The majority of these events were attributed to exercise or heavy physical exertion.

One subject in the DTG + TDF/FTC group experienced a drug-related SAE of Grade 3 rhabdomyolysis with CK elevation of 11,732 μ/L on local laboratory testing (m2.7.4 Section 2.1.4.1).

5.4.1.4. Lipid Parameters

In both studies, a small proportion of subjects in each treatment arm experienced adverse changes in lipid parameters.

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 $p < 0.001$). 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 ($p=0.044$) (Data Source: GEMINI ISS/ISE Table 3.40). 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). 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.

See m2.7.4 Section 3.5, and Study 204861 Week 48 CSR Section 7.4.5, and Study 205543 Week 48 CSR Section 7.4.5, for full results on lipid profiles.

5.4.1.5. Lipase Elevations

Adverse events and laboratory data related to lipase elevations and pancreatitis are discussed in m2.7.4 Section 3.1 and m2.7.4 Section 3.6. Post-baseline-emergent chemistry toxicities of lipase elevations were similar between the treatment groups (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 (a Grade 2 event occurring at Study Day 234 that was non-serious and was not related to study drug).

5.4.2. Hematology Parameters

Overall, there were few post-Baseline toxicities. The maximum intensity of post-Baseline emergent hematology toxicities was comparable across treatment groups (m2.7.4 Section 3.7, Data Source: Study 204861 CSR Table 3.56, Study 205543 CSR Table 3.56, GEMINI ISS/ISE Table 3.56).

5.5. Biomarkers

5.5.1. Bone Biomarkers

At Week 48, markers of bone turnover increased from Baseline in both treatment groups; however, larger increases in bone turnover markers were observed in the DTG + TDF/FTC group (Data Source: GEMINI ISS/ISE Table 3.43). This difference between the treatment groups was statistically significant for all bone biomarkers evaluated (serum bone-specific alkaline phosphatase, serum osteocalcin, serum procollagen 1 N-terminal propeptide, and serum type 1 collagen C- telopeptide) in favor of the DTG + 3TC treatment group (Data Source: GEMINI ISS/ISE Table 3.49, Table 3.51).

5.5.2. Renal Biomarkers

Refer to m2.7.4 Section 3.3 for summaries of changes from Baseline to Week 48 in serum cystatin C, estimated GFR using CKD-EPI -cystatin C equation, serum creatinine, estimated GFR using CKD-EPI -creatinine (serum), urine albumin/creatinine ratio, urine

protein/creatinine ratio, beta-2 microglobulin/creatinine ratio, and retinol binding protein/creatinine ratio.

At 48 weeks, DTG + 3TC treatment was associated with a significantly greater increase in the estimated GFR from cystatin C adjusted using CKD-EPI equation compared with DTG + TDF/FTC treatment (Data Source: GEMINI ISS/ISE Table 3.521). For the change from Baseline in urine protein/creatinine ratio, there was a modest reduction in the DTG + 3TC arm (indicating improvement) and a minimal increase in the DTG + TDF/FTC arm, which resulted in the difference between treatments being statistically significant (Data Source: GEMINI ISS/ISE Table 3.522).

5.6. 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 (m2.7.2, Section 3.1.6.2), and results from completed clinical studies of Triumeq also demonstrate a lack of drug-drug interaction between DTG and 3TC. Hence, there is no need for a dose adjustment from approved doses when both products are used in combination. Any interactions that have been identified with DTG and 3TC individually can be extrapolated to DTG + 3TC.

5.7. Historical 3TC Data Supporting the DTG/3TC FDC

As detailed in m2.7.1 Section 2.1.1.1, the 3TC Cmax for the proposed commercial DTG/3TC [redacted] FDC was ~32% higher compared with Epivir when administered concurrently with DTG. This reflects differences in the rate of absorption but not the extent of absorption. Clinical safety data from registrational studies of 3TC, where doses of 600 mg or higher were administered, demonstrate that the observed ~32% increase in 3TC Cmax exposure does not impact patient safety (m2.7.4 Section 5.6.2).

5.8. Special Patient Populations

No studies in special populations have been conducted for DTG + 3TC. The effects of DTG + 3TC are anticipated to be consistent with those observed for DTG and 3TC.

Effects of renal and hepatic impairment were evaluated as part of the development programs for DTG and 3TC.

5.8.1. 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 DTG or 3TC. Existing safety data for the individual components of DTG and 3TC and other FDCs containing DTG and/or 3TC, and a summary of post-marketing experience are provided in GSK Document 2018N363795_00.

In the 204861 and 205543 pooled analysis, a smaller proportion of female subjects compared with male subjects reported AEs; the difference was primarily due to

differences in reporting rates of Grade 1 events, particularly for subjects in the DTG + 3TC group (m2.7.4 Section 5.1.1) (Data Source: GEMINI ISS/ISE Table 3.11).

5.8.2. Adolescents

The proposed FDC formulation consists of 50 mg DTG and 300 mg 3TC. These are adult doses already authorized as individual agents for the treatment of HIV infection in adolescents ≥12 years of age weighing ≥40 kg (DTG), or in pediatric patients weighing ≥25 kg (3TC). Prior studies demonstrated that DTG and 3TC PK exposures in adolescents are sufficiently similar to those in adults to permit extrapolation of efficacy data based on pharmacokinetic correlation. Historical data in the adolescent population are provided in GSK Document 2018N363795_00.

5.8.3. Hepatitis B and/or C Virus Co-Infection

DTG + 3TC has not been studied in patients with hepatitis B virus co-infection. In studies with the SEs, DTG or 3TC, a higher incidence of liver chemistry elevations was observed in patients co-infected with hepatitis B and/or C. In Studies 204861 and 205543, subjects were excluded if they had evidence of chronic hepatitis B at Screening. Subjects with chronic hepatitis C infection were allowed to participate in the study but were excluded if they had an anticipated need for hepatitis C therapy during the first 48 weeks of the study, or for use of interferon therapy. Thus, while there are no data on the use of this 2-drug regimen in hepatitis B, data using the 2-drug regimen in a small number of HCV-positive subjects are available (m2.7.4 Section 5.1.2).

The pooled data were consistent with what has been observed previously; subjects with HCV at Baseline have a higher incidence of liver enzyme elevations on study than HCV negative subjects (Data Source: GEMINI ISS/ISE Table 3.71).

5.8.4. Hepatic Impairment

Based on data obtained during development of the SEs of DTG and 3TC, no dose adjustment of DTG + 3TC is required in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). DTG + 3TC has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

5.8.5. Renal Impairment

No dose adjustment of DTG + 3TC is required in patients with creatinine clearance ≥50 mL/min/1.73 m^2. DTG + 3TC has not been studied in patients with creatinine clearance <50 mL/min/1.73 m^2. In Study 204861 and Study 205543, subjects were required to discontinue study treatment and withdraw from the study if eGFR was <50 mL/min/1.73m^2.

5.9. Pregnancy and Lactation

No studies have been conducted with DTG + 3TC in pregnant women, and pregnant women were excluded from the studies. Subjects who became pregnant (intrauterine) were required to discontinue from the clinical studies. The Week 48 data from Study 204861 and Study 205543 did not add new information relative to DTG and pregnancy.

Human pregnancy data are discussed in m2.7.4 Section 5.4. Data concerning reports of neural tube defects from one birth outcomes surveillance study are discussed in m2.7.4 Section 6.1. Based on the potential risk of NTD, DTG + 3TC should not be used at the time of conception and through the first trimester. Women of childbearing age should be on effective contraception while on DTG + 3TC, and pregnancy testing should be done prior to initiation of DTG + 3TC.

Health experts recommend that, where possible, HIV infected women do not breast feed their infants to avoid transmission of HIV.

5.10. Withdrawal Effects, Abuse Potential, Overdose

Neither of the SE components have a known drug abuse potential, and there are no data suggesting the potential to imply illicit use, abuse, or dependency.

Experience with overdose of DTG + 3TC, or the individual components (DTG and 3TC) is limited. There is no specific treatment for overdose with DTG + 3TC. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Since 3TC is dialyzable, continuous hemodialysis could be used in the treatment of overdose, although this has not been studied. As DTG is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

5.11. Post-Marketing

DTG + 3TC, as a 2-drug regimen, is not currently approved or marketed in any country.

The estimated post-marketing exposure to DTG is >560,000 patient years. DTG's safety profile is well-characterized due to extensive clinical trial data and the relatively rapid post-marketing uptake of the drug. Risks are characterized in the RMP and appropriate risk mitigation strategies are in the product label.

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 m2.7.4 Section 6.1.1).

Based on review of post-marketing cases, the event of acute hepatic failure was added to the DTG Global Data Sheet/RSI in [redacted] with a frequency category of 'rare'. No other significant safety concerns or risks have been identified from marketing experience through to April 2018 for DTG.

3TC is a well-established NRTI, first licensed in HIV treatment over 20 years ago, (regulatory approval in the US in 1995, EU in 1996) and now has an estimated exposure of over 7 million patient years across all 3TC-containing products. 3TC is a well-tolerated treatment with no major safety concerns in patients with HIV when used as part of an HIV regimen.

5.12. Safety Conclusion

The Week 48 safety data from Studies 204861 and 205543 support the proposition that DTG + 3TC is a well-tolerated regimen for HIV-infected treatment-naïve patients. Over 48 weeks, the safety data from the randomized, double-blind Phase III studies 204861 and 205543 comparing DTG + 3TC to a standard of care regimen DTG + TDF/FTC is consistent with the known safety profile for the individual products. Week 48 safety data from the identical Phase III studies 204861 and 205543 generally were consistent with one another, and support the following conclusions:

- 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%), 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 only 3TC.
- The frequency of SAEs was similar between treatment groups. There were few drug-related SAEs reported, with <1% incidence observed for both treatment groups and no discernible patterns of related events.
- Two fatalities were reported (both in the DTG + 3TC group); neither death was related to study drug.
- Serious rash was not observed in the studies, including no reports of SJS, 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 of 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 SE 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. The total cholesterol/HDL ratio category, often used to estimate long-term cardiovascular risk, was generally improved from Baseline for both treatment groups, with similar favorable improvements between the 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. An increase in bone turnover has been associated with increased risk of loss of bone mineral density. These findings suggest there could be less risk of an adverse effect on bone health in the group of subjects taking DTG + 3TC.
- While the 3TC Cmax for the proposed commercial DTG/3TC [redacted] FDC was ~32% higher compared with Epivir when administered concurrently with DTG, this higher rate of absorption does not impact patient safety based on data from historical EPIVIR studies that used a higher dose of 3TC
- 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.

6. BENEFITS AND RISKS CONCLUSIONS

DTG + 3TC is a 2-drug regimen intended for the long-term treatment of HIV-1 infection. It is the combination of 2 well-established marketed products, DTG and 3TC. Based on the primary analysis of Week 48 data from the 2 large pivotal Phase III clinical studies (204861, 205543), DTG + 3TC is an effective, and well tolerated regimen for the treatment of HIV-1 infection in ART-naïve patients. Safety in Studies 204861 and 205543 is consistent with the established safety profile for the SEs. The Phase III studies did not identify an increased incidence of ART resistance selection with the use of this novel 2-drug regimen. There were no newly identified risks in the GEMINI studies that would alter the potential benefit of the DTG + 3TC 2-drug regimen.

6.1. Therapeutic Context

Currently, there are no approved 2-drug regimens for treatment of HIV-1 infection in ART-naïve patients. By limiting the number of ARVs to which a patient is chronically exposed, 2-drug therapy has the potential benefit of maintaining virologic suppression and preserving future treatment options, while minimizing long term toxicity, and decreasing the likelihood of DDIs.

6.1.1. HIV-1 Infection

In 2017, an estimated 36.9 million people worldwide were living with HIV/AIDS and 1.8 million people were newly infected with HIV [UNAIDS, 2018]. While the rate of new HIV infections has declined over time, the pace of decline in new infections is too slow to reach the Fast-Track Target agreed upon by the United Nations General Assembly in 2016: fewer than 500,000 new infections per year by 2020 [UNAIDS, 2017]. Of the people living with HIV in 2017, 21.7 million were on ARV therapy [UNAIDS, 2018]. Increasing access to treatment is contributing to a reduction in AIDS-related deaths among adults and children. Global scale-up of ART therapy has been the primary contributor to a 48% decline in deaths from AIDS-related causes between 2005 and 2016 [UNAIDS, 2017], and efforts to strengthen HIV prevention and treatment programs are reducing the transmission rate of HIV.

Where treatment is available, HIV infection has become a manageable chronic disease. Better treatment coverage means that a growing number of people will be living with HIV into old age. Globally, 17% of adults living with HIV are 50 years or older. In high-income countries, 31% of adults living with HIV are 50 years or older. As people living with HIV age, they are more susceptible to the adverse effects of ART and must manage long-term side-effects. They are also more likely to take ART medication in combination with other medications, and to experience age-related diseases as comorbidities.

6.1.2. Current Therapies and Unmet Medical Need

Historically, HIV treatment guidelines have recommended first-line ARV regimens consisting of 2 NRTIs as a "backbone" combined with a third agent from the NNRTI, PI or INSTI classes [BHIVA, 2016; DHHS, 2018; EACS, 2017; Günthard, 2016]. More recent guidelines recommend DTG + RPV as a new 2-drug regimen option in virologically suppressed individuals switching from effective 3-drug regimens [DHHS, 2018; EACS, 2017]. While 3-drug regimens are highly effective and generally well tolerated, there is concern about NRTI-related long-term toxicities, and interest from patients and clinicians in equally effective regimens that might minimize such toxicities. Also, the use of one less drug in a treatment regimen that is taken over the course of life may result in less side effects overall. Even modest improvements in side effects will have a big impact on the tolerability of, and adherence to life-long treatment.

The longer life expectancy of HIV-infected patients on ART has been accompanied by higher rates of cardiovascular, liver, kidney, bone, neoplastic and other diseases. The etiologies of these co-morbidities are multi-factorial and may include chronic inflammation and immune activation, aging, behavioral and lifestyle-related factors, but also the adverse effects of some ARVs. TDF has significant bone and kidney toxicity. The risk of HSR with ABC use has been reduced greatly by screening for HLA-B*5701, yet testing is still recommended. There are still inconclusive data regarding increased risk for myocardial infarction for use of ABC and some PIs, though it remains a consideration for some health care providers when selecting ARV regimens. There is an unmet need for treatment regimens that provide effective long-term antiviral suppression and that avoid these long term/irreversible toxicities.

In addition, the multi-morbidity seen as individuals with HIV age often requires the concomitant use of other medications, many of which have significant drug-drug interactions with many commonly used ARVs. These interactions may lead to diminished efficacy of these concomitant medications and/or ARVs, and may increase the adverse reactions/intolerance to these medications. Hence, there is also an ongoing need for streamlined effective regimens that also minimize these drug-drug interactions, and allow the safe and effective treatment of these other co-morbidities.

6.1.2.1. Two-drug regimens

With the advent of potent and safer antiretrovirals, there has been renewed interest in two-drug regimens (2DR) that provide equally effective long-term virologic suppression with less cumulative drug exposure and potentially less long-term toxicities compared to standard 3-drug regimens. However, while some 2DRs have shown inferior virologic efficacy compared to 3-drug regimens (e.g., maraviroc with darunavir), others have unacceptable pill burdens or tolerability issues (boosted-PI containing regimens). 2DRs consisting of 3TC paired with a potent ARV have been shown to be non-inferior and well tolerated to 3-drug regimens in ART-naïve subjects. These investigations have included 3TC in combination with DRV/RTV (ANDES), with LPV/RTV (GARDEL), and with DTG (PADDLE, and ACTG A5353) (Section 8.1).

The ANDES trial showed non-inferiority of a dual therapy regimen of DRV/RTV (800/100 mg) FDC, plus 3TC (300 mg), to triple therapy with DRV/RTV (800/100 mg) plus 3TC/TDF (300/300 mg) FDC [Figueroa , 2018].

The GARDEL study was a proof-of-principle study that compared a 2-drug regimen of 3TC paired with LPV/RTV twice daily with LPV/RTV twice daily + 2 NRTIs (either 3TC or FTC in a 2-NRTI FDC) in ART-naïve subjects without IAS-USA-defined PI or NRTI resistance [Cahn, 2014]. The study demonstrated that dual therapy was non-inferior to triple therapy after 48 weeks of treatment, regardless of baseline viral load. In that study, dual therapy also tended to have better safety and tolerability, with statistically significantly fewer Grade 2-3 drug-related AEs, and less frequent toxicity-related or tolerability-related discontinuations compared with triple-therapy.

More pertinent to the proposed DTG + 3TC regimen is the PADDLE study, a single-arm 96-week pilot study of a once-daily, 2-drug regimen of DTG 50 mg + 3TC 300 mg in 20 HIV-infected, ART-naïve adult subjects having no evidence of genotypic resistance to 3TC and a viral load of <100,000 c/mL at Screening [Cahn , 2017]. At Week 48, 18 of 20 participants (90%) achieved the primary endpoint of a viral load <50 c/mL. No new virologic failures, new AIDS-defining illnesses, treatment discontinuations, or SAEs (related/possibly related to study drugs) were observed through 96 weeks of treatment [Figueroa , 2017].

ACTG A5353 is a pilot study of DTG plus 3TC for initial treatment of HIV-1 infection in participants with HIV-1 RNA <500,000 c/mL [Taiwo , 2018, ClinicalTrials.gov Study number NCT02582684, 2018]. Among 120 people who began DTG 50 mg + 3TC 300 mg once daily, 31% had a viral load of >100,000 copies. At 24 weeks, 108/120 (90%) met the primary endpoint of HIV-1 RNA <50 c/mL, with comparable results in the

>100,000 c/mL and ≤100,000 c/mL strata, i.e. 89% and 90%, respectively. At 48 weeks, 88% in the <100,000 c/mL group and 78% in the >100,000 c/mL group met the study definition of virologic success (HIV-1 RNA <50 c/mL) for an overall success rate of 85%. Six (5%) participants had virologic non-success by Snapshot (HIV-1 RNA ≥50 copies/mL) at Week 48, including 3 participants who were lost to follow-up/deemed non-compliant by site investigators. In 1 person with no measurable DTG in sampling before subsequently meeting virologic failure, genotyping detected an integrase mutation mixture (R263R/K) and a reverse transcriptase mutation (M184V); additional resistance evaluations currently are underway. In this pilot study of treatment-naïve participants, once-daily DTG plus 3TC was effective and well tolerated [ViiV Healthcare, [redacted], [redacted] MD ([redacted], USA). [redacted]].

DTG + 3TC may provide a novel, well-tolerated, 2-drug regimen that can durably treat ART-naïve patients while limiting the risk of adverse reactions and long-term toxicity associated with other ARV drugs. This regimen offers once-daily dosing, with limited potential for drug-drug interactions, and can be taken without regard for food. Both DTG and 3TC are well-tolerated (backed by extensive safety databases); of note, 3TC has a favorable safety profile that distinguishes it from other NRTIs, which have been associated with various tolerability and toxicity issues [Carr, 2000].

6.2. Benefits of DTG + 3TC in the Treatment of HIV-1 Infection

New therapeutic options that combine potency, tolerability and ease of use, and minimize the long-term toxicities of current ARVs will be beneficial across HIV populations, including treatment-naïve adults and adolescents. Highly effective conveniently-dosed treatment regimens that have less adverse effects and a better safety profile in the long-term will increase tolerance of and adherence to lifelong treatment regimens. As persons with HIV infection live longer, aging-associated and other co-morbidities are being seen with greater frequency, and often requires concomitant use of other medications. As a complete treatment regimen, DTG + 3TC may provide effective long-term antiviral suppression while minimizing drug-related adverse events and avoiding some of the longer term/irreversible toxicities associated with NRTIs (e.g., bone and kidney toxicities related to TDF).

DTG + 3TC is a 2-drug regimen intended for the long-term treatment of HIV-1 infection. Based on the Week 48 data from the 2, large pivotal Phase III clinical studies (204861, 205543), DTG + 3TC is an effective, and well tolerated regimen for the treatment of HIV-1 infection in treatment-naïve patients.

DTG + 3TC has distinct advantages over many of the current widely-used therapies as follows:

- Simplified 2-drug regimen with a known tolerability profile. The use of 1 less ARV may decrease the risk of both short-term and long-term adverse drug reactions, and will increase the tolerance for, and adherence to long-term ART.

- No treatment-emergent drug resistance was identified in Studies 204861 and 205543 through Week 48. This may preserve future treatment options in a disease requiring life-long treatment.
- Lower risk of NRTI-related long-term toxicities, such as bone and kidney toxicities related to TDF.
- A FDC combination enables a one-tablet, once daily dosing, and enhanced compliance with treatment regimen.
- Once-daily dosing, without the need for a PK booster, which significantly decreases drug interactions with concomitant drugs. A favorable drug interaction profile with few clinically relevant interactions that require a dose adjustment, dose separation, or contraindication. Only the most significant CYP3A4 inducers, and metal cations dosed in close proximity (DTG) need management. This favorable drug-drug interaction profile allows the safe use of many commonly used concomitant medications that are needed to manage an aging HIV-positive person's other co-morbidities.
- DTG + 3TC may be administered with or without food.

6.2.1. Contributions of Individual Agents

The DTG/3TC FDC was developed in alignment with both EMA [EMA, 2017] and FDA [DHHS, 2006] guidance to provide a safe, effective and conveniently dosed 2-drug regimen of DTG + 3TC as a FDC. Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. The contributions of each DTG and 3TC single entity agent to the initial, and to the maintained virologic response is discussed in Section 6.2.1.1 and Section 6.2.1.2.

6.2.1.1. Contribution of each agent to initial virologic response

In a double-blind, 24-week study, the antiretroviral activity and safety of lamivudine plus zidovudine was compared with either drug alone as treatment for patients with HIV infection [Eron , 1995]. In a subgroup of 224 patients who began the study with HIV-1 RNA ≥20,000 c/mL, the maximal mean decreases in HIV-1 RNA were 1.18 log10 (median, 1.37 log10) in the lamivudine-only group. At Week 24, despite the emergence of M184V in most subjects, there was a mean decrease of 0.42 ±0.05 log 10 in the lamivudine-only group.

The effect of DTG alone in the initial virologic response can be seen in a Phase IIa, randomized, double-blind, dose-ranging study, of INI-naive, HIV-1-infected adults currently off antiretroviral therapy randomized to receive DTG (2, 10, or 50 mg) or placebo once daily for 10 days. DTG monotherapy given once daily was associated with a 2.5 log10 mean decline in HIV-1 RNA after 10 days of treatment with a 50 mg dose [Min , 2011].

6.2.1.2. Contribution of each agent to the maintenance of virologic response

The contribution of either DTG or 3TC to the maintenance of virologic suppression after the initial response can be inferred from the results of monotherapy with either drug, and from studies of treatment switch to DTG monotherapy.

Historical early studies with 3TC in treatment-naïve HIV-infected persons show that monotherapy rarely leads to virologic suppression and also leads to the rapid emergence of M184V in nearly all recipients [Eron , 1995; Schuurman , 1995]. Of note, despite rapid emergence of M184V resistance with 3TC monotherapy, a lower viral load was maintained at Week 52 with a~0.3 to 0.4 log10 decrease compared with baseline [Eron , 1995]. However, in studies with 3TC-based 2-drug therapy in treatment-naïve persons, including with DTG, virologic failure occurred at a similar rate as the comparator 3-drug therapy, and with DTG+3TC, emergent resistance was rarely seen in those with virologic failure [Cahn, 2014; Cahn , 2017; Taiwo , 2018].

DTG monotherapy in treatment-naïve HIV-infected persons has only been studied in a single-arm observational study that enrolled 20 subjects with screening viral loads < 100,000 c/mL and no baseline resistance. An average 2.5 log10 initial drop in plasma HIV-1 RNA was seen in all subjects and over 24 weeks, only one virologic blip (145 c/mL) was seen, while 1 other subject discontinued for a treatment-related enanthem [Lanzafame , 2017]. This study has limitations which makes extrapolation of its results challenging. More robust data is available from comparative switch studies wherein subjects were de-intensified from standard 3-drug ART to monotherapy with DTG. The DOMONO study randomized virologically suppressed persons into an early vs delayed switch to DTG monotherapy from a standard 3-drug regimen and showed that DTG monotherapy had inferior virologic suppression (92% vs 98% in a concurrent control group) over 48 weeks, and led to the emergence of DTG resistance mutations in 3/8 virologic failures [Wijting, 2017]. The DOLAM study, randomized subjects who were undetectable on 3-drug ART to either DTG alone or DTG + 3TC [Blanco , 2018]. By 24 weeks, virologic failure had occurred in 1/29 (3.4%) in the DTG + 3TC arm and 2/31 (6.4%) in the DTG arm. While the virologic failure in the DTG + 3TC arm did not have any emergent resistance mutations, the 2 failures in the DTG arm had emergent resistance mutations to the INSTI class. Other DTG monotherapy switch studies have observed similar unacceptable rates of virologic failure with emergence of resistance to INSTIs in many cases [Hocqueloux , 2018].

In contrast to the results with DTG and 3TC monotherapy, in the GEMINI studies, by Week 48, confirmed virologic failure occurred in <1% of subjects in both the DTG ++ 3TC and DTG + TDF/FTC arms. More importantly, among those with confirmed virologic failure, no treatment-emergent resistance to either DTG or 3TC developed. In the PADDLE study, median viral load decay with DTG + 3TC was 2.75 log10 over the first 12 weeks, which is similar to the median viral load change (-2.82 log10) observed at Week 12 in subjects receiving DTG + 3TC in the GEMINI studies, and to the initial viral load decay reported with DTG-based 3-drug regimens [Cahn 2017].

From the clinical observations it can be inferred that in a DTG + 3TC combination, both components are important in delivering efficacy and preventing the development of

resistance to the other drug. In particular, for 3TC, a residual clinical response is observed despite the presence of M184V; this may be due to a number of characteristics associated with this RT mutation [Wainburg , 2004], including a substantial decrease in viral replication caused by the defective enzyme activity. In terms of benefit across drug classes, the M184V mutation has been shown to increase reverse transcriptase fidelity that decreases incorporation of incorrect nucleotides during HIV replication and thus is expected to reduce development of primary resistance and/or additional compensatory mutations. DTG has been well characterized regarding its high barrier to resistance. DTG's key non-pharmacologic characteristic is prolonged binding to the integrase:HIV DNA formed catalytic pocket [Hightower , 2011] (m2.7.2.4 Section 4.1.13) and an associated antiviral activity [Kobayashi , 2011] (m2.7.2.4 Section 4.1.12) against wildtype and most single and multiple mutation integrases. Thus, emergent resistance for either DTG or the background agents has not been observed to date in DTG Phase 3 studies with ART naïve patients. Hence, DTG and 3TC each contribute to achieving and maintaining virologic suppression while preventing virologic failure without resistance to either drug.

The DTG and 3TC doses contained in the FDC are the single entity doses that are approved for use in adults and adolescents for the treatment of HIV infection. These doses have been shown to be efficacious and safe for the treatment of HIV in numerous registrational and other comparative studies, including the GEMINI-1 and GEMINI-2 studies.

6.3. Risks Associated with DTG + 3TC in the Treatment of HIV-1 Infection

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. As such, there is no pharmacologic reason that would predict an increased safety risk with DTG + 3TC beyond that identified for the DTG and 3TC SEs. The pivotal Phase III studies (204861, 205543) demonstrate that the safety and tolerability profile of DTG + 3TC is consistent with that of the SEs, and that there were no new AEs identified that alter the benefit-risk profile.

All medications have AE profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Considerations when using DTG + 3TC are:

- Incidence of elevated liver chemistries in subjects treated with DTG + 3TC, including cases of hypersensitivity with liver involvement are predicted to be low. There is no evidence of increased risk of hepatotoxicity from DTG + 3TC over and above that of the SEs.
- Events in the hypersensitivity category in these ongoing DTG + 3TC studies are small in number, and were either mild and atypical for a "hypersensitivity" type reaction, or had explanations other than exposure to DTG. HSR is an uncommon, but manageable, risk for DTG. From analysis of data from the DTG SE and DTG + 3TC development program, the risk of hypersensitivity reaction with DTG + 3TC is not expected to be any different from that observed with DTG.

- As expected based on prior history of the SEs, no instances of DAIDS Grade 3, Grade 4, or serious skin reactions (including SJS, TEN, or erythema multiforme), were seen with DTG + 3TC.
- Since DTG is known to inhibit OCT-2, mild serum creatinine elevations are expected to occur.
- Across both DTG-containing treatment groups, the psychiatric AE profile was comparable to the known safety profile of DTG, with a low rate of withdrawal for psychiatric AEs (<1%). The incidence of insomnia in the DTG + 3TC clinical program is less than that observed for ING114467 (SINGLE) [Walmsley, 2015] and in line with other Phase III/IIIb studies for DTG.
- Resistance may develop to any antiretroviral regimen, particularly in the setting of incomplete adherence to therapy. However, the risk of developing drug resistance in patients receiving DTG + 3TC is expected to be low because DTG, with its high barrier to resistance and ability to confer a very rapid decline in HIV-1 RNA, may be less likely to select for resistance, consistent with other clinical studies of DTG-based ART [GlaxoSmithKline Document Number RM2007/00683/11; Walmsley, 2015]. Moreover, through at least 48 weeks in the GEMINI studies, no drug resistance mutations have emerged among subjects with confirmed virologic failure.
- The 3TC Cmax for the proposed commercial DTG/3TC [redacted] FDC was ~32% higher compared with Epivir when administered concurrently with DTG. Clinical safety data from registrational studies of 3TC demonstrate that the observed ~32% increase in 3TC Cmax exposure does not impact patient safety. Results from these historical studies that used high dose 3TC (600 mg/day) support the safety of the FDC [redacted]'s higher 3TC Cmax.

The safety profile seen for DTG + 3TC in Studies 204861 and 205543 is consistent with the established safety profile for DTG and 3TC. There is no predicted additive or synergistic effect on the risk of hepatic disorders, psychiatric AEs, depression, or suicide-related events in patients taking the DTG + 3TC beyond that expected for the SEs. Previous clinical data support that there is no additional safety risk associated with the higher 3TC Cmax of the proposed FDC, based on historical study data (see m2.7.4, Section 5.6).

The new information about neural tube defects has the potential to alter the benefit risk assessment for DTG in the treatment of HIV in women of child bearing potential. A number of actions have been taken by the MAH to inform prescribers and study investigators of this potential risk for dolutegravir-containing products and updates to the product information are underway. The DTG/3TC product information will describe this potential risk and requirements for effective contraception whilst taking DTG/3TC FDC. The potential risk is considered manageable through the communications to healthcare providers and changes to the product information.

6.4. Benefit-Risk Assessment

The individual efficacy and safety profiles of DTG and 3TC have been evaluated in the SE clinical programs, and supported a favorable risk-benefit profile for their respective indications.

Based on a 10% non-inferiority margin, DTG + 3TC demonstrated a high level of efficacy and was non-inferior to treatment with DTG + TDF/FTC FDC in suppressing HIV-1 in treatment-naïve HIV-infected persons at Week 48 in pivotal studies 204861 and 205543. The pooled Week 48 efficacy analysis was supportive of the individual study results.

The 2-drug regimen of DTG + 3TC was not found to increase the incidence of virological failure in the individual studies, nor increase the incidence of treatment-emergent drug resistance.

There are no additive or synergistic adverse effects seen with the combined use of DTG + 3TC beyond those observed for the SEs, and no new safety signals were identified in Studies 204861 and 205543 over 48 weeks. These pivotal Phase III studies demonstrate that the tolerability profile of the 2-drug regimen is similar with the SEs' profiles. The potential benefit of this 2-drug regimen is not downgraded by any newly identified risk associated with the use of these 2 agents.

DTG + 3TC compared well with DTG + TDF/FTC FDC in efficacy and tolerability. This 2-drug regimen has the potential to limit the long-term toxicities associated with other ARV drugs while maintaining virologic suppression. DTG + 3TC offers patients a novel 2-drug treatment option that is non-inferior to a current standard of care 3-drug regimen over 48 weeks.

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8. APPENDIX

A descriptive approach was used to conduct the benefit-risk assessment. Therefore, no quantitative methods and results are presented.

8.1. Two-Drug Regimen Studies

See Table 5 for a summary of current studies using a 2-drug regimen of ARVs for the treatment of HIV-infection

Table 5 Two Drug Regimen Studies

Study Name/ Study Treatments, Study Duration	Study Design, No. of Patients	Key Inclusion/Exclusion Criteria Demography	Key Conclusions
ANDES: DRV/r (800/100 mg) FDC+ 3TC (300mg) once daily versus DRV/r (800/100mg) + 3TC/TDF (300mg/300mg) once daily	Randomized, open-label, Phase IV n=145 patients Primary endpoint: Proportion patients with VL <50 c/mL at week 48 (Snapshot analysis)	Inclusion: VL HIV RNA ≥1000c/mL, ART naive Exclusions: Resistance to any of the drug components in either treatment, Chronic HBV, Active AIDS defining illness, Grade 3 or 4 lab abnormalities per DAIDS grading. Median age 30, 91% males, 8% CDC Stage B, screening VL 4.5 log c/mL, median CD_4 count 383 cells/mm^3	ITT snapshot= 94% triple therapy and 93% double therapy; ITT snapshot for baseline VL> 100,000c/mL = 92% triple therapy and 91% double therapy; One virologic failure at Week 48. Median CD4+ change between baseline and week 48 was similar in both arms The most frequent AEs were gastrointestinal (TT: 14%; DT: 7%; p:0.17) and rash. AEs leading to discontinuation were rare and similar between arms. No treatment-related SAEs or deaths were reported DRV/r plus 3TC showed non-inferiority to a standard of care triple drug regimen of DRV/r plus TDF/3TC at 48 weeks
GARDEL: LPV/r (400mg/100mg) + 3TC (150mg) both twice daily versus LPV/r (400mg/100mg) twice daily + 3TC or FTC + another NRTI in a FDC.	Randomized, controlled, open-label, non-inferiority, multicenter, international 48 week, Phase III trial. Randomization stratified by baseline viral load. n=416 patients received study drug Primary endpoint: Proportion of participants with plasma viral load less than 50 c/mL at	Inclusion: At least 18 years old, were naive to ART, had a plasma HIV RNA viral load of at least 1000 copies per mL at screening, were hepatitis B surface antigen negative. Exclusions: pregnant or breastfeeding; HIV-2 infection; moderate or severe hepatic impairment; any clinically significant active disease; and any medical history or physical examination findings (including active AIDS-associated opportunistic diseases within 30 days after screening) that, in the investigator's opinion, might	NRTIs used in the 3-drug arm in order of frequency were zidovudine and lamivudine (54%), tenofovir and emtricitabine (37%), and abacavir and lamivudine (9%). Dual therapy was non-inferior to the 3-drug-therapy: 189 patients (88·3%) in the dual-therapy group and 169 (83·7%) in the 3-drug group had viral loads less than 50 copies per mL at 48 weeks. 22 participants had protocol-defined virological failure:7 were confirmed at week 24 (one in the dual-therapy group and six in 3-drug group) and 15 at week 48 (nine in the dual-therapy group and six in the 3-drug group). Twelve of 22 samples from study participants were successfully amplified (five in the dual-therapy group and seven in the 3-drug group). In 2 dual-therapy patients the Met184Val mutation was present at treatment failure. None of the amplified samples at treatment failure in the 3-drug group showed any resistance mutations. Mutations associated with PIs were not identified in either arm. Most patients experienced at least one adverse event over the 48-week study period. Most common adverse events were hyperlipidemia, diarrhea, nausea, and dyspepsia. Toxicity-related or tolerability-related discontinuations (n=11) were

Study Name/ Study Treatments, Study Duration	Study Design, No. of Patients	Key Inclusion/Exclusion Criteria Demography	Key Conclusions
	48 weeks (Snapshot) analysis). Virological failure: two consecutive quantitative viral loads (≥7 days and not >30 days apart) greater than 400 c/mL at week 24 or thereafter or 50 c/mL or higher at week 48.	risk the patient's safety, the results of the study, or protocol adherence,	more frequent in 3-drug arm (n=10 [4·9%]) than in the dual-therapy arm (n=1 [0·4%]; difference 4·5%, 95% CI –8·1 to –0·9; p=0·01).
PADDLE: DTG (50mg) + 3TC (300 mg) once daily	Single arm, proof of concept study, n=20 patients. Primary endpoint: Proportion patients with VL <50 c/mL at week 48 (Snapshot analysis). Virologic failure: VL ≥1000 c/mL at week 12, VL ≥400 c/mL at week 24 or 36 or a confirmed viral rebound (>200 c/mL) after VL <50 c/mL.	Inclusions: ≥18 years, treatment naïve, screening plasma HIV-1 RNA >5000 and ≤100,000 c/mL, CD4+ T-cell count >200 mm^3, no evidence of genotypic of viral resistance to lamivudine per IAS-USA 2013l Exclusions: pregnancy or breastfeeding, severe hepatic impairment, grade 4 lab abnormalities or ALT >5x ULN or ALT ≥3x ULN and bilirubin ≥1.5x ULN (with >35% direct bilirubin), or creatinine clearance of <50 mL/min via Cockroft–Gault method.	At week 48, 18 out of 20 subjects (90%, 95% CI), had plasma HIV-1 RNA <50 c/mL in ITT-exposed analyses. All subjects, including the four subjects that entered the study with baseline plasma viral load (pVL) above 100,000 c/mL, achieved VL <400 c/mL at week 3 and HIV-1 RNA <50 c/mL at 8 weeks. Through week 48, one patient met the criteria for protocol-defined virologic failure. This patient entered the study with a pVL of 106,320 copies, achieved pVL below 400 c/mL at day 10 and pVL below 50 c/mL at week 4 and remained so until week 24. At Week 36, his pVL. was 99 c/mL. After reviewing patient's compliance with the protocol, and ruling out potential intercurrent infections or vaccinations, a retest was performed three weeks later, showing a pVL of 246 c/mL. The patient was discontinued from study, per the protocol, but followed off-study to week 48. The Week 48 pVL <50 c/mL, without any change on his ARV regimen. Genotypic testing at confirmed virological failure showed no mutations. Baseline genotypic test revealed no integrase mutations. The DTG concentration in a sample collected 12 h after drug intake was consistent with adherence with DTG dosing. 3TC drug levels were not measured. Eight drug-related AEs were reported in six patients: headache (3), somnolence (1), epigastric pain (1), diarrhea (1) and nausea (2) (grade 1 to 2), with no AEs leading to discontinuation of study drug. The most frequent drug-related AE was headache in three patients. One patient died during the study due to suicide, in the context of severe stress and

Study Name/ Study Treatments, Study Duration	Study Design, No. of Patients	Key Inclusion/Exclusion Criteria Demography	Key Conclusions
			emotional trauma. This patient had a prior failed suicide attempt (per relative), not disclosed by patient at clinical visits.
ACTG A5353: DTG (50mg) + 3TC (300mg) once daily	Single-arm, open-label, 52-week pilot study, Phase II, n= 120 patients Primary endpoint-proportion patients with VL <50 c/mL at week 24 (Snapshot analysis). Virologic success at 48 week was a secondary endpoint Virologic failure (VF): confirmed HIV-1 RNA >400 c/mL at week 16/20 or >200 c/mL at or after week 24.	Inclusion: ART naive; HIV-1 RNA ≥1000 and <500 000 c/mL, with at least 25% of participants with screening HIV-1 RNA >100 000 c/mL prespecified. No CD4 count restriction. Exclusions: active hepatitis B, anticipated hepatitis C treatment or major protease, reverse transcriptase, or integrase resistance, unstable or severe hepatic impairment; and pregnancy n=122 patients, 30 with screening HIV RNA >100,000 c/mL and a median age 30: 87% males, racially diverse, screening VL 4.61 log c/mL, median CD_4 count 387 c/mm^3	Virologic success (HIV-1 RNA < 50 copies/mL and on study treatment) rate= 90% at Week 24, 85% at Week 48 and comparable between baseline HIV-1 RNA strata. Four participants experienced protocol defined virologic failure with one failing at week 20, two at week 24, and one at week 32. Of these 4 participants, one started non-study medication, another was noted to have poor adherence and withdrawn by the investigator. The Week 24 publication indicated three participants with VF, had undetected plasma dolutegravir at ≥1 time points; the M184V and R263R/K mutations developed in 1 participant. Final resistance data is pending. A total of 16 (13.3%) participants reported at least one Grade 3 or higher adverse event.