MODULE 2.6.4. PHARMACOKINETICS WRITTEN SUMMARY

TABLE OF CONTENTS

PAGE

1. BRIEF SUMMARY 5

2. METHODS OF ANALYSIS 7

3. ABSORPTION 8
   3.1. Dog 8
      3.1.1. Oral administration 8
         3.1.1.1. Pharmacokinetics after single doses using a DTG/RPV FDC tablet 8
         3.1.1.2. Pharmacokinetics/toxicokinetics after repeated administration 8

4. METABOLISM 11
   4.1. In Vivo 11
      4.1.1. Human 11
         4.1.1.1. Rilpivirine 11

5. PHARMACOKINETIC DRUG INTERACTIONS 13
   5.1. In Vitro 13
      5.1.1. Rilpivirine 13

6. DISCUSSION AND CONCLUSIONS TO PHARMACOKINETICS STUDIES 15

7. REFERENCES 16

APPENDIX 1 ANALYTICAL METHODS USED FOR THE DETERMINATION OF DOLUTEGRAVIR AND RILPIVIRINE USED IN COMBINATION IN BIOLOGICAL FLUIDS 17

LIST OF TABLES

PAGE

LIST OF ABBREVIATIONS 4

Table 3.1 List of Single and Repeat Dose Pharmacokinetic/Toxicokinetic Studies Performed with Dolutegravir and Rilpivirine 10

Table 4.1 List of Metabolism Studies Performed with Rilpivirine 12

Table 5.1 List of Drug Interaction Studies Performed with Rilpivirine 14

LIST OF FIGURES

PAGE

Figure 1.1 Structure of [^{14}C]-Dolutegravir 5

Figure 1.2 Structure of ^{14}C-Rilpivirine and ^{3}H-Rilpivirine 5

LIST OF ABBREVIATIONS

AUC_{0-t}	Area under the plasma concentration verses time curve (from time 0 to last time point)
C_{max}	Maximum observed plasma drug concentration
DTG	Dolutegravir
MATE	Multidrug and toxin extrusion protein
RPV	Rilpivirine

1. BRIEF SUMMARY

Both dolutegravir (DTG) and rilpivirine (RPV) have each undergone full development programmes as individual products and approved in the US as monotherapies [see Table 1.1, m2.6.1] and in combination with other antivirals. New pharmacokinetic studies completed in support the DTG/RPV FDC or new monotherapy studies which have not been previously submitted are summarized in this module.

In support of the dolutegravir/rilpivirine fixed dose combination (DTG/RPV FDC), the pharmacokinetics of varying formulations of a FDC tablet were investigated in dogs. Additionally, an in vitro study investigating rilpivirine as a potential transporter inhibitor and in vivo metabolism data collected in human plasma have been include for completeness.

A brief summary of the important findings from the pharmacokinetic studies is provided below. In Sections 3, 4 and 5, a discussion of the findings from these studies is presented. An overall assessment of the findings from these investigations is provided in Section 6, Discussion and Conclusions. Tabulations of these studies are provided in m2.6.5. A listing of the studies conducted, together with the location of the reports within Module 4 and their GLP status, is provided in Table 3.1, Table 4.1 and Table 5.1.

The structures of DTG and RPV are given below in Figure 1.1 and Figure 1.2, respectively, with the location of the radiolabel shown for each compound.

Figure 1.1 Structure of [^{14}C]-Dolutegravir

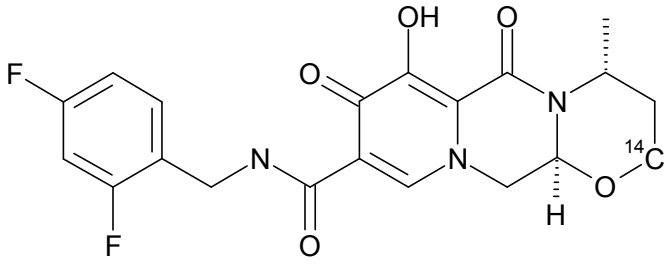
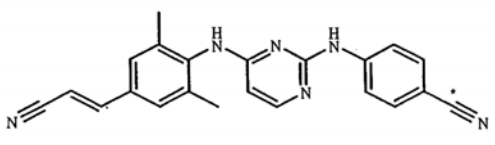
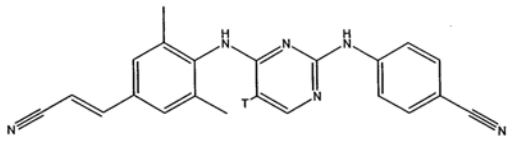


Figure 1.2 Structure of ^{14}C-Rilpivirine and ^{3}H-Rilpivirine





* = ^{14}C-label.
T = ^{3}H-label.

Summary of Findings

Absorption

- In a number of FDC tablet formulations of DTG and RPV, generally there was no notable (i.e., >2-fold) difference in exposure to either DTG or RPV; however, there was a notable increase in DTG and RPV systemic exposure in the fed state (compared to fasted state dosing).

Distribution

No new information.

Metabolism

- Following administration of RPV for 11 days in healthy subjects there was no disproportionate increase in exposure of any of the relevant metabolites compared to the parent compound exposure.

Drug interactions

- RPV inhibited MATE-1 with an IC_{50} value of 7.51 μM and inhibited MATE-2K by 65% at the lowest concentration investigated (0.05 μM).

Other PK studies

No new information.

2. METHODS OF ANALYSIS

In pharmacokinetic studies where DTG and RPV were co-administered, plasma DTG and RPV concentrations were measured following protein precipitation (DTG) or liquid/liquid extraction (RPV) liquid chromatographic tandem mass spectrometric (LC/MS/MS) methods. All methods and limits of quantification were adequate with regard to specificity and sensitivity to support the pharmacokinetic analyses of DTG and RPV. Summaries of the assay methodologies and validation are provided in Appendix 1 and the reports are provided in m4.2.2.1, Analytical Methods and Validation Reports. A listing of the studies is provided in Section 3, m2.6.5.

3. ABSORPTION

3.1. Dog

3.1.1. Oral administration

3.1.1.1. Pharmacokinetics after single doses using a DTG/RPV FDC tablet

For each single dose combination study summarized in this section, control combinations consisted of individual Tivicay™ (50 mg) and Edurant™ (25 mg) immediate release (IR) tablets. All FDC tablets [redacted]. The FDC [redacted] tablet formulations were also prepared via different manufacturing methods such as [redacted] and [redacted]. Each study used a crossover design with at least 10 day between doses.

3.1.1.2. Pharmacokinetics/toxicokinetics after repeated administration

Fed

The relative bioavailability of dolutegravir and rilpivirine when administered as separate tablets and fixed dose combination (FDC) tablets was compared using 4 fed male beagle dogs [Report 2015N228863, m4.2.2.2]. In addition to standard plasma pharmacokinetic profiling of both active ingredients, the post dosing gastrointestinal (GI) transit of the tablets was tracked using gamma scintigraphic imaging. The imaging data captured the location and dispersion of the treatment doses and identified occasional outliers, for improved understanding of the PK data. A tabulated summary of this study is provided in Table 3.1, m2.6.5.

Results from combination dosing indicated no significant difference in systemic absorption of the experimental FDC formulations compared to the individual Tivicay™ and Edurant™ tablets (control formulations). Gamma scintigraphy identified two occasions in which two of the animal subjects experienced prolonged gastric retention of the treatment doses; these data were excluded from summary calculations.

Fasted

The relative bioavailability of dolutegravir and rilpivirine when administered as separate tablets and fixed dose combination (FDC) tablets was compared using 3 fasted beagle dogs [Report 2015N239160, m4.2.2.2]. In addition to standard pharmacokinetic profiling of both active ingredients, the post dosing gastrointestinal (GI) transit of the tablets was tracked using gamma scintigraphic imaging. The imaging data captured the location and dispersion of the treatment doses and identified occasional outliers, for improved understanding of the PK data. A tabulated summary of this study is provided in Table 3.1, m2.6.5.

Specifically, on 6 occasions, tablets emptied from the stomach intact and/or dispersed poorly in the GI tract. This correlated with variable PK results on the same occasions. On 8 occasions, extended residence time in the cecum/ascending colon were observed for the radiolabeled materials; the correlation between this and the resulting PK data is unclear.

For the [redacted], variable gastric emptying (GE) and small intestinal transit (SIT) times for the radiolabeled materials were observed but it is unclear how or if this impacted resulting PK data.

For dolutegravir, no difference (<2-fold) in systemic exposure (C_{max} and AUC_{0-t}) was detected between any of the test formulations and the control formulation. However, for rilpivirine there was a >2-fold increase in systemic exposure (C_{max} and AUC_{0-t}) between test formulations prepared by [redacted] but was not observed for the [redacted] formulations.

Fed and fasted

In a further study, the relative oral bioavailability of dolutegravir and rilpivirine when administered as clinical fixed dose combination (FDC) tablets was investigated in fed and fasted beagle dogs using 2 groups of 3 dogs [Report 2015N239161, m4.2.2.2]. A food effect with both the [redacted] and the [redacted] was observed compared to control, with ~3- to 9-fold increases in exposure [C_{max} and AUC_{0-t} for dolutegravir in fed state (compared to fasted state dosing) and ~4- to 19-fold increases in exposure (C_{max} and AUC_{0-t}) for rilpivirine in fed state (compared to fasted state dosing)]. A tabulated summary of this study is provided in Table 3.1, m2.6.5.

No difference (≤2-fold) in exposure (C_{max} and AUC_{0-t}) to dolutegravir and rilpivirine, between either test formulation and the control formulation, was observed within the fed groups and this was also the case in the fasted groups.

Table 3.1 List of Single and Repeat Dose Pharmacokinetic/Toxicokinetic Studies Performed with Dolutegravir and Rilpivirine

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Dose (mg/kg/day)	Duration of Dosing (Sampling Occasions)	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Pharmacokinetics	Dog (beagle)	4M	Oral	50 (DTG) + 25 (RPV)[a]	Single	No	GSK	2015N228863 (14EDS006)	m4.2.2.2
Pharmacokinetics	Dog (beagle)	3M	Oral	50 (DTG) + 25 (RPV)[a]	Single	No	GSK	2015N239161 (15EDS002)	m4.2.2.2
Pharmacokinetics	Dog (beagle)	3M (Fed) 3M (Fasted)	Oral	50 (DTG) + 25 (RPV)[a]	Single	No	GSK	2015N239160 (15EDS001)	m4.2.2.2

Key:
a = Different formulations using a FDC [redacted] tablet.

Testing Facility:
GSK = GlaxoSmithKline.

4. METABOLISM

4.1. In Vivo

4.1.1. Human

4.1.1.1. Rilpivirine

After repeated administration of RPV for 11 days in healthy subjects at 75 and 300 mg q.d., there was no disproportionate increase in exposure of any of the relevant metabolites compared to the parent compound exposure [Report 2017N324685, m4.2.2.4].

Table 4.1 List of Metabolism Studies Performed with Rilpivirine

Type of Study	Species/Strain	Route/Method of Administration (Vehicle/Formulation)	GLP Compliance	Testing Facility	Study/Report Number	Location in CTD
Metabolism	Human	Oral (TMC278 75 mg tablet)	No	[redacted]	2017N324685 FK10104	4.2.2.4

Note: Plasma samples were obtained from Clinical Study TMC278-TiDP6-C131.

Testing Facility: [redacted] = [redacted].

5. PHARMACOKINETIC DRUG INTERACTIONS

5.1. In Vitro

5.1.1. Rilpivirine

Rilpivirine inhibited the uptake of ^{14}C-TEA (Tetra Ethyl Ammonium, a MATE-1 and MATE-2K substrate) with an IC_{50} value of 7.51 μM (MATE-1) and inhibited MATE-2K by 65% at the lowest concentration investigated (0.05 μM) [Report 2017N324686, m4.2.2.6] [see Table 4.1, m2.6.5]. Therefore, no IC_{50} value could be calculated for MATE-2K but would be lower than 0.05 μM. The fraction of ^{3}H-rilpivirine not bound to proteins (1% BSA) was calculated as the ratio of the concentration not bound to proteins to the total concentration in Krebs-Henseleit buffer (pH 8.0, + 1% BSA) after dialysis. This calculation resulted in an IC_{50} corrected for protein binding to 1% BSA of 413 nM for MATE-1 and lower than 2.75 nM for MATE-2K.

Table 5.1 List of Drug Interaction Studies Performed with Rilpivirine

Type of Study	Species/ Strain	Route/Method of Administration (Vehicle/Formulation)	GLP Compliance	Testing Facility	Study/Report Number	Location in CTD
Drug-drug interactions	Human	CHO cells expressing MATE-1 or MATE-2K transporter	No	[redacted]	2017N324686 FK10420	4.2.2.6

Key:
MATE = Multidrug and toxin extrusion protein.

Testing Facility:
[redacted] = [redacted].

6. DISCUSSION AND CONCLUSIONS TO PHARMACOKINETICS STUDIES

The pharmacokinetics of DTG and RPV were assessed in the beagle dog, to investigate the effect of on the bioavailability of either DTG or RPV, when co-administered in a number of FDC tablet formulations, in the fed and fasted states. Generally there was no notable (i.e., >2-fold) difference in exposure to either DTG or RPV with the various FDC formulations. However, there was a notable increase in DTG and RPV systemic exposure in the fed state (compared to fasted state dosing).

Following repeated oral administration of RPV tablets there was no disproportionate increase in exposure of any of the relevant metabolites compared to the parent compound exposure.

RPV inhibited MATE-1 with an IC_{50} value of 7.51 μM and inhibited MATE-2K by 65% at the lowest concentration investigated (0.05 μM). The effect of RPV on MATE-1 is unlikely to be clinically relevant, but it cannot be excluded that RPV would inhibit MATE-2K at clinically relevant concentrations.

7. REFERENCES

None.

APPENDIX 1 ANALYTICAL METHODS USED FOR THE DETERMINATION OF DOLUTEGRAVIR AND RILPIVIRINE USED IN COMBINATION IN BIOLOGICAL FLUIDS

Validation Report	Nonclinical Studies Supported	Method Description and Performance
Dog (Beagle) Plasma (K_2EDTA) [redacted] **Title:** Quantitation of GSK1349572 in Canine Plasma via HPLC with MS/MS. Method ID: P1316 Document Number: 2014N222838	Dog pharmacokinetics (fasted) of dolutegravir and rilpivirine to evaluate fixed dose combination tablet formulations Study 15EDS001 Document: 2015N239160 Dog pharmacokinetics (fed and fasted) of dolutegravir and rilpivirine to evaluate fixed dose combination tablet formulations Study 15EDS002 Document: 2015N239161 Dog pharmacokinetics (fed) of dolutegravir and rilpivirine to evaluate fixed dose combination tablet formulations Study 14EDS006 Document: 2015N228863	Dolutegravir was extracted from 25 μL dog plasma by protein precipitation using acetonitrile containing [$^2H_7{}^{15}N$]-dolutegravir as an internal standard. Extracts were separated by HPLC with a Waters, Xbridge C18 column (50 mm x 2.1 mm; 3.5 μm) and analyzed by MS/MS detection using a Turbo IonSpray interface in the positive ion mode and multiple reaction monitoring (m/z 420>277 and m/z 428>283). **Validated Range:** 10 to 10000 ng/mL **Lower Limit of Quantification (LLQ):** 10 ng/mL Within-run Precision (%CV): 1.98% to 4.39% Accuracy (% Bias): -2.11 to 2.60% **QC Levels:** 10, 30, 75, 300, 1200 and 7500 ng/mL Within-run Precision (%CV): 1.93 to 6.18% Accuracy (% Bias): 3.15 to 9.29% **Dilution Effects:** 5-fold Within-run Precision (%CV): 3.48 and 4.40% Accuracy (% Bias): 6.44% and 6.21% **Recovery:** 94.5 to 103% dolutegravir 80.0 to 102% internal standard **Stability in Dog Plasma:** 2 freeze-thaw cycles from -20°C At least 76 days at -20°C At least 19 hours at ambient temperature **Processed Extract Stability:** Not determined

Validation Report	Nonclinical Studies Supported	Method Description and Performance
Dog (Beagle) Plasma (K_2EDTA) [redacted] **Title:** Quantitation of Rilpivirine in Canine Plasma via HPLC with MS/MS. Method ID: P1320 Document Number: 2014N223101	Dog pharmacokinetics (fasted) of dolutegravir and rilpivirine to evaluate fixed dose combination tablet formulations Study 15EDS001 Document: 2015N239160 Dog pharmacokinetics (fed and fasted) of dolutegravir and rilpivirine to evaluate fixed dose combination tablet formulations Study 15EDS002 Document: 2015N239161 Dog pharmacokinetics (fed) of dolutegravir and rilpivirine to evaluate fixed dose combination tablet formulations Study 14EDS006 Document: 2015N228863	Rilpivirine was extracted from 50 μL dog plasma by protein precipitation using acetonitrile containing rilpivirine-d_6 as an internal standard. Extracts were separated by HPLC with a Waters, Xbridge C18 column (100 mm x 2.1 mm; 5 μm) and analyzed by MS/MS detection using an APCI interface in the positive ion mode and multiple reaction monitoring (m/z 367>195 and m/z 373>201). **Validated Range:** 1 to 1000 ng/mL **Lower Limit of Quantification (LLQ):** 1 ng/mL Within-run Precision (%CV): 4.78% to 7.19% Accuracy (% Bias): -1.90 to 2.54% **QC Levels:** 1, 3, 8, 30, 120 and 750 ng/mL Within-run Precision (%CV): 4.99 to 9.05% Accuracy (% Bias): 1.56 to 6.84% **Dilution Effects:** 5-fold Within-run Precision (%CV): 5.34 and 6.46% Accuracy (% Bias): 4.67% and 1.10% **Recovery:** 17.2 to 19.0% rilpivirine 19.0 to 20.2% internal standard **Stability in Dog Plasma:** 2 freeze-thaw cycles from -20°C At least 58 days at -20°C At least 24 hours at ambient temperature **Processed Extract Stability:** Not determined

MODULE 2.6.5. PHARMACOKINETICS TABULATED SUMMARY

TABLE OF CONTENTS

PAGE

1. PHARMACOKINETICS: OVERVIEW FOR DOLUTEGRAVIR AND RILPIVIRINE 4

2. ANALYTICAL METHODS AND VALIDATION REPORTS 7

3. PHARMACOKINETICS: ABSORPTION AFTER A SINGLE DOSE 8

4. PHARMACOKINETICS: DRUG-DRUG INTERACTIONS 11

LIST OF TABLES

PAGE

Table 1.1 List of Single and Repeat Dose Pharmacokinetic/Toxicokinetic Studies Performed with Dolutegravir and Rilpivirine 4

Table 1.2 List of Metabolism Studies Performed with Rilpivirine 5

Table 1.3 List of Drug Interaction Studies Performed with Rilpivirine 6

Table 2.1 Pharmacokinetics: Analytical Methods and Validation Reports 7

Table 3.1 Plasma Pharmacokinetic Parameters for Dolutegravir and Rilpivirine Following Single Oral Administration of Different Fixed Dose Combination Formulations in Dogs 8

Table 4.1 Pharmacokinetics: Rilpivine Drug-Drug Interactions 11

1. PHARMACOKINETICS: OVERVIEW FOR DOLUTEGRAVIR AND RILPIVIRINE

Table 1.1 List of Single and Repeat Dose Pharmacokinetic/Toxicokinetic Studies Performed with Dolutegravir and Rilpivirine

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Dose (mg/kg/day)	Duration of Dosing (Sampling Occasions)	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Pharmacokinetics	Dog (beagle)	4M	Oral	50 (DTG) + 25 (RPV)[a]	Single	No	GSK	2015N228863 (14EDS006)	m4.2.2.2
Pharmacokinetics	Dog (beagle)	3M	Oral	50 (DTG) + 25 (RPV)[a]	Single	No	GSK	2015N239161 (15EDS002)	m4.2.2.2
Pharmacokinetics	Dog (beagle)	3M (Fed) 3M (Fasted)	Oral	50 (DTG) + 25 (RPV)[a]	Single	No	GSK	2015N239160 (15EDS001)	m4.2.2.2

Key:
a = Different formulations using a FDC [redacted] tablet.

Testing Facility:
GSK = GlaxoSmithKline.

Table 1.2 List of Metabolism Studies Performed with Rilpivirine

Type of Study	Species/Strain	Route/Method of Administration (Vehicle/Formulation)	GLP Compliance	Testing Facility	Study/Report Number	Location in CTD
Metabolism	Human	Oral (TMC278 75 mg tablet)	No	[redacted]	2017N324685 FK10104	4.2.2.4

Note: Plasma samples were obtained from Clinical Study TMC278-TiDP6-C131.

Testing Facility: [redacted] = [redacted].

Table 1.3 List of Drug Interaction Studies Performed with Rilpivirine

Type of Study	Species/ Strain	Route/Method of Administration (Vehicle/Formulation)	GLP Compliance	Testing Facility	Study/Report Number	Location in CTD
Drug-drug interactions	Human	CHO cells expressing MATE-1 or MATE-2K transporter	No	[redacted]	2017N324686 FK10420	4.2.2.6

Key:
MATE = Multidrug and toxin extrusion protein.

Testing Facility:
[redacted] = [redacted].

2. ANALYTICAL METHODS AND VALIDATION REPORTS

Table 2.1 Pharmacokinetics: Analytical Methods and Validation Reports

Type of Study	Species	Quantification Limits	Report No. (Method Reference)	Location in CTD
Quantitation of GSK1349572 in canine plasma via HPLC with MS/MS.	Dog	10 to 10000 ng/mL	2014N222838 (P1316)	m4.2.2.1
Quantitation of rilpivirine in canine plasma via HPLC with MS/MS.	Dog	1 to 1000 ng/mL	2014N223101 (P1320)	m4.2.2.1

3. PHARMACOKINETICS: ABSORPTION AFTER A SINGLE DOSE

Table 3.1 Plasma Pharmacokinetic Parameters for Dolutegravir and Rilpivirine Following Single Oral Administration of Different Fixed Dose Combination Formulations in Dogs

Test Article: Dolutegravir and Rilpivirine
Administration: Oral **Location in CTD:** m4.2.2.2
Analyte: Dolutegravir and Rilpivirine
Assay: HPLC/MS/MS
Sample: Plasma

Report No.:	2015N228863	2015N239160	2015N239161
Gender (M/F)/Number of Animals:	(M)4	(M)3	(M)3/group
Feeding Condition:	Fed	Fasted	Fed and Fasted
Sample Collection Intervals (hours):	0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 24, 48, 96	0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 24, 48, 96	0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 24, 48, 96

Report No.: 2015N228863

Analyte	Dose (mg)	Tablet Formulation (TX)[a,b]	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	% Relative Bioavailability[c]
Dolutegravir	50	Control: Individual tablets co-dosed **(TX A)**	1.0	4340	14800	100
Rilpivirine	25		2.0	512	12300	100
Dolutegravir	50	[redacted] **(TX B)**	0.8	4320	13500	91
Rilpivirine	25		1.0	395	10500	85
Dolutegravir	50	[redacted] **(TX C)**	1.5	4120	15100	102
Rilpivirine	25		1.0	517	13600	110
Dolutegravir	50	[redacted] **(TX D)**	1.0	4460	14100	95
Rilpivirine	25		1.0	495	12100	98
Dolutegravir	50	[redacted] **(TX E)**	1.0	4170	14700	99
Rilpivirine	25		1.5	553	14800	120

Plasma Pharmacokinetic Parameters for Dolutegravir and Rilpivirine Following Single Oral Adminstration of Different Fixed Dose Combination Formulations in Dogs (Continued)

Report No.:		2015N239160				
Analyte	**Dose (mg)**	**Tablet Formulation (TX)[a,b]**	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{0-t} (ng.h/mL)**	**% Relative Bioavailability[c]**
Dolutegravir Rilpivirine	50 25	Control: Individual tablets co-dosed **(TX A)**	0.5 2.0	792 53.6	2860 1080	100 100
Dolutegravir Rilpivirine	50 25	[redacted] **(TX B)**	1.0 2.0	1014 127	3770 2380	132 221
Dolutegravir Rilpivirine	50 25	[redacted] **(TX C)**	3.0 3.0	890 116	3740 2180	131 202
Dolutegravir Rilpivirine	50 25	[redacted] **(TX D)**	0.5 3.0	721 49.4	2761 1160	96 108
Dolutegravir Rilpivirine	50 25	[redacted] **(TX E)**	1.0 2.0	825 33.3	26690 1060	94 69
Report No.:		2015N239161				
Fasted						
Dolutegravir Rilpivirine	50 25	Control: Individual tablets co-dosed **(TX A)**	1.0 2.0	473 37.0	1690 1040	100 100
Dolutegravir Rilpivirine	50 25	[redacted] **(TX C)**	1.0 1.0	411 21.0	1200 450	100 100
Dolutegravir Rilpivirine	50 25	[redacted] **(TX D)**	1.0 1.0	825 61.6	2860 2860	100 100

Plasma Pharmacokinetic Parameters for Dolutegravir and Rilpivirine Following Single Oral Adminstration of Different Fixed Dose Combination Formulations in Dogs (Continued)

Analyte	Dose (mg)	Tablet Formulation (TX)[a,b]	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	% Relative Bioavailability[c]
Fed						
Dolutegravir Rilpivirine	50 25	Control: Individual tablets co-dosed **(TX A)**	2.0 4.0	3160 395	10800 18200	642 1740
Dolutegravir Rilpivirine	50 25	[redacted] **(TX C)**	1.0 1.0	3600 320	9140 8720	758 1940
Dolutegravir Rilpivirine	50 25	[redacted] **(TX D)**	1.0 2.0	3440 420	10500 12200	368 906

Additional Information:

a = For controls, individual Tivicay™ and Edurant™ tablets were co-administered.

b = Coated [redacted] immediate release (IR) tablets containing 50 mg Dolutegravir and 25 mg. [redacted].

c = For the fed only and fasted only studies, % relative bioavailability calculated as mean AUC_{TX}/AUC_{TA} x 100 and for the fed and fasted comparison, % relative bioavailability calculated as mean AUC_{Fed}/AUC_{Fasted} x 100.

4. PHARMACOKINETICS: DRUG-DRUG INTERACTIONS

Table 4.1 Pharmacokinetics: Rilpivine Drug-Drug Interactions

Location in CTD	**4.2.2.6** **Test Article:** rilpivirine
Report No. / Study No.	**2017N324686 / FK10420**
	Type of Study: Inhibition of MATE-1 (SLC47A1) and MATE-2K (SLC47A2) by TMC278
	Method The aim of this study was to test whether TMC278 inhibits MATE-1/-2K –mediated transport of ^{14}C-Tetra Ethyl Ammonium (TEA, MATE-1 and MATE-2K substrate) in CHO cells stably transfected with cDNA encoding for MATE-1 or MATE 2K transporter TMC278 concentrations: 50, 10, 1.5, 0.3, 0.05 µM (^{3}H-TMC278 specific activity 700 GBq/mmol)

^{14}C-TEA transport (30 µM, 10 min; n=3; 1% BSA)				**^{14}C-TEA transport (30 µM, 10 min; n=3; 1% BSA)**			
	CHO-parent	**CHO-MATE-1**			**CHO-parent**	**CHO-MATE-2K**	
	average (pmol/mg protein.min)	average (pmol/mg protein.min)	Maximal activity (%)		average (pmol/mg protein.min)	average (pmol/mg protein.min)	Maximal activity (%)
TEA	1.85	43.7	100	TEA	1.31	7.47	100
TEA + 0.05 µM TMC278	2.58	50.1	114	TEA + 0.05 µM TMC278	1.83	3.98	35.0
TEA + 0.3 µM TMC278	3.51	38.9	84.7	TEA + 0.3 µM TMC278	1.31	3.61	37.4
TEA + 1.5 µM TMC278	2.20	40.4	89.5	TEA + 1.5 µM TMC278	1.38	3.35	32.1
TEA + 10 µM TMC278	1.91	19.7	42.4	TEA + 10 µM TMC278	1.13	2.75	26.4
TEA + 50 µM TMC278	1.91	6.60	11.2	TEA + 50 µM TMC278	1.72	1.91	3.1
TEA + 1 µM Quinidine	2.09	34.8	78.3	TEA + 0.03 µM Pyrimethamine	1.22	3.50	37.0
TEA + 50 µM Quinidine	2.69	10.1	17.6	TEA + 3 µM Pyrimethamine	1.34	2.44	17.8