Clinical Pharmacology Review

NDA 204,790	Submission Date: December 17, 2012
Drug	Dolutegravir, GSK1349572
Trade Name	TIVICAY
Applicant	GSK/Viiv
Relevant IND(s)	75,382
Submission Type; Code	505(b)(1) NME, priority review
Formulation; Strength	50 mg tablet
Proposed Indication	Treatment of HIV in combination with other antiretroviral agents in adults and pediatric patients aged 12 years and older
Dosage and Administration	Treatment-naïve adults: 50 mg once daily Treatment-experienced, integrase inhibitor-naïve adults: 50 mg once daily Integrase inhibitor-experienced adults: DTG 50 mg twice daily Treatment-experienced, integrase inhibitor-naïve children 12 to < 18 years of age and weighing ≥ 40 kg: DTG 50 mg once daily
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1. Executive Summary

Dolutegravir (DTG) is a new molecular entity in the integrase strand transfer inhibitor class, indicated for the treatment of HIV-1. Two other drugs in this same class, raltegravir and elvitegravir (as a component of a fixed-dose combination product, Stribild®) are approved and marketed in the U.S. The proposed dosing regimen of DTG, in combination with other antiretroviral therapy agents for the treatment of HIV-1 infection in adults and children ≥ 12 years of age (weighing at least 40 kg) is based on prior treatment experience.

- Treatment-naïve adults: DTG 50 mg once daily
- Treatment-experienced, integrase inhibitor (INI)-naïve adults: DTG 50 mg once daily
- Integrase inhibitor (INI)-experienced adults: DTG 50 mg twice daily
- Treatment-naïve or treatment-experienced and integrase inhibitor (INI)-naïve children 12 to < 18 years of age and weighing ≥ 40 kg: DTG 50 mg once daily

The following is a list of studies conducted by the applicant in support of this NDA.

- Twenty-nine *in vitro* studies investigating metabolic pathways using supersomes, microsomes and hepatocytes; the potential for CYP induction, inhibition, transporter inhibition (P-gp, OCT1, OCT2, OATP1B1, OATP1B3, MRP2 and BCRP), P-gp transport, and plasma protein binding were evaluated
- Ten phase I studies including single and multiple ascending dose studies in healthy volunteers, food effect studies, tissue distribution, relative bioavailability of various formulations of DTG and a mass balance study
- One hepatic impairment study conducted in subjects with moderate hepatic impairment and one renal impairment study conducted in subjects with severe renal impairment
- One thorough QTc study and one study investigating the effects of DTG on renal function
- Seventeen drug interaction studies with commonly co-administered drugs in the patient population (other anti-retrovirals, oral contraceptive, methadone, antacids, and rifampin) and a sensitive CYP3A4 substrate (midazolam).
- Three phase 2 studies in which the safety and efficacy of DTG were evaluated (including proof of concept and dose ranging studies)
- Four pivotal phase 3 studies (in the following populations: 2 in treatment naïve, 1 in treatment-experienced and INI-naïve, and 1 in INI-experienced)
- One pediatric study investigating the pharmacokinetics (PK), safety and tolerability of DTG in adolescents
- Two population pharmacokinetics (popPK) analysis reports
- One meta-analysis report for the effects of CYP/UGT polymorphism on the pharmacokinetics of DTG

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed this submission and has concluded that the application is acceptable from a clinical pharmacology perspective. The OCP has proposed some revisions to the labeling text that are pending the applicant's agreement.

1.2 Phase 4 Commitments

The post-marketing commitments are under discussion at the time of this review.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

ADME

Absorption

Following oral administration of tablet formulations, DTG is absorbed with no absorption lag time and a median tmax of 2 to 3 hours post dose. DTG absorption is increased with co-administration of food. Administration of DTG at a single dose of 50 mg with a low fat, moderate fat and high fat meal increased DTG AUC by 33%, 41%, and 66%, respectively. The moderate food effect is not considered clinically significant; therefore DTG can be taken without regard to food. Dosing separation is needed when DTG is to be given together with polyvalent cation containing drugs including cation-based antacids, oral iron supplements, oral calcium supplements, and buffered medication due to DTG's chelation with polyvalent cations. DTG should be taken 2 hours before or 6 hours after the dose of polyvalent cation-containing drugs.

Distribution

The apparent volume of distribution is estimated at 17.4 L after administration of DTG in a tablet formulation. DTG is highly bound to human plasma proteins (approximately 99.3%) *in vitro*. The free fraction of DTG in plasma is estimated at ~0.23% to 1.10% in healthy subjects, ~0.4 to 0.5% in subjects with moderate hepatic impairment, 0.84 to 1.01% in subjects with severe renal impairment, and 0.49% in HIV-positive subjects.

DTG is present in cerebrospinal fluid (CSF) and in the genital tract. DTG concentration in CSF averaged 18 ng/mL at steady state. CSF:plasma concentration ratio of DTG ranged from 0.11% to 0.66%. DTG is also present in the female and male genital tract. DTG exposure (expressed as AUC) in cervicovaginal fluid, cervical tissue, and vaginal tissue was 6%, 10%, and 9%, respectively, of that in plasma at steady state. DTG exposure in seminal fluid and rectal mucosal tissue was 7% and 17%, respectively, of that in plasma at steady state.The clinical relevance of these findings is unknown at this time.

Metabolism and Excretion

The mass balance study results indicated that 53% percent of the total oral dose is excreted as unchanged DTG in feces. Thirty-one percent of the total oral dose is excreted in urine, represented by the glucuronide metabolite of DTG (18.9% of total dose), N-dealkylated metabolite (3.6% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and other minor metabolites.

Renal elimination of unchanged DTG represents less than 1% of the total dose administered. DTG is primarily metabolized via UGT1A1 with CYP3A4 as a secondary metabolic pathway (approximately 10% in a human mass balance study).

DTG has a terminal half-life of ~14 hours and a low apparent clearance (CL/F) of 0.56 L/hr. The hepatic extraction ratio of DTG is low (lower than 2%). As CYP3A-mediated metabolism represents only a minor route of elimination of DTG (less than 10% of a total oral dose), first-pass metabolism of DTG following oral dosing is expected to be low.

Intrinsic and Extrinsic Factors

Population pharmacokinetic analyses using pooled pharmacokinetic data from Phase II and Phase III adult trials identified weight, age, gender, albumin levels, and smoking status as statistically significant covariates of DTG exposures. However, these factors resulted in changes in DTG exposures less than 30% and are not considered clinically significant. The analyses indicated that race/ethnicity, HCV co-infection, CDC classification of HIV infection, creatinine clearance (CrCL), ALT, or AST did not influence the exposure of DTG. There were limited PK data from subjects with HBV co-infection (n=8, 1%) and subjects above 65 years of age (n=1).

Drug-Drug Interactions

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In general, DTG has a low potential to cause drug interactions. *In vitro*, DTG demonstrated little or no direct inhibition of major drug metabolizing enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1 or UGT2B7) or major transporters (BCRP, MRP2, OATP1B1, OATP1B3, OCT1, and P-gp). *In vitro*, DTG did not induce CYP1A2, CYP2B6 or CYP3A4.

In vitro, DTG inhibited the renal organic cation transporter 2 (OCT2, IC_{50}=1.9 μM or 0.82 μg/mL). This value is lower than the C_{max} of DTG observed in the phase III trials (3.6 μg/mL and 4.1 μg/mL at 50 mg q.d. and 50 mg b.i.d, respectively) by approximately 5-fold. Based on this observation, DTG may increase plasma concentrations of drugs for which excretion is highly dependent on transport by OCT2, such as dofetilide and metformin.

Effect of Other Agents on the Pharmacokinetics of Dolutegravir and Dose Recommendations

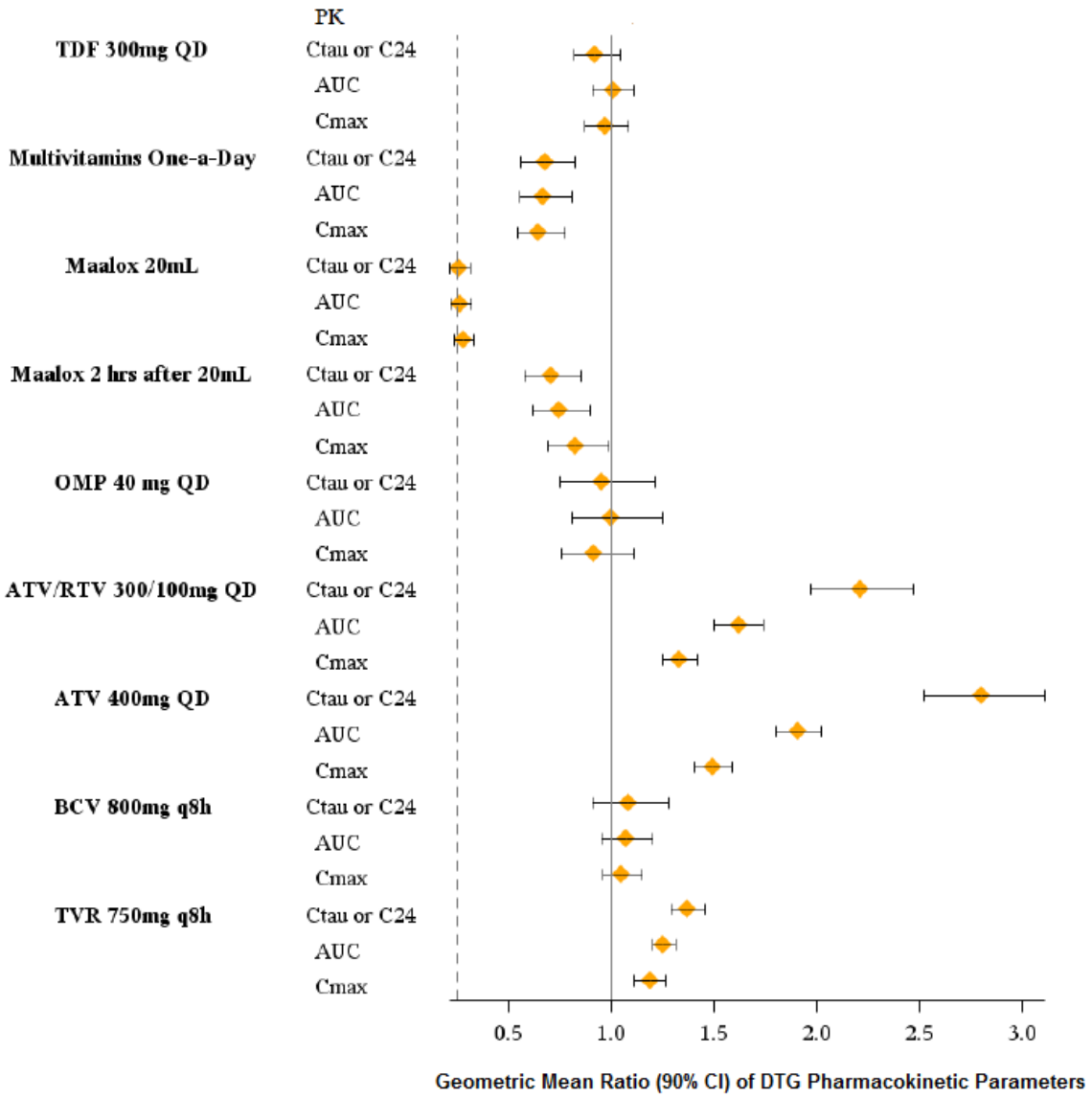
DTG is eliminated mainly through metabolism by UGT1A1 with CYP3A4 as a minor route. DTG is also a substrate of UGT1A3, UGT1A9, P-gp, and BCRP; therefore drugs that affect UGT1A1, UGT1A3, UGT1A9, CYP3A4, P-gp, and/or BCRP may theoretically affect DTG plasma concentration.

Moderate to strong inducers of UGT1A1 and/or CYP3A4, such as etravirine (ETR), efavirenz (EFV), fosamprenavir/ritonavir (FPV/rtv), tipranavir/ritonavir (TPV/rtv), and rifampin (RIF), reduced the plasma

concentrations of DTG. The PopPK analysis using Study ING111762 data indicated that subjects receiving DTG 50 mg once daily in combination with TPV/rtv and EFV had significantly lower C_{0h} and lower virologic response. The analysis also indicated that use of fosamprenavir/ritonavir (FPV/rtv) was associated with significantly lower C_{0h} although the effects on virologic response were inconclusive due to limited number of subjects. Based on the results of the drug interaction studies as well as the PopPK analysis, DTG 50 mg twice daily dosing is recommended in INI-naïve subjects (either ARV-naïve or ARV-experienced) receiving DTG in combination with EFV, FPV/rtv, or TPV/rtv. As RIF reduced DTG exposure to a similar extent as TPV/rtv and EFV, DTG 50 mg twice daily is also recommended for subjects who require RIF therapy for treatment of tuberculosis infection. Caution is warranted when those moderate to strong inducers are used with the DTG 50 mg twice daily dose in INI-experienced subjects.

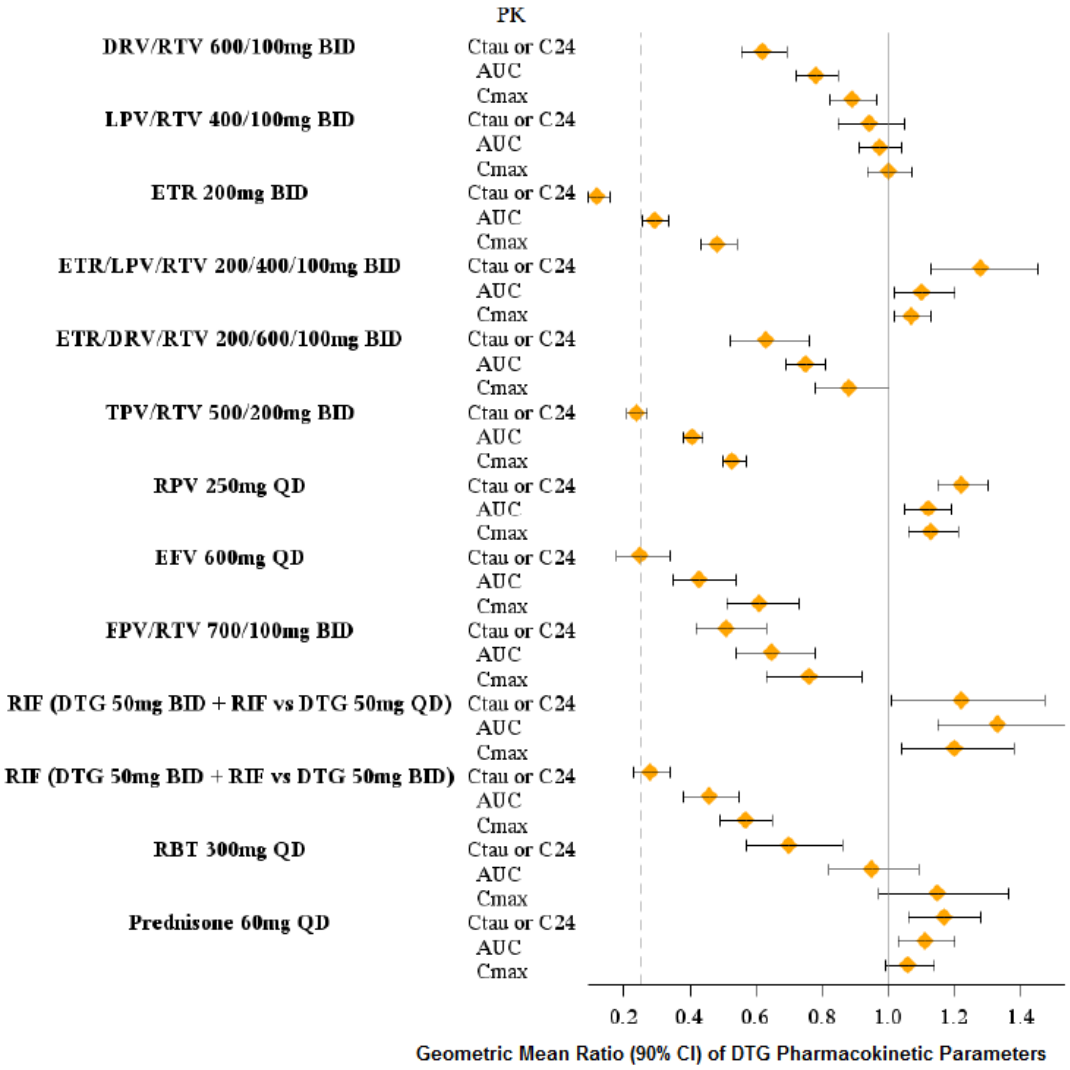
Etravirine (ETR) reduced DTG $C\tau$ by more than 80%; however, the effect of ETR was mitigated by co-administration of lopinavir/ritonavir (LPV/rtv) and darunavir/ritonavir (DRV/rtv). Additionally, the UGT1A1 inhibitor, atazanavir (ATV) or ATV/rtv increased DTG AUC by 62% and 91%, respectively. Thus, the co-administration of DTG 50 mg once daily with ETR is not recommended unless the regimen includes atazanavir/ritonavir (ATV/rtv), LPV/rtv or DRV/rtv.

Fig 1. The effects of co-administered drugs (non-inducers) on the pharmacokinetics of dolutegravir



Dashed line represents 0.25 or 75% reduction in DTG exposure.
TDF; tenofovir, OMP; omeprazole, ATV; atazanavir, RTV; ritonavir, BCV; boceprevir, TVR; telaprevir

Fig 2. The effects of co-administered drugs (inducers) on the pharmacokinetics of dolutegravir



DRV; darunavir, RTV; ritonavir, ETR; etravirine, LPV; lopinavir, TPV; tipranavir, RPV;rilpivirine, EFV; efavirenz, FPV; fosamprenavir, RIF;rifampin, RBT; rifabutin.

Pharmacodynamic effects

Effect of DTG on Cardiac Conduction (QT prolongation)

DTG did not prolong the QTc interval for 24 hours post dose after a single supratherapeutic dose of DTG 250 mg as suspension. After baseline and placebo adjustment, the maximum mean QTc change based on QTcF was 2.4 msec (one-sided 95% upper CI: 4.9 msec).

Effect of DTG on Renal Function

A modest decrease (10-15%) in creatinine clearance (CrCL) was observed with repeated DTG dosing in clinical studies. The applicant hypothesized that this is due to inhibition of the organic cation transporter 2 (OCT2) in the proximal renal tubules, which mediates the tubular secretion of creatinine. A study

examining the effect of DTG on serum creatinine (SCr), glomerular filtration rate (GFR) using iohexol as the probe, and effective renal plasma flow (ERPF) using para-aminohippurate (PAH) as the probe was conducted in healthy volunteers receiving DTG 50 mg once daily or twice daily for 14 days. A modest decrease (approximately 10-15%) in CrCL was observed with DTG within the first week of treatment, consistent with that observed in clinical studies. DTG at both doses had no significant effect on actual GFR or ERPF. These data support *in vitro* studies which suggest that the decrease in CrCL observed in clinical studies are likely due to OCT2 inhibition and the changes likely do not pose significant safety concerns. No significant renal safety issues were observed throughout the development of the product.

Specific Populations

Pediatrics

The pharmacokinetics of DTG in antiretroviral treatment-experienced, INI-naive HIV-1 infected pediatric subjects 12 to <18 years of age (n=10) was assessed (study P1093, ING112578) with weight-based dosing of ~1 mg/kg (maximum 50 mg) daily. In 9 children weighing at least 40 kg, a DTG 50 mg once daily dose resulted in DTG exposure comparable to the predefined target range based on data in adults receiving DTG 50 mg once daily. Eight of 10 subjects achieved virologic suppression (HIV-1 RNA <400 c/mL) at Week 24, with 7 of 10 subjects achieving HIV-1 RNA <50 copies/mL. DTG was safe and well-tolerated in children 12 to <18 years of age. The PK and antiviral activity data support the use of DTG 50 mg once daily in treatment-naïve or treatment-experienced, INI-naïve patients aged 12 years and older and weighing at least 40 kg.

Renal impairment

A study of the pharmacokinetics of DTG was performed in subjects with severe renal impairment (CLcr <30 mL/min, not on dialysis) and matched healthy adult controls. The AUC, C_{max}, and C_{24} of DTG was unexpectedly decreased by 40%, 23% and 44% respectively in subjects with severe renal impairment compared to matched healthy subjects. The cause of the decreased DTG exposure in subjects with renal impairment is unknown.

The PopPK analysis indicated that subjects with moderate and mild renal impairment (creatinine clearance 30 to < 60, and 60 to < 90 mL/min) showed no difference in DTG exposure compared to subjects with normal creatinine clearance. This supports use of DTG in patients with moderate to mild renal impairment without a dose adjustment.

Based on the exposure-response relationship, no dose adjustment of DTG is needed in treatment-naïve or treatment-experienced, INI-naïve patients with severe renal impairment (not on dialysis). Caution is warranted when DTG is used in INI-experienced patients with severe renal impairment as such decreases may compromise efficacy.

Hepatic impairment

In a trial comparing DTG PK in subjects with moderate hepatic impairment (Child-Pugh Grade B) to matched healthy adult controls, the exposure of DTG was similar between the two groups after a single

dose 50 mg administration. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child Pugh grade A or B). The effect of severe hepatic impairment on the pharmacokinetics of DTG has not been studied and thus DTG is not recommended for use in patients with severe hepatic impairment.

Dose Selection

The 50 mg once daily dose for DTG in ART-naïve and ART-experienced/INI-naïve subjects was selected based on the following study results:

- In study ING111521, 10-day DTG monotherapy in ART-naïve or ART-experienced/ INI-naïve patients demonstrated increasing antiviral activity with increasing dose. DTG 2 mg, 10 mg, and 50 mg doses resulted in 1.54, 2.04, and 2.48 $\log_{10}$ copies/mL declines in HIV viral load, respectively. A PK/PD analysis using a maximum effect (Emax) model indicated that the 50 mg dose was on the plateau of the concentration-response curve after 10 days monotherapy. The 50 mg once daily dose achieved an inhibitory quotient of 19, providing considerable coverage above the target concentration of 0.064 ng/ml (protein-adjusted IC90).
- In study ING112276 (a Phase IIb dose-ranging study in treatment-naive subjects), DTG at doses of 10 mg, 25 mg, and 50 mg once daily with 2 NRTIs all demonstrated similar antiviral responses (91%, 88%, and 90% at week 48 with no evidence of a dose response relationship for efficacy and safety). The 50 mg once daily regimen was selected for phase III trials to accommodate a decrease in DTG due to drug interactions, imperfect adherence or other causes.

The 50 mg BID regimen selection for DTG in INI-experienced subjects was based on the following study results:

- In study ING11296, INI-experienced patients taking DTG 50 mg once daily (cohort I) resulted in a lower response rate as compared with response rates in treatment-naïve or treatment-experience INI-naïve subjects (41% vs. > 79%) after 24 weeks of treatment. This was due to some subjects harboring INI-resistant virus, which required higher drug concentrations due to lower susceptibility to DTG. A higher response rate (75%) was observed in cohort II (50 mg twice daily) without an overt increase in clinical or laboratory adverse events (AEs) compared to the 50 mg once daily regimen.

PK/PD Relationship for Efficacy

INI-Naïve Subjects

In treatment naïve patients who received DTG 50 mg q.d. with 2 NRTIs (nucleoside reverse transcriptase inhibitors), a flat exposure response was observed over the observed C_{0h} range. In ARV-experienced, INI-naïve patients who received DTG 50 mg q.d. with an optimized background regimen, C_{0h} was a statistically significant predictor of antiviral response at Week 24. This relationship was primarily influenced by a subset of subjects with DTG C_{0h} measurements below the limit of quantification or with moderate or strong inducers in the background regimen. Specifically, the use of moderate to strong inducers, such as TPV/rtv and EFV, in the background therapy was associated with reduced C_{0h} and

reduced virologic efficacy. Use of FPV/rtv was also associated with significantly low C_{0h}, but the small number of subjects limited the evaluation of effects of low C_{0h} on virologic efficacy.

INI-experienced Subjects
The applicant conducted a Phase IIb and a Phase III trial (ING112961 and ING112574) in treatment-experienced, INI-experienced HIV-1 infected subjects to support the selected DTG 50 mg BID dose. ING112961 included DTG PK from 51 subjects administered DTG 50 mg QD or BID given in combination with at least one active agent in the optimized background therapy (OBT). The response observed in the lowest quartile (51%) was comprised of subjects predominantly from the 50 mg QD treatment arm (41%, n/N=11/27, geometric mean of C_{0h} in the lowest quartile: 1.14 μg/mL) while a higher response rate was observed in the upper quartiles consisting of subjects administered 50 mg BID (response rate 63-68%; C_{0h} 2.29 μg/mL). This observation supports the use of 50 mg BID in the treatment-experienced, integrase inhibitor-experienced population.

In the Phase III study (ING112574) evaluating DTG 50 mg twice daily, plasma DTG C_{0h} was not predictive of Day 8 (n=183) or Week 24 (n=114) antiviral response. However, a relationship between inhibitory quotient (IQ) values [the IQ is the ratio of C_{0h} (exposure) at steady state and EC_{50} (a measurement of the ability of DTG to inhibit HIV-1 virus)] and virologic success was observed. The differences in IQ values in each quartile were primarily driven by changes in EC_{50} due to the baseline susceptibility changes with specific mutations. The average C_{0h} values were 1.84, 2.25, 2.34, and 3.86 μg/mL in 1st, 2nd, 3rd and 4th quartile respectively, while average EC_{50} values were 5.11, 1.38, 0.96 and 0.71 μg/mL in the corresponding quartiles.

A decrease in overall response rate was observed between those subjects with a Q148 mutation and one or more additional integrase inhibitor mutations (19-43%) compared to the remaining subjects (74-83%) despite similar exposure across the treatment groups (DTG C_{0h}: 2.26-2.53 μg/mL).

PK/PD Relationship for Safety
Plasma DTG exposure was not correlated with the presence of the most frequent AEs including diarrhea, nausea, and headache or with most clinical laboratory tests of interest.

2. Question Based Review

2.1 General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

DTG sodium is a polycyclic, nitrogen containing heterocycle possessing amide functionality. It is white to light yellowish white powder. DTG possesses two chiral centers and has potential for stereoisomerism (one enantiomer and two diastereomers).

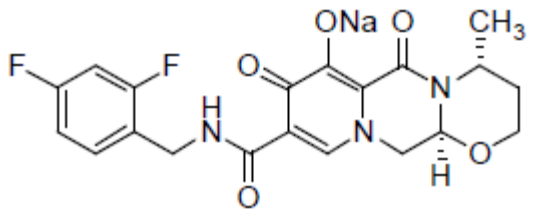
Formula and molecular weight

$C_{20}H_{18}F_2N_3NaO_5$ (441.36 g/mol as DTG sodium, 419.38 as DTG free acid)

Chemical name (IUPAC name)

Sodium (4R, 12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1`,2`:4,5]pyrazino[2,1-b][1,3]oxazol-7-olate

Chemical structure



Solubility profile:

The solubilities of [redacted] (b) (4) DTG sodium in various solvents at 25 ºC are provided below.

Table 2.1.1-1 Solubility of DTG sodium in various solvents at 25ºC

Solvent	Solution pH	Solubility (mg/mL)	Descriptor
Methanol		0.499	Very slightly soluble
Ethanol		0.076	Practically insoluble
2-propanol		0.009	Practically insoluble
Acetonitrile		0.006	Practically insoluble
Water		3.176	Slightly soluble at pH 5.0 and 6.5 Practically insoluble at pH 1.2 in aqueous media
FaSSIF (Fasted State simulated intestinal fluid)	6.5	0.239	Very slightly soluble
FeSSIF (Fed state simulate intestinal fluid)	5.0	0.170	Very slightly soluble
SGF (Simulated gastric fluid)	1.2	0.021	Practically insoluble

Partition Coefficient (Log P)

2.16 ± 0.01 at 23ºC

Composition of DTG 50 mg tablets used in Phase III studies

The formulation used in pivotal phase III studies is identical to the commercial formulation with the following exceptions.

- The phase III tablet is deep convex round and the commercial tablet is normal convex round
- The phase III tablet is film coated (b) (4) and the commercial tablet is film coated (b) (4)

Table 2.1.1-2 Composition of DTG 50 mg tablets used in Phase III studies

Component	Quantity mg/tablet
Strength (as free base)	50 mg
(b) (4)	
Dolutegravir sodium[a]	52.6
d-Mannitol	(b) (4)
Microcrystalline cellulose	
Povidone	
Sodium starch glycolate	
(b) (4	
Sodium stearyl fumarate	
(b) (4	
Total (mg/tablet)[d]	
	(b) ( )

d. The tablet shape for Phase III clinical tablets is a deep convex, the tablet shape for NDA Stability/Commercial tablets is normal convex. Both images are debossed with SV 572 on one side and 50 on the other side.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

DTG is an inhibitor of HIV integrase strand transfer and inhibits the integrase catalyzed viral DNA strand transfer with IC_{50} values in the nanomolar range (2.7 to 12.6 nM) *in vitro*. The applicant is seeking indications for DTG in combination with other antiretrovirals for the treatment of HIV-1.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dosing regimen of DTG, in combination with other antiretroviral therapy agents, for the treatment of HIV infection in adults and children ≥ 12 years of age (weighing at least 40 kg) is based on prior treatment experience. DTG can be taken without regard to meals.

- Treatment-naïve adults: DTG 50 mg once daily

- Treatment-experienced, integrase inhibitor-naïve adults: DTG 50 mg once daily
- Integrase inhibitor-experienced adults: DTG 50 mg twice daily
- Treatment-naïve or treatment-experienced, integrase inhibitor-naïve patients of 12 to < 18 years of age and weighing ≥ 40 kg: DTG 50 mg once daily

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant conducted the following clinical studies to support this NDA

- Twenty-nine *in vitro* studies investigating metabolic pathway using supersomes, microsomes and hepatocytes; the potential for CYP induction, inhibition, transporter inhibition (P-gp, OCT1, OCT2, OATP1B1. OATP1B3, MRP2 and BCRP), P-gp transport, and plasma protein binding were evaluated.
- Ten phase I studies including single and multiple ascending dose studies in healthy volunteers, food effect studies, tissue distribution, and relative bioavailability of various formulation and dosing regimens of DTG and a mass balance study.
- One hepatic impairment study conducted in subjects with moderate hepatic impairment and one renal impairment study conducted in subjects with severe renal impairment.
- One thorough QTc studies and one study investigating the effects of DTG on renal function.
- Seventeen drug interaction studies with commonly co-administered drugs in the patient population (other anti-retrovirals, oral contraceptive, methadone, antacids, and rifampin) and a sensitive CYP3A4 substrate (midazolam).
- Three phase 2 studies in which the safety and efficacy of DTG were evaluated (proof of concept and dose ranging studies).
- Four pivotal phase 3 studies (in the following populations: 2 in treatment naïve, 1 in treatment-experienced and INI-naïve, and 1 in INI-experienced).
- One pediatric study investigating the PK, safety and tolerability of DTG in adolescents
- Two PopPK analysis reports.
- One meta-analysis report for the effects of CYP/UGT polymorphism on the pharmacokinetics of DTG.

The key findings in efficacy and safety from Phase III pivotal trials are summarized below.

1. Phase III (ING113086)-SPRING2

Study design

ING113086 is a Phase III randomized, double-blind, double-dummy, active-controlled, multicenter, parallel group, fully-powered non-inferiority study in HIV-1 infected antiretroviral treatment (ART)-naïve subjects. Subjects were randomized 1:1 to receive DTG 50 mg once daily or raltegravir (RAL) 400 mg twice daily, both in combination with fixed-dose dual NRTI therapy

[either abacavir (ABC)/lamivudine (3TC) or tenofovir (TDF)/emtricitabine (FTC), selected by investigators] for 96 weeks.

Efficacy results

In this study, DTG has shown non-inferior efficacy and a safety profile similar to RAL; at 48 weeks, 88% of study participants on the DTG arm were virologically suppressed (<50 copies/mL) vs. 85% of participants on the raltegravir arm [no statistical difference, 95% CI; 2.5% (-2.2% to +7.1%)]. DTG performed as well as RAL regardless of baseline viral load or background dual NRTI. DTG performed as well as RAL across demographic subgroups, including race, gender, age, HIV risk factors, Baseline CD4+ cell count and Baseline CDC category. No treatment emergent primary INI or NRTI resistance mutations were observed for those subjects on DTG with PDVF (protocol defined virologic failure).

Table 2.2.1-1 Summary of study outcomes (HIV-1 RNA < 50c/mL) at week 48 (ITT-E population) in ING113086

Outcome at Week 48	DTG 50 mg once daily N=411 n (%)	RAL 400 mg BID N=411 n (%)
Virologic Success	**361 (88)**	**351 (85)**
Virologic Non-Response[a]	**20 (5)**	**31 (8)**
Data in window not <50 c/mL	8 (2)	5 (1)
Discontinued for lack of efficacy	5 (1)	13 (3)
Discontinued for other reason while not <50 c/mL	2 (<1)	11 (3)
Change in ART	5 (1)	2 (<1)
No Virologic Data at Week 48	**30 (7)**	**29 (7)**
Discontinued due to Adverse Event or Death	9 (2)	6 (1)
Discontinued for Other Reasons	21 (5)	23 (6)

Safety results

DTG demonstrated a safety and tolerability profile that was similar to that of RAL over the period of the study. Based on Week 48 data, the most commonly reported clinical AEs among subjects in both study groups were nausea, headache, diarrhea and nasopharyngitis, with no appreciable difference between treatment groups. Preclinical evidence for GI toxicity with DTG use did not translate into significant clinical findings for DTG in this trial.

2. Phase III (ING114467)-SINGLE

Study design

This was a randomized, double-blind, double-dummy, active-controlled, multicenter, parallel group non inferiority study to assess safety and efficacy of DTG plus ABC/3TC fixed dose combination therapy versus Atripla® (a fixed dose combination product of efavirenz, emtricitabine, and tenofovir disoproxil fumarate) over 48 weeks in HIV-1 infected ARV naïve patients.

Efficacy Results

At 48 weeks, 88% of study participants on the DTG + ABC/3TC regimen were virologically suppressed (<50 copies/mL) vs. 81% of participants on the single tablet regimen Atripla [difference and 95% CI were 7.4% (+2.5% to +12.3%), p=0.003]. The differences in efficacy were primarily driven by a higher rate of discontinuation due to AEs on the Atripla arm. Response rates on DTG+ABC/3TC and Atripla were consistent across the baseline stratification factors (i.e., viral load and CD4+ cell count) as well as demographic subgroups (race, gender, age, baseline CDC category). CD4+ recovery was significantly higher in the DTG + ABC/3TC arm at Week 48. No treatment emergent primary INI or NRTI resistance mutations were observed for those subjects on DTG + ABC/3TC with protocol defined virologic failure (PDVF).

Table 2.2.1-2 Summary of study outcomes (plasma HIV-1RNA < 50 c/mL) at week 48 snapshot analysis (ITT-E population) in ING114467

Outcome at Week 48	DTG 50 mg once daily N= 414 n (%)	Atripla once daily N=419 n (%)
Virologic Success	**364 (88)**	**338 (81)**
Virologic Non-Response[a]	**21 (5)**	**26 (6)**
Data in window not <50 c/mL	6 (1)	5 (1)
Discontinued for lack of efficacy	7 (2)	9 (2)
Discontinued for other reason while not <50 c/mL	8 (2)	12 (3)
No Virologic Data at Week 48	**29 (7)**	**55 (13)**
Discontinued due to Adverse Event or Death	9 (2)	40 (10)
Discontinued for Other Reasons	20 (5)	14 (3)
Missing data during window but on study	0	1 (<1)

Safety Results

DTG+ABC/3TC showed a safety and tolerability profile that was generally favorable to that of Atripla over the period of the study. The superiority of the DTG+ABC/3TC efficacy response rate was due to a higher rate of discontinuation due to adverse events (AEs) or death on the Atripla arm; specifically from the psychiatric disorders, nervous system disorders, gastrointestinal disorders and general disorders. Nervous system and psychiatric disorders were more frequent with Atripla, with the exception of insomnia, which was more frequent with DTG+ABC/3TC.

3. Phase III (ING111762)-SAILING

Study Design

This was a randomized, double-blind study of the safety and efficacy of DTG 50 mg once daily versus raltegravir 400 mg twice daily, both administered with an investigator-selected background regimen (based on screening and historic resistance results) over 48 weeks in HIV-1 infected

integrase inhibitor-naïve, antiretroviral therapy-experienced adults. The background therapy was limited to no more than two antiretroviral agents.

Efficacy Results

There was a statistically significant difference in favor of DTG (79%) compared to the RAL treatment group (70%) using the Snapshot algorithm of the proportion of subjects with plasma HIV-1 RNA < 50c/mL at week 24. The adjusted treatment difference was 9.7% [90% CI (93.4, 15.9), p=0.003]. The subgroup analysis indicated that the overall treatment difference in favor of DTG was maintained across the subgroups (baseline HIV-1 RNA, gender, and race) except subjects > 50 years old (comparable between DTG and RAL) or subjects with less than 70% adherence (assessed by a pill count).

DTG exhibited a higher barrier to treatment failure than RAL; the proportion of subjects harboring virus with evidence of INI resistance by week 24 was statistically greater for RAL compared to DTG, with 0.6% (2/354) of subjects receiving DTG and 2.8% (10/361) of subjects receiving RAL harboring treatment emergent genotypic or phenotypic INI resistance at the time of protocol-defined virologic failure.

Table 2.2.1-3 Summary of study outcomes (HIV-1 RNA < 50 copies/mL) at week 48 (ITT-E population) in ING111762

	DTG N=354	RAL N=361
Virologic Success	**281 (79%)**	**252 (70%)**
Virologic Failure	**53 (14%)**	**86 (24%)**
Data in window not below threshold	40 (11%)	66 (18%)
Discontinued for lack of efficacy	2 (<1%)	4 (1%)
Discontinued for other reason while not below threshold	7 (2%)	6 (2%)
Change in ART	4 (1%)	10 (3%)
No Virologic Data at Week 24	**20 (6%)**	**23 (6%)**
Discontinued due to AE or Death	6 (2%)	9 (2%)
Discontinued for Other Reasons	12 (3%)	11 (3%)
Missing data during window	2 (<1%)	3 (<1%)

Safety Results

The safety profile for DTG was similar to RAL, with similar rates of occurrence in both arms. The most common AEs were diarrhea, nausea, vomiting, and fatigue. The rates of discontinuation due to AEs were low for both arms (2% in DTG, 4% in RAL)

4. ING112575 (VIKING-3)

Study design

This study is a multicenter, single arm, open-label study to assess the antiviral activity and safety of a DTG containing regimen in HIV-1 infected, ART-experienced adults who have experienced virological failure on an INI containing regimen with historical or current evidence of genotypic and/or phenotypic resistance to RAL or EVG. Subjects must have had documented genotypic and/or phenotypic resistance to at least one compound in two or more of the other approved classes of ART but must also have been able to include at least one active drug in the OBR (optimized background regimen) to be commenced at Day 8.

Efficacy Results

The majority of subjects with RAL and/or EVG resistant virus showed a response to DTG 50 mg BID administered with failing background therapy on Day 8 and with OBR thereafter. The mean HIV-1 RNA reduction at Day 8 was 1.4 log10 c/mL and 63% achieved <50 c/mL by Week 24. Immune recovery was observed with median $CD4^+$cell increase of 65 cells/mm^3 at Week 24.

Multivariate analyses indicated baseline resistance to DTG to be the strongest predictor of response at both Day 8 and Week 24. Higher FC (fold change) in susceptibility to DTG and the presence of virus with Q148+2 mutations significantly reduced the antiviral responses. Please refer to section 2.2.4 for detailed information.

Table 2.2.1-4 Summary of study outcomes (HIV-1 RNA < 50c/mL) at week 24 (ITT-E population) in ING112575

Outcome	50 mg DTG BID N=114 N (%)
Virological success	72 (63)
Virological Failure (Non-response)	
Data in window not below threshold (< 50c/mL)	37 (32)
Discontinued for lack of efficacy	23 (20)
Discontinued for other reason while not below threshold	6 (5)
Change in ART	2 (2)
	6 (5)
No virological data at week 24	5 (4)
Discontinued study due to AE or death	5 (4)

Safety Results

DTG 50 mg BID was well tolerated in this INI-experienced population. The safety profile observed for DTG 50 mg BID in INI-experienced subjects was similar to that described for DTG 50 mg once daily from 48 Week data in ARV-naive subjects participating ING113086 and ING114467.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint was the proportion of subjects achieving and maintaining HIV-1 RNA < 50 copies/mL through Week 48. The quantitation of plasma HIV-1 RNA has been validated as a surrogate marker for the efficacy of HIV-1 drugs.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Plasma DTG concentration and its major metabolite (DTG-glucuronide) were measured using validated HPLC-MS/MS methods. Other medications used in drug interaction studies were also all measured using validated analytical methods.

2.2.4 Exposure-response

2.2.4.1 What are characteristics of the exposure response relationships (dose-response, concentration-reponse) for efficacy? Does the dolutegravir (DTG) exposure-response relationship with virologic outcome (percent of subjects <50 HIV-1 copies/mL at week 48) support the selected DTG dose in treatment-naïve, treatment-experienced/integrase naïve, and treatment-experienced/ integrase-experienced HIV-1 infected subjects?

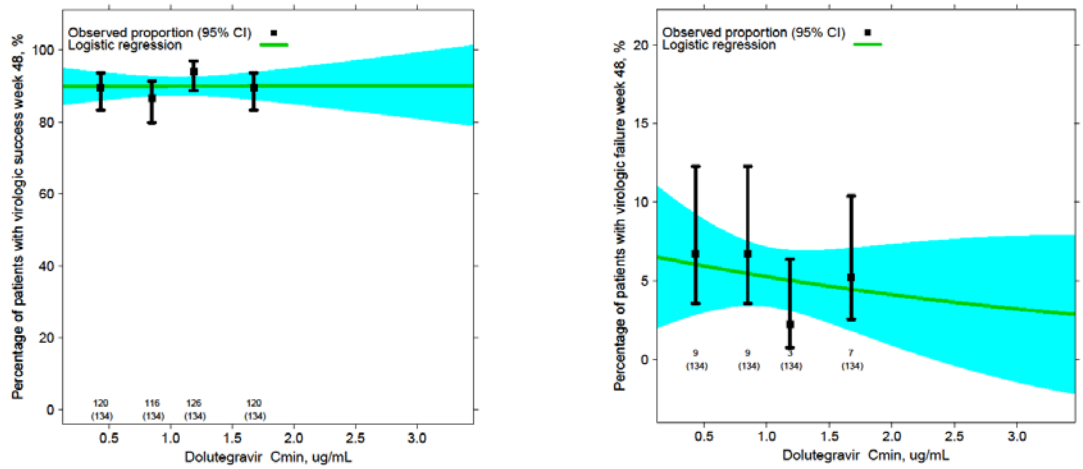
Yes, the trials conducted by the applicant in treatment-naïve and treatment-experienced/ integrase-naïve subjects supports DTG 50 mg QD, though addition DTG dose adjustments (DTG 50 mg BID) are recommended for subjects on regimens containing fosamprenavir. In addition, the results of the applicant's Phase IIb and Phase III trial in treatment-experienced/integrase inhibitor-experienced subjects support the use of DGT 50 mg BID in this population. Details of the exposure-response analyses for each of these populations is described more below.

Treatment-naïve

The applicant conducted three Phase IIb and III trials (ING112276, ING113086, and ING114467) in treatment-naïve HIV-1 infected subjects to support the selected DTG 50 mg QD dose. ING114467 did not include DTG PK collection and was excluded from this exposure-response analysis. ING112276 included DTG PK from 141 subjects (out of 155) administered DTG 10, 25, or 50 mg QD with a background NRTI regimen of tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC). ING113086 included DTG PK from 403 subjects (out of 411) administered DTG 50 mg QD with a background NRTI regimen of TDF/FTC or ABC/3TC. Using DTG PK data from ING112276 and ING113086, a flat exposure response was observed over the DTG exposure range (Figure 2.2.4.1-1, left). Geometric mean C_{0h} for DTG 10, 25, and 50 mg QD was 0.31, 0.53, and 1.11 µg/mL, respectively, with a model predicted response rate of 90-91% over the exposure range. These predictions are similar to those observed from the combined study results in subjects with PK data available (89-91% over DTG 10, 25, and 50 mg QD). The predicted virologic response in the lowest DTG exposure quartile was 90% which was within the range of response rates for all other quartile with higher DTG exposure (82-94%).

The only significant factors for predicting virologic success were baseline viral load (higher baseline viral load associated with a lower response rate) and baseline $CD4^+$ count (lower $CD4^+$ count was associated with a lower response rate); however, these are known covariates that impact response based and do not necessitate any DTG dose adjustments. A flat exposure-response relationship was also identified between virologic failure and DTG C_{0h} (Figure 2.2.4.1-1, right). Similar flat-exposure response relationships were observed for virologic success and virologic failure when using DTG AUC as the independent variable. There was insufficient data regarding baseline DTG susceptibility (e.g., EC_{50}; n=20) to evaluate relationships between EC_{50} and response from the treatment-naïve trials.

Figure 2.2.4.1-1:
Percentage of Subjects Achieving Virologic Success (<50 Copies/mL, left) and Virologic Failure (right) Versus DTG C_{0h} from ING112276 and ING113086.



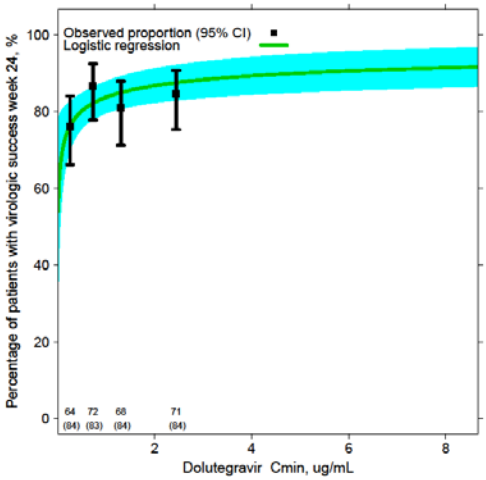
Treatment-experienced/integrase-naive

The applicant conducted one Phase III trial (ING111762) in treatment-experienced/integrase-naive HIV-1 infected subjects to support the selected DTG 50 mg QD dose. ING111762 included DTG PK from 335 subjects (out of 354) administered DTG 50 mg QD with an investigator selected background consisting of at least two drugs, one of which was considered fully active by susceptibility assessment. Based on initial general additive model (GAM) evaluation, subjects with one or more PK samples below the limit of quantification, baseline $CD4^+$ count, and DTG C_{0h} were identified as factors influencing virologic success.

Evaluation of response with respect to EC_{50} could not be performed for this trial due to the limited number of subjects with baseline EC_{50} data available (n=22). The univariate exposure-response for virologic success versus DTG C_{0h} is shown below in Fig 2.2.4.1-2 and confirms the initial observation that subjects with lower exposure, primarily in the lowest exposure quartile (median C_{0h} in first quartile was 0.26 µg/mL), had lower response rates (76%) compared to the reminder of the population (response rates ranging between 81-87% across the remaining quartiles). Of note, the DTG C_{0h} in this first quartile is similar to the median DTG C_{0h} observed following DTG 10 mg QD.

Figure 2.2.4.1-2: Percentage of Subjects Achieving Virologic Success (<50 Copies/mL) Based on All

Subjects Versus DTG C_{0h} from ING111762.



Closer inspection of the subjects with the lowest DTG C_{0h} indicated that such subjects were more likely to have one or more on treatment BLQ measurements or have been on a CYP3A inducer (e.g., tipranavir, fosamprenavir, efavirenz). In all, there were 28 subjects with one or more DTG PK BLQ measurements on treatment and 26 subjects on an inducer (3 subjects had a BLQ measurement and were on an inducer for a total of 51 subjects with either a BLQ measurement or on an inducer). Seventeen of the 28 subjects (61%) were in the first DTG exposure quartile while 22 of 26 (85%) of subjects on an inducer were in the first DTG exposure quartile. As expected, the DTG exposure for these subgroups was lower than that observed for the remainder of the population (Table 2.2.4.1-1). In addition, the observed geometric C_{0h} for subjects with one or more BLQ measurements (possibly indicative of a lack of adherence) was overall similar to the observed DTG exposures in subjects on a CYP3A inducer in their regimen.

Table 2.2.4.1-1: Geometric DTG C_{0h} and Response Rate for Subjects from ING111762 According to Whether the Subject was on An Inducer or Had A BLQ Measurement

Category	Geometric Mean C_{0h}, µg/mL	Response %
DTG (all, n=335)	0.85	79%
DTG (no inducer/no BLQ, n=286)	1.04	81%
DTG (BLQ, n=28)	0.24	57%
DTG (inducer, n=26)* TPV/rtv, EFV, FPV/rtv	0.20	73%
DTG (EFV, n=13)	0.17	62%
DTG (FPV, n=11)	0.28	73%
DTG (DRV, n=140)	0.70	84%

* The analysis included one subject who mistakenly took etravirine (a strong inducer)

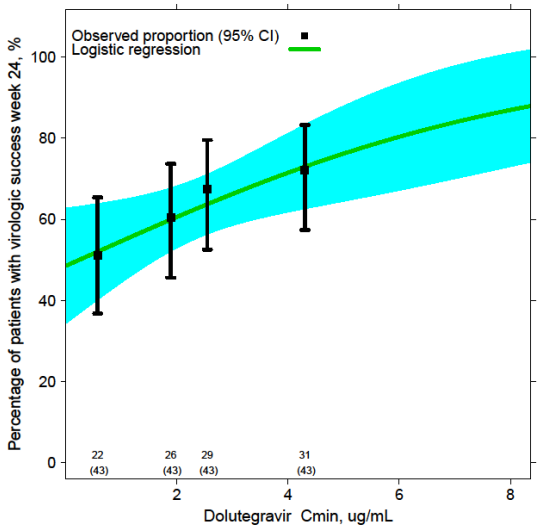
Based on the observed PK and response data from the trial, the applicant proposed using DTG 50 mg BID in subjects with a background regimen including an inducer such as efavirenz or tipranavir. This is supported by the PK observations and response data from ING111762. The applicant did not propose DTG dose adjustment when used with fosamprenavir as the response rate in this subgroup was closer to that of the overall treatment population. However, due to the lower exposure observed in this treatment group, the review team recommends increasing the DTG dose to 50 mg BID when coadministered with fosamprenavir. This recommendation is based on the DTG C_{0h} (0.2 µg/mL) observed and the slightly lower response rate (73%) observed among subjects receiving fosamprenavir.

Also included in the summary table was the DTG PK and response when coadministered with DRV/rtv. DTG PK was slightly reduced in this group compared to subjects from ING111762 who were not coadministered an inducer and who did not have a BLQ measurement on treatmnet (0.70 versus 1.04 µg/mL) but there was no difference in the response rate (84% versus 81%). As such, the review team does not recommend an increase in DTG dose from 50 mg QD to 50 mg BID when coadministered with DRV. Please refer to section 2.4.2.8 for detailed information on drug interactions and dose adjustment recommendations.

Treatment-experienced/integrase inhibitor-experienced

The applicant conducted a Phase IIb and III trial (ING112961 and ING112574) in treatment-experienced/integrase inhibitor-experienced HIV-1 infected subjects to support the selected DTG 50 mg BID dose. ING112961 included DTG PK from 51 subjects (out of 51) administered DTG 50 mg QD or BID given in combination with at least one active agent in the optimized background. ING112574 included DTG PK from 183 subjects (out of 183 subjects; efficacy data was only available through week 24 for 114 subjects) administered DTG 50 mg BID in combination with at least one active agent in the optimized background. Based on initial analysis, DTG C_{0h}, baseline $CD4^+$ count (lower baseline associated with lower response), and viruses with Q148 and 2 or more additional integrase inhibitor mutations were identified as predictors of virologic response. Upon closer inspection the dependence of C_{0h} as a predictive factor for virologic response at week 24 was driven by the 50 mg QD treatment arm from ING112961. The response observed in the lowest quartile (51%) was, as would be expected, comprised of subjects predominantly from the 50 mg QD treatment arm (41%, n/N=11/27, C_{0h} 1.14 µg/mL) while a higher response rate was observed in the upper quartiles consisting of subjects administered 50 mg BID (response rate 63-68%; C_{0h} 2.29 µg/mL). This observation supports the use of 50 mg BID in the treatment-experienced/integrase inhibitor-experienced population

Figure 2.2.4.1-3: Percentage of Subjects Achieving Virologic Success (<50 Copies/mL) Versus DTG C_{0h} from ING112961 and ING112574. Two DTG Doses (50 mg QD and 50 mg BID) Were Included in This Analysis (Geometric Mean C_{0h} 1.14 and 2.29 µg/mL, Respectively)



If the subjects that were administered DTG 50 mg QD are removed from the analysis, a relationship between inhibitory quotient (IQ) values [the IQ is the ratio of C_{0h} (exposure) at steady state and EC_{50} (a measurement of the ability of DTG to inhibit HIV-1 virus)] and virologic success was observed (Fig 2.2.4.1-4); however, this relationship is primarily dependent on the baseline susceptibility of the virus and to a lesser extent DTG exposure. This observation is illustrated in Table 2.2.4.1-2 where a 7-fold difference in EC_{50} was noted between the first and fourth inhibitory quotient compared to a 2-fold difference in C_{0h} across the same quartiles.

Figure 2.2.4.1-4: Percentage of Subjects Achieving Virologic Success (<50 Copies/mL) Versus DTG IQ from ING112961 and ING112574 (only 50 mg BID).

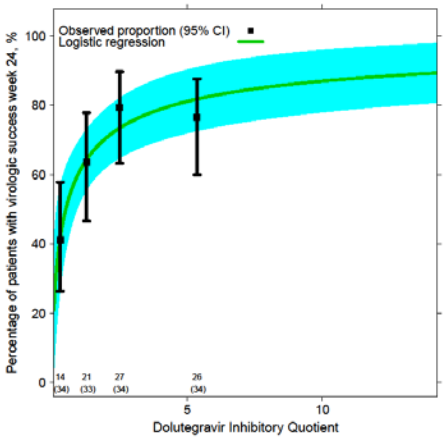


Table 2.2.4.1-2: Median DTG C_{0h} and EC_{50} for Each IQ Quartile from ING112961 and ING112574 (only 50 mg BID)

Quartile	C_{0h}, µg/mL	EC_{50} µg/mL
1st	1.84	5.11
2nd	2.25	1.38
3rd	2.34	0.96
4th	3.86	0.71

This observation is further illustrated by evaluating the geometric mean inhibitory quotient values for subjects who achieved virologic success (responders) compared to subjects who did not achieve virologic success (nonresponders) (1.09 versus 1.84) compared to the geometric mean C_{0h} (2.48 versus 2.31 µg/mL). Essentially, responders and nonresponders administered DTG 50 mg BID had similar exposures, but divergent responses. A final analysis illustrating the importance of baseline susceptibility on treatment response in treatmentent-experienced/integrase-experienced subjects is shown in Table 2.2.4.1-3. A decrease in overall response rate was observed between those subjects with a Q148 mutation and one or more additional integrase inhibitor mutations (19-43% [categories [1] and [2])] and the remaining subjects [74-83% (categories [3] and [4])] despite similar exposure across the treatment groups (DTG C_{0h}: 2.26-2.53 µg/mL). However, a decreasing trend in IQ values was observed across the category labeled [4] to [1], which must be driven by EC_{50} (baseline viral susceptibility) based on how IQ is defined. The observations in this table suggests that if IQ is the primary factor for efficacy then increasing DTG C_0 3-fold in subjects with a Q148 mutation may be sufficient to achieve response rates similar to those subjects without Q148 mutations. However, the review team ultimately did not recommend for evaluation of a higher DTG dose in such subjects as DTG doses necessary to achieve DTG C_0 values of the required magnitude have not been evaluated. In addition, there is saturable absorption of DTG with higher individual doses, which may necessitate DTG doses >150 mg BID in order to achieve the desired C_0 values.

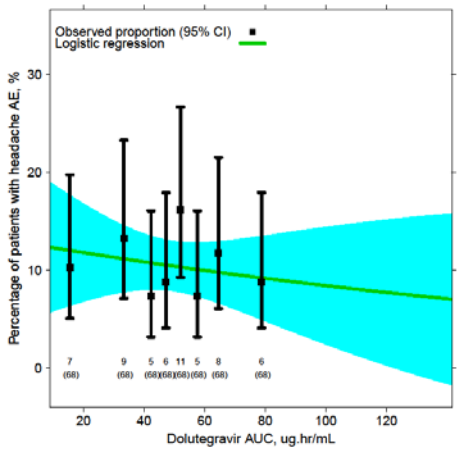
Table 2.2.4.1-3 Geometric Mean DTG C_{0h}, IQ, and Response Based on Four Mutation Categories from ING112961 and ING112574 (only 50 mg BID)

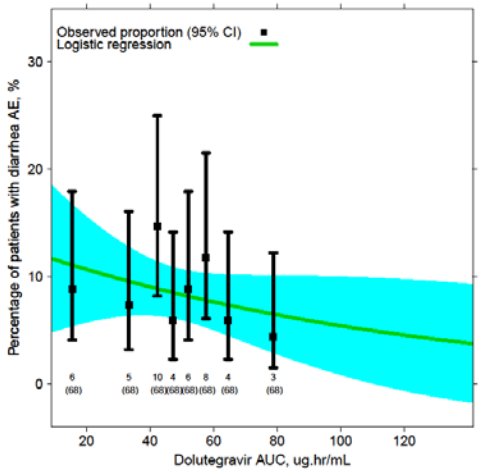
Category	IQ	C_{0h} (µg/mL)	Outcome
[1] Q148+2 or 2+ primary	0.42	2.26	19% (3/16)
[2] Q148 + 1	0.70	2.30	43% (10/23)
[3] All groups with other mutations	2.07	2.53	83% (39/47)
[4] No primary mutations	2.92	2.31	74% (28/38)

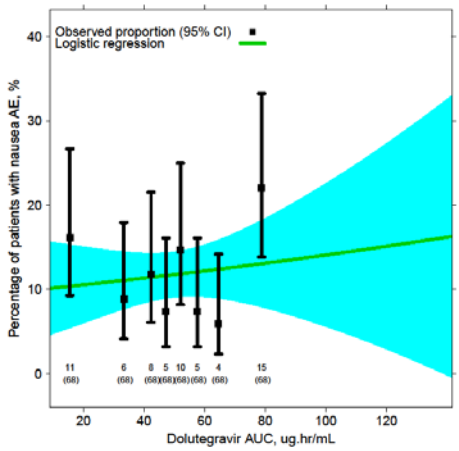
2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration response) for safety? -Is there evidence of DTG exposure-safety relationships for headache, nausea, or diarrhea (adverse events of interest from the Phase III trials)

An exposure-response relationship could not be established for headache, nausea, or diarrhea and DTG exposures. Logistic regression models were evaluated for DTG C_{max}, $C_{0h,}$ and AUC_{τ} based on data from ING112276 and ING113086 in treatment naïve subjects with no significant relationships identified. Modeling results for adverse event rates versus DTG AUC_{τ} are shown below.

Figure 2.2.4.2-1: Percentage of Subjects with Headache (top left), Diarrhea (top right), and Nausea (bottom left) Adverse Events Versus DTG AUC_{τ} for Treatment Naïve Subjects from ING112276 and ING3086







An exposure-response analysis on changes in renal function versus DTG exposure was also conducted as elevations in serum creatinine and subsequently, reduced estimated glomerular filtration rate (eGFR), was observed in the DTG treatment arms. No relationship between DTG dose (50 mg QD or 50 mg BID) or exposures (C_{0h}) with serum creatinine change from baseline or change in eGFR were observed based on the available DTG pharmacokinetic data. The onset of on-treatment serum creatinine increases with DTG was rapid with the largest increases occurring over the first 1-2 weeks of treatment. The mean increase in

serum creatinine for DTG 50 mg QD at week 2 ranged between 0.11-0.13 mg/dL (standard deviation range: 0.09-0.17 mg/dL) which was similar to the mean increase in serum creatinine for DTG 50 mg BID at week 2 (0.12 mg/dL: standard deviation: 0.13 mg/dL).

2.2.4.3 Does this drug prolong the QT or QTc interval?

A thorough QTc trial in healthy subjects was conducted using a single supratherapeutic dose of DTG 250 mg (Study ING111856). No significant QTc prolongation effect of DTG was detected. For the primary endpoint, QTcF, all time-matched values and their corresponding upper bounds of the 90% CI were below 10 msec after DTG administration. The maximum observed time-matched change from Baseline in QTcF for DTG 250 mg was at 4 hours (2.4 msec, 90% CI: -0.2, 4.9 msec). The maximum observed time-matched change from baseline in QTcF for moxifloxacin in this study was at 4 hours (10.0 msec, 90% CI: 7.5, 12.6 msec).

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

Please refer to Table 2.2.5.2-1 and 2.2.5.2-2

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

No study has been performed to directly compare the PK parameters of DTG in HIV-1 positive patients *vs.* healthy subjects. However, based on accumulated data and meta-analysis, it appears that there is no significant difference in pharmacokinetics between healthy and HIV-infected subjects. DTG exposure from 50 mg twice daily dosing appears to be lower in HIV-1infected subjects (integrase inhibitor-experienced) than in healthy subjects, and this is likely due to the wide use of inducers (e.g. DRV/rtv) in the background regimen and in the treatment-experienced HIV-1-infected subjects.

Table 2.2.5.2-1 Summary of DTG PK parameters following single dose of 50 mg tablet administration in healthy and HIV infected subjects

Population	Data Source	Cmax (µg/ml)	AUC(0-τ) (µg h/mL)	C24 (µg/ml)	CL/F (L/h)	Vz/F (L/h)	t½ (h)
Healthy	Phase I Meta- analysis	2.20 (43)	43.7 (45)	0.65 (49)	1.14 (45)	23.3 (45)	14.4 (19)
HIV-1 Infected[#]	ING111521 n=10	2.46 (32)	40.5 (33)	0.59 (31)	1.23 (33)	ND	11.2 (29)

Data presented are geometric mean (CV%)

#: Subjects received DTG without background antiretroviral regimens.

Table 2.2.5.2-2 Summary of DTG PK parameters following multiple dose of 50 mg tablet administration in healthy and HIV-infected subjects (meta-analysis by the applicant)

Population	DTG Dosing Regimen	Cmax (µg/ml)	AUC(0-τ) (µg h/mL)	AUC(0-24) (µg h/mL)	Cτ (µg/mL)
Healthy	50 mg once daily (overall)	3.62 (35)	49.1 (41)	49.1 (41)	1.05 (56)
	50 mg once daily (fasted)	2.90 (34)	38.4 (40)	38.4 (40)	0.79 (59)
	50 mg once daily (fed)	4.21 (27)	58.2 (30)	58.2 (30)	1.28 (41)
Healthy	50 mg twice daily (overall)	6.00 (39)	53.0 (42)	106 (42)	3.02 (52)
	50 mg twice daily (fasted)	5.33 (38)	47.1 (42)	94.3 (42)	2.66 (53)
	50 mg twice daily (fed)	7.77 (23)	68.6 (27)	137 (27)	4.00 (36)
HIV-1 infected	50 mg once daily (no food restriction)	3.67 (20)	53.6 (27)	53.6 (27)	1.11 (46)
HIV-1 infected	50 mg twice daily (no food restriction)	4.15 (29)	37.5 (35)	75.1 (35)	2.12 (47)

Data presented are geometric mean (CV%)

2.2.5.3 What are the characteristics of drug absorption? *(This may include discussion of transporter or pH effect.)*

DTG is absorbed following oral administration with no absorption lag time. The median tmax is 2-3 hours post dose. The AUC is increased with co-administration of food by 33%, 41%, and 66% when 50 mg DTG was administered with low fat, moderate fat, and high fat food, respectively. The food effect is not considered clinically significant and all pivotal Phase III trials were conducted without regard to food. Please refer to section 2.5.3 for detailed information of food effects on DTG PK.

DTG is a 2-metal-binding integrase inhibitor and the mechanism of action involves binding to magnesium in the active site of the integrase enzyme. As such, DTG is susceptible to chelation-type drug interactions with polyvalent cations. Accordingly, the applicant conducted a drug interaction study with Maalox and multivitamins (ING111602).

DTG absorption is significantly decreased by co-administration of polyvalent cation containing antacids (e.g., Maalox), likely due to chelation. The exposure of DTG was decreased more than 70% when DTG was administered with Maalox simultaneously. When Maalox was administered 2 hour after DTG, the interaction was attenuated to a 25% decrease in AUC. The applicant did not evaluate when DTG can be administered if Maalox is administered prior to DTG. However, based on previous experience with other drugs forming a chelation complex with antacids (e.g., quinolones), administration of DTG 6 hours after administration of antacids is considered to be a sufficient amount of time to avoid significant interactions. The effects of antacids are not thought to be due to changes in pH. No significant drug interaction was

observed when DTG was co-administered with omeprazole (study ING112941). The AUC of DTG was also decreased by approximately 35% when DTG was administered with a multivitamin (One A Day Maximum). The applicant concluded that the magnitude of change is not considered clinically relevant.

The review team also suggests using the same recommendation when DTG is administered with oral iron supplements, oral calcium supplements, and buffered medications such as didanosine pediatric formulation and aspirin.

Table 2.2.5.3 Summary of DTG PK following a single dose of DTG with Maalox or a multivitamin (One A Day Maximum)

Treatment Regimen	N	AUC(0-t) (hr*µg/mL)	AUC(0-∞) (hr*µg/mL)	CL/F (L/hr)	Cmax (µg/mL)	C24 (µg/mL)	t1/2 (hr)	tlag (hr)	tmax[2] (hr)
GSK1349572	16	34.55 (31)	35.6 (33)	1.40 (33)	2.03 (25)	0.51 (38)	13.7 (15)	0.00	2.50 (0.50-8.00)
GSK1349572 + Multivitamin	16	23.07 (29)	23.74 (30)	2.11 (30)	1.31 (25)	0.34 (33)	13.52 (12)	0.00	2.50 (0.50-8.00)
GSK1349572 + Maalox	16	9.11 (36)	9.40 (36)	5.32 (36)	0.56 (29)	0.13 (41)	13.8 (15)	0.00	2.50 (0.50-8.00)
GSK1349572 2 hours prior + Maalox	16	25.66 (44)	26.33 (45)	1.90 (45)	1.67 (51)	0.36 (42)	13.31 (13)	0.00	2.50 (0.50-8.00)

2.2.5.4 What are the characteristics of drug distribution? *(Include protein binding)*

Volume of distribution

The apparent volume of distribution was estimated at 12.5 L in the human mass balance study (ING111853, following 20 mg administration of suspension formulation) and 17.4 L based on the PopPK analysis (following 50 mg administration of tablet formulation). The estimated Vd/F is greater than the total plasma volume (approximately 3 L for a 70-kg person), but similar to the volume of total water in the extracellular space (approximately 15 L for a 70-kg person). The mass balance study (ING111853) results indicated that there is a minimal association of DTG with blood cellular components; The mean blood:plasma concentration ratios of radiolabeled DTG ranged from 0.441 to 0.535 over the timecourse evaluated (0.5 hr to 72 hr post-dose).

Plasma protein binding

DTG is highly bound to plasma proteins. The unbound fraction of DTG was determined in 3 clinical studies (ING113097, ING113125, and ING116070). The free fraction of DTG in plasma is estimated at ~0.23% to 1.10% in healthy subjects, ~0.4 to 0.5% in subjects with moderate hepatic impairment, 0.84 to 1.01% in subjects with severe renal impairment, and 0.49% in HIV-positive subjects. Binding was independent of DTG concentrations over the therapeutic range. The results are comparable with *in vitro* protein binding study results (~99.3%).

The specific types of proteins to which DTG is bound have not been directly characterized. However, DTG appears to primarily bind to albumin rather than α-1 acid glycoprotein (AAG) based on the following observation; the DTG unbound fraction appeared to be better correlated with albumin than AAG in Study ING113097. The in *vitro* study evaluating the protein binding effect of both human serum albumin and AAG on the antiviral activity of DTG indicated that DTG binding to AAG is minimal in comparison with its binding to albumin (RH2007/00071/00).

Table 2.2.5.4-1 Summary of unbound fraction of DTG in plasma estimated in clinical studies

Study	ING113097		ING113125		ING116070
Subject Population	Healthy match	Moderate Hepatic Impairment	Healthy match	Severe Renal Impairment	HIV-1 infected
n	8	8	8	8	12
Unbound fraction,%	3hr: 0.23 (0.2, 0.3) 24hr: 0.23 (0.2, 0.3)	3hr: 0.58 (0.2, 0.8) 24hr: 0.48 (0.2, 0.6)	3hr: 0.87 (0.8, 0.9) 24hr: 1.10 (1.0, 1.3)	3hr: 0.84 (0.6, 1.4) 24hr: 1.01(0.7, 1.7)	2-6hr: 0.49 (0.33, 0.65)

Data source: ING113097, Table 11.3; ING113125, Table 11.3; ING116070, Table 9.3.
Data presented are median (range).

Tissue distribution

The applicant conducted 3 studies determining the specific tissue distribution of DTG (cerebrospinal fluid, female genital tract, and male genital tract). DTG is present in cerebrospinal fluid (CSF) at levels similar to the unbound concentration of DTG in plasma (median 18 ng/mL, ranging from 4 ng/mL to 232 ng/mL) after 2 weeks of DTG administration (50 mg daily) in 11 HIV-1 patients. The CSF to plasma concentration ratio of DTG ranged from 0.11% to 0.66% (ING116070). DTG is also present in the female and male genital tract. DTG AUC in cervicovaginal fluid, cervical tissue, and vaginal tissue was 6 to 10% of that in corresponding plasma at steady-state. AUC in semen and rectal tissue were 7% and 17%, respectively, of that in corresponding plasma at steady-state.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Hepatic elimination is thought to be the major route of elimination of DTG based on the mass balance study (ING111853). Renal elimination of unchanged DTG is less than 1% of the total dose administered (please refer to 2.2.5.6 and 2.2.5.7).

2.2.5.6 What are the characteristics of drug metabolism? ***(This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.***

Following oral administration of DTG in humans, DTG is primarily eliminated via hepatic/bile route, and renal elimination of unchanged DTG represents less than 1% of the total dose administered (ING111853).

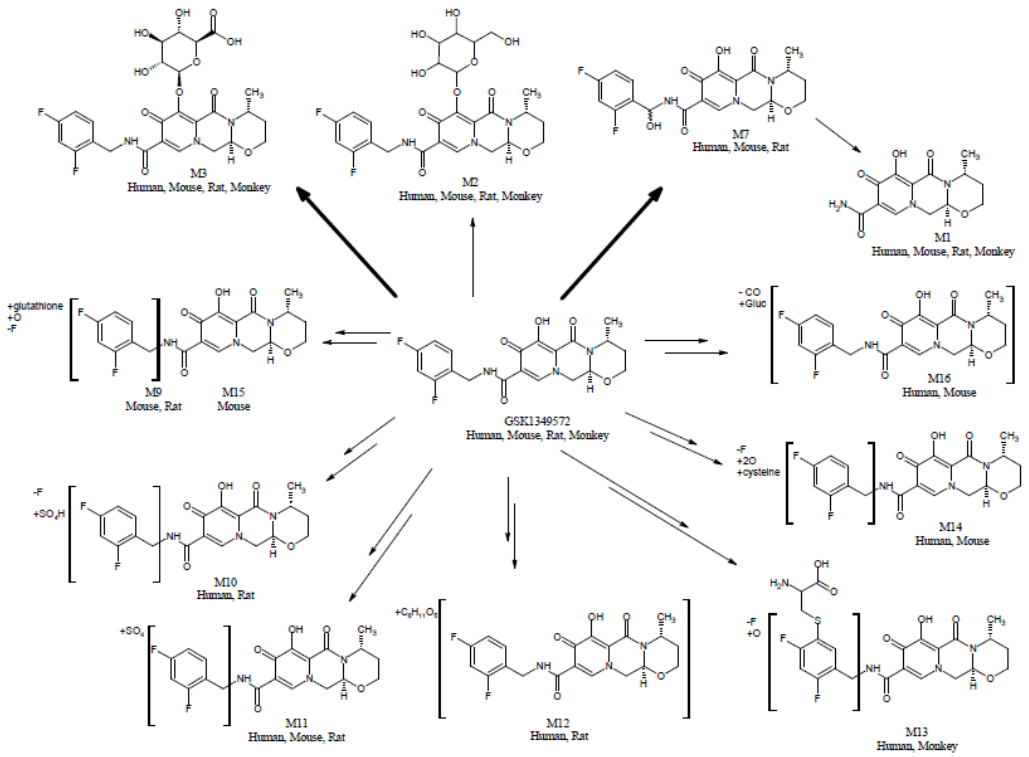
In vitro metabolism assays, as well as the metabolites detected in the mass balance trial, suggest that UGT1A1 is the primary route of metabolism and CYP3A4 is a minor route in humans.

The major metabolite in urine is an ether glucuronide of DTG (M3, representing 18.9% of the total dose administered), followed by an N-dealkylation metabolite (M1), a product from oxidation at the benzylic carbon (M7), and a product of oxidative defluorination with cysteine addition (M13). The enzymes responsible for the formation of M3 are UGT1A1 (major), UGT1A3 (minor) and UGT1A9 (minor). Although DTG-glucuronide is the major metabolite in the plasma, DTG is still the major circulating component in plasma. M3 is present at a mean value of <1% of DTG in healthy volunteers without an enzyme inducer.

The total radioactivity of the metabolites formed through oxidation (M1, M7, and M13) that are recovered in urine and feces accounts for approximately 9.7% of the total dose administered. The enzyme responsible for forming M7 is CYP3A4, while the enzyme responsible for forming M13 is unknown. M1 is formed by hydrolysis of M7.

DTG has a terminal half-life of approximately 14 hours and a low apparent oral clearance (CL/F) of 0.56 L/hr, which represents <2% of liver plasma flow; therefore, the hepatic extraction ratio is low (lower than 2%). As CYP3A4 is a minor route of elimination of DTG (less than 10%), the first-pass metabolism of DTG following oral administration is expected to be low.

Fig 2.2.5.6 Metabolic scheme of DTG in human and nonclinical species



2.2.5.7 What are the characteristics of drug excretion?

DTG has a terminal half-life of approximately 14 hours. Following oral administration, unchanged DTG is primarily eliminated by the hepatic route. 53% of the total oral dose is excreted as unchanged DTG in the feces. It is unknown if all or part of the parent compound in feces is due to unabsorbed drug or biliary excretion of the glucuronide conjugate, which can be converted back to the parent compound in the gut lumen. 31% of the total oral dose is excreted in the urine; the major form of urine DTG is glucuronide DTG (18.9% of total dose), N-alkylation metabolite (3.6% of total dose), and a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose) (ING111853). Renal elimination of unchanged DTG is less than 1% of the total dose administered.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The linearity of DTG PK is dependent on dose and formulation. DTG exhibited linear pharmacokinetics following a single oral dose of 2 to 100 mg DTG in suspension (ING111207), but it appears to be less

than dose proportional between 100 mg and 250 mg (ING112941 and ING111856). Increase in DTG exposure with the tablet formulation appears dose proportional from 25 mg to 50 mg (ING112276) but less than dose proportional from 50 mg to 100 mg (ING114005).

Table 2.2.5.8-1 Summary of DTG PK following a single dose of DTG in suspension

Study ID	Dose	N	C_{max} (µg/mL)	$AUC_{(0-\infty)}$ (µg·h/mL)	$t_{1/2}$ (h)	C_{24} (µg/mL)
111207	2 mg	8	0.231 (20)	2.78 (26)	12.7 (20)	0.038 (41)
	5 mg	7	0.661 (20)	8.87 (27)	14.3 (25)	0.126 (28)
	10 mg	8	1.23 (9)	14.6 (21)	12.7 (9)	0.196 (34)
	25 mg	8	2.76 (12)	35.2 (30)	12.7 (21)	0.469 (41)
	50 mg	6	4.56 (21)	73.2 (19)	14.2 (19)	1.06 (27)
	100 mg	5	8.14 (12)	136 (24)	14.7 (23)	1.80 (33)
112941	250 mg	8	14.1 (10)	278 (15)	14.5 (10)	4.08 (17)
111856	250 mg	41	12.4 (27)	N.D	N.D	3.86 (48)

*N.D: Not determined
All trials were conducted under fasted conditions.

Table 2.2.5.8-2. Summary of DTG PK following a single oral dose (50 mg tablet q.d vs 100 mg tablet q.d) (ING114005)

Treatment	N	Cmax (µg/mL)	AUC(0-24) (µg.h/mL)	C24 (µg/mL)	tlag[b] (h)	tmax[b] (h)
100 mg	12	2.77 (35)	34.3 (41)	0.80 (53)	0.00 (0.00-0.00)	2.00 (1.0-4.0)
50 mg	12	1.83 (35)	24.3 (44)	0.53 (59)	0.00 (0.00-0.00)	2.00 (1.0-4.0)

There is no study directly comparing the PK of 50 mg q.d. vs. 50 mg. b.i.d. However, accumulated data from phase I studies indicate that with 50 mg b.i.d. dosing, C_{max}, AUC_{24h}, and C_{τ} are increased by 66%, 102%, 193%, respectively, in healthy volunteers as compared with 50 mg q.d.dosing. In HIV-infected populations, the magnitude of increase in exposure is less than what was observed in healthy populations. The PopPk analysis indicates that C_{max}, AUC_{24h}, and C_{τ} are increased by 14%, 40%, 91%, respectively, when the dose is increased from 50 mg q.d. to 50 mg b.i.d. The difference appears to be due to the differences associated with study populations (INI-naïve vs INI-experienced) including concomitant medication or adherence.

Table 2.2.5.8-3 Summary of DTG PK parameters following multiple dose of 50 mg tablet administration in healthy and HIV-infected subjects (meta-analysis)

Population	DTG Dosing Regimen	C_{max} (µg/ml)	$AUC_{(0-\tau)}$ (µg.h/mL)	$AUC_{(0-24)}$ (µg.h/mL)	C_{τ} (µg/mL)
Healthy[%]	50 mg once daily	3.62 (35)	49.1 (41)	49.1 (41)	1.05 (56)

Healthy[%]	50 mg twice daily	6.00 (39)	53.0 (42)	106 (42)	3.02 (52)
HIV-1 infected[*]	50 mg once daily	3.67 (20)	53.6 (27)	53.6 (27)	1.11 (46)
HIV-1 Infected[#]	50 mg twice daily	4.15 (29)	37.5 (35)	75.1 (35)	2.12 (47)

%: Meta-analysis of phase I studies
*: Treatment naïve or treatment-experienced and INI naïve
#: Treatment experienced and INI-experienced

2.2.5.9 How do the PK parameters change with time following chronic dosing? ***(This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)***

Following repeated oral administration, DTG achieved steady state within 5 days of dosing, consistent with the estimated $t_{1/2}$ (14 hours). DTG showed time-invariant PK. Accumulation ratios for DTG 50 mg once daily dosing were 1.43, 1.36 and 1.42 for AUC_τ, C_{max}, and C_τ, respectively.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

DTG exhibits low to moderate between-subject variability. In phase I studies in healthy subjects, CV% for AUC and C_{max} ranged from 20 to 40% and CV% for Cτ ranged from 30 to 65%. The PK variability of DTG is slightly higher in HIV-infected subjects than healthy subjects; the CV% of C_0 ranged from 55% to 140% across studies. The variability is mainly due to use of metabolic inhibitors or inducers in the background therapy and less optimal compliance compared to the controlled phase I intensive PK studies in healthy volunteers.

Potential sources of variability based on the PopPK analysis are inter-individual variability of UGT1A1 activities, weight (a shallow weight-DTG oral clearance has been identified in the PopPK analysis), smoking status, and concomitant medications in HIV-1 infected subjects.

Intra-subject variability was lower than inter-subject variability, ranging 8 to 20% for DTG PK parameters in phase I studies conducted in healthy subjects and ranged from 17% to 29% in HIV infected subjects conducted in healthy subjects and ranged from 17 to 29% in HIV-infected subjects based on PopPK modeling.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The applicant conducted the following clinical pharmacology studies to identify effects of intrinsic factors on the pharmacokinetics of DTG

- Pharmacokinetics of DTG in healthy Japanese subjects following a single oral dose of 50 mg DTG (ING115381)
- Pharmacokinetics of DTG in subjects with moderate hepatic impairment and matching healthy subjects (ING11397)
- Pharmacokinetics of DTG in subjects with severe renal impairment and matching healthy subjects (ING11397)

The PopPK analysis was conducted using data from studies with treatment-naïve subjects (Study ING 111521, ING112276, and ING113086) and treatment-experienced subjects (Study ING112961, ING112574, and ING111762) to identify intrinsic factors influencing exposures and/or response of DTG. The following is a summary of key findings of PopPK analysis in regard to intrinsic factors influencing the DTG exposure.

- In treatment naïve patients, higher weight, older age (> 55 years old) and lower bilirubin were associated with higher DTG CL/F. Higher F was associated with female gender. Race, ethnicity, HCV co-infection, CDC classification, ALT or AST did not influence the PK of DTG in this analysis.
- In treatment experienced patients, higher weight and lower albumin level were associated with higher DTG V/F. Female gender was associated with higher F. Race, ethnicity, HCV co-infection, CDC classification, renal impairment, CrCL, ALT or AST did not influence the PK of DTG in this analysis.
- The magnitude of effect on the intrinsic factors listed above on CL/F, V/F, or F was relatively small (all less than 30%), and the magnitude of effect on steady-state AUC, C_{max}, and C_{min} of DTG was <32%. The effect of these covariates was not considered clinically significant; therefore, no DTG dose adjustment for these covariates is necessary.
- There was limited PK data on subjects with HBV co-infection and subjects of +65 years of age.
- Overall, inter-individual variability for CL/F was relatively low (23.5% in treatment naïve subjects and 28.7% in treatment experienced subjects).

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation

2.3.2.1 Elderly

Pharmacokinetics of DTG in subjects > 65 years old are limited (n=11 in treatment experienced subjects, n=1 in treatment naïve subjects). In the PopPK analysis using treatment-naïve subject data, CL/F was

increased with age. Age was a significant covariate in the model with CL/F increasing with age. For >55 yrs, C_{max}, $AUC_{0-\tau}$ and C_{τ} was 10%, 14% and 18% lower compared to the ≤55 yrs. The difference is not clinically significant; no dose adjustment is required based on age.

2.3.2.2 Pediatric patients

The pharmacokinetics of DTG was assessed in treatment-experienced, INI-naïve pediatric HIV -1 patients of 12 to <18 years old (n=10) (IMPAACTP1093, ING112578, cohort I). Nine subjects weighing at least 40 kg received DTG 50 mg once daily and one subject weighing 37 kg received 35 mg DTG once daily. Steady-state pharmacokinetic parameters were estimated.

DTG exposures in pediatric subjects were comparable to the sponsor predefined target as well as data observed in the adult phase III pivotal trials as shown in Table 2.3.2.2. Excluding one outlier (subject 290207) or the subject weighing less than 40 kg (subject ID: 8503351) did not significantly alter the study results and conclusion.

A secondary objective of this study was an efficacy assessment. Eighty percent of subjects (8/10) achieved virologic suppression (RNA <400 c/mL) at week 24, with 70% (7/10) achieving RNA <50c/mL. This efficacy data also support the validity of the current dosing regimen for adolescent (50 mg once daily weighing at least 40 kg). DTG was safe and well tolerated. Based on the PK, safety and antiviral activity data submitted, DTG can be used in adolescent (12 to <18 years old) HIV-1 patients weighting at least 40 kg without dose adjustments.

Table 2.3.2.2 Summary of DTG PK in pediatric HIV infected patients 12 to <18 years old

	Geometric Mean (%CV)	
	AUC (µg·h/mL)	C_{24} (µg·h/mL)
Pre-defined target by the Sponsor	46	0.96
Results including all subjects	46.0 (43)	0.90 (58)
Results: 290207 excluded	52.9 (34)	1.06 (50)
Results: 8503351 excluded	46.8 (44)	0.94 (58)
Phase III PK	53.5 (26)	1.11 (44)
Ratio pediatric/adult	0.86-0.99	0.81-0.95

*Expressed as geometric mean (%CV)

2.3.2.3 Gender

Female subjects accounted for ~20% of the total subjects included in the PopPK analysis. The analysis indicated that gender was a predictor of bioavailability (F) following the same dosing regimen. Females have 21% (95% CI: 13-29%) higher F compared to males. The DTG AUC_{τ}, C_{max}, and C_{min} were higher by 22-36 %, 23-36%, 14-37% respectively in females compared to males based on the simulated steady-state DTG PK parameters using Phase III study data.

The effect of gender on DTG PK was also evaluated in the definitive QT study (ING111856) in healthy subjects as ~60% of the subjects enrolled were females. Following a single oral dose of DTG 250 mg as suspension, C_{max}, AUC_{24}, and C_{24} were higher by 24%, 20%, 6%, respectively in healthy female subjects compared to those in male healthy subjects.

Table 2.3.2.3 Summary of plasma DTG PK parameters following a single dose DTG 250 mg (ING111856)

Treatment	Sex	n	Cmax (µg/mL)	AUC(0-t) (µg.h/mL)	AUC(0-24) (µg.h/mL)	tmax[b] (h)	C24 (µg/mL)
GSK1349572 250 mg	F	24	13.5 (22)	180 (31)	179 (31)	3.08 (1.52-4.12)	3.96 (52)
	M	17	10.9 (28)	151 (35)	150 (35)	3.05 (2.05-6.05)	3.71 (42)
	Overall	41	12.4 (27)	167 (33)	167 (33)	3.08 (1.52-6.05)	3.86 (48)

Based on the known safety a profile and PK/PD relationship for the antiviral activity of DTG, the difference is not considered as clinically significant; no dose adjustment is required based on gender.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

In Phase II and III trials, Caucasians, African-Americans, and Asians represented 60-80%, 10-30%, and 1%, respectively. PopPk analysis indicated that race (Caucasian, African-American, and Japanese ancestry) or ethnicity (Hispanic/latino vs. Nonhispanic/Latino) has no effect on DTG PK parameters. A Phase I study evaluating DTG PK in a Japanese population (ING115381) also indicates that the pharmacokinetics of DTG following a single oral dose (50 mg) to healthy Japanese subjects were consistent with the DTG PK parameters reported in healthy subjects in the US who were predominantly Caucasian. No DTG dose adjustment according to race or ethnicity is neccessary.

2.3.2.5 Renal impairment

The applicant conducted an open label, single-dose pharmacokinetic study to evaluate plasma dolutegravir (DTG) pharmacokinetics following a single dose of DTG 50 mg to 8 subjects with severe renal impairment (creatinine clearance [CLcr] <30 mL/min, not on dialysis) and 8 matched healthy controls.

As urinary excretion of unchanged DTG is less than 1% of a total oral dose, renal impairment was not expected to affect DTG exposures. However, the results showed that DTG exposure was unexpectedly lower in subjects with severe renal impairment (CLcr <30mL/min) compared to healthy, matched subjects: $AUC_{(0-\infty)}$ and C_{max} were 40% and 23% lower, respectively. However, as shown in Fig 2.3.2.5-2, there was considerable overlap in DTG concentration between the groups. Values for $AUC_{(0-\infty)}$ ranged from 13.6 to 46.7 µg*h/ml in renally impaired subjects and from 14.1 to 60.9 µg*h/ml in

matched healthy subjects. C_{max} ranged from 0.79 to 2.1 µg/ml in renally impaired subjects and from 0.82 to 3.2 µg/ml in matched healthy subjects. The exposure of the DTG glucuronide metabolite in renally impaired subjects was 3-fold (for C_{max}) and 4-fold (for AUC) higher than those of normal subjects.

The cause or mechanism of decreased exposures of DTG in subjects with severe renal impairment is unknown. While renal impairment can have a multitude of effects on drug-metabolizing enzymes and transporters, the possible explanations (e.g., impaired hepatic metabolism in subjects with renal impairment) would suggest a higher exposure in the renally impaired group and does not support the findings in this study. The free fraction of DTG in both groups was comparable, indicating that changes in plasma protein binding are unlikely the cause of the observed decreases in DTG exposure in subjects with renal impairment. A possible explanation is that there may be changes in absorption or volume of distribution in subjects with severe renal impairment.

While it is unclear what caused decreased exposures to DTG, the applicant concluded that the moderate reduction in DTG exposure in subjects with severe renal impairment is not considered clinically significant and no dose adjustment of DTG is needed in subjects with mild to severe renal impairment (not on renal replacement therapy). This is a reasonable conclusion in INI-naïve patients as the exposure-response relationship is relatively flat in this population and an approximately 40% decrease in DTG exposure would not be expected to clinically relevant. However, in subjects with INI-resistance, such decreases may affect efficacy depending on the baseline susceptability.

The PopPK analysis from the phase III trials indicated that subjects with mild to moderate renal impairment (creatinine clearance 60 to < 90 mL/min and 30 to < 60 mL/min) demonstrated no difference in DTG exposure compared to subjects with normal creatinine clearance. This supports the use of DTG in patients with mild or moderate renal impairment without dose adjustment. There was an insufficient number of subjects with severe renal impairment in the phase III trials to conduct a similar comparison with this population.

Table 2.3.2.5 -1 Summary of plasma DTG harmacokinetic parameters and statistical comparison

Cohort	Renal Impaired (n=8)	Healthy (n=8)	Ratio of GLS Means (90% CI)
$AUC_{(0-\infty)}$ (µg.h/mL)	23.5 (48)	37.1 (58)	0.601 (0.370, 0.975)
$AUC_{(0-t)}$ (µg h/mL)	22.6 (47)	35.3 (58)	0.606 (0.375, 0.978)
C_{max} (µg/mL)	1.50 (34)	1.86 (45)	0.774 (0.532, 1.13)
C_{min} (µg/mL)	0.318 (43)	0.563 (57)	0.566 (0.352-0.908)
$t_{1/2}$ (hr)	12.7 (31)	15.4 (15)	0.818 (0.639, 1.05)
t_{max} (hr)	2.00 (1.0, 3.0)	2.00 (1.0, 4.0)	No difference
CL/F (L/hr)	2.12 (48)	1.35 (58)	1.67 (1.03, 2.70)

Vz/F (L)	38.8 (43)	29.9 (44)	1.36 (0.918, 2.02)

Fig 2.3.2.5 Comparative plot of plasma AUC and C_{max} of DTG (subjects with severe renal impairment vs. matched healthy subjects)

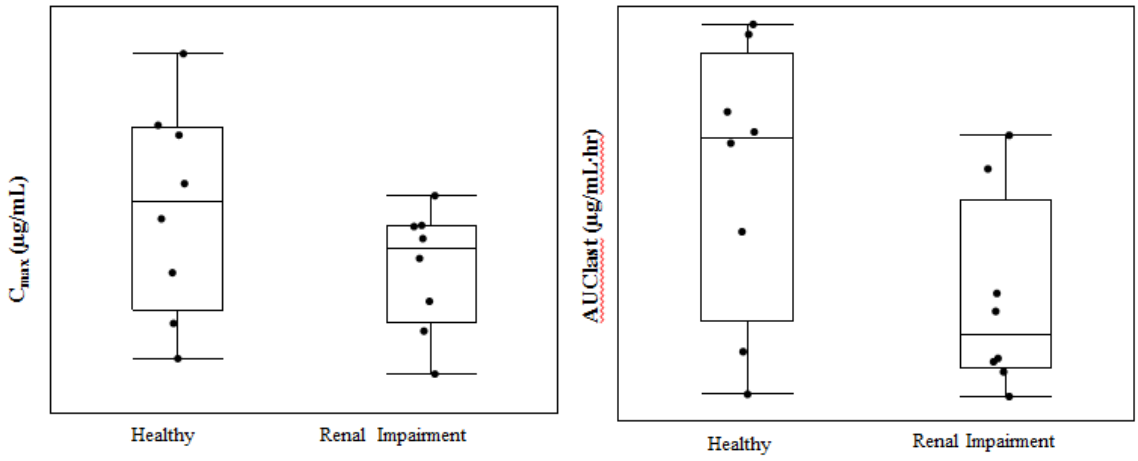


Table 2.3.2.5-2 Simulated exposure of DTG in treatment-experienced subjects with renal impairment

		N	Cmax µg/mL	Cτ µg/mL	AUCτ µg/mL·hr
50 mg QD	Normal	287	3.11 (3.02-3.20)	0.824 (0.764-0.888)	43.3 (41.5-45.2)
	Mild	71	3.43 (3.21-3.65)	0.835 (0.693-1.01)	46.6 (42.1-51.5)
	Moderate	8	3.45 (2.81-4.21)	0.818 (0.509-1.32)	46.2 (34.9-61.2)
	Severe	1	3.64	0.857	48.7
50 mg BID	Normal	152	4.10 (3.91-4.29)	2.10 (1.95-2.26)	37.1 (35.1-39.2)
	Mild	45	4.37 (4.04-4.93)	2.21 (1.94-2.51)	39.3 (35.8-43.3)
	Moderate	9	4.11 (3.47-4.88)	1.97 (1.62-2.41)	36.3 (30.4-43.2)
	Severe	1	4.23	2.36	40.2

2.3.2.6 Hepatic impairment

The sponsor conducted a pharmacokinetic study comparing subjects with moderate hepatic impairment (Child-Pugh grade B) to matched healthy subjects at a single dose of 50 mg DTG (ING113097). The

pharmacokinetics of total plasma DTG was not affected by moderate hepatic impairment. The fraction unbound (%) of DTG in moderate hepatic impairment subjects was ~76-120% higher than those in healthy subjects. The difference is thought to be primarily due to lower albumin concentrations in subjects with moderate hepatic impairment. Based on this study result, the applicant did not conduct a pharmacokinetic study in subjects with mild hepatic impairment. In conclusion, DTG can be administered without dose adjustment in subjects with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of DTG has not been studied and thus DTG is not recommended for use in this population.

Table 2.3.2.6 Summary of Plasma DTG pharmacokinetic parameters and statistical comparison

PK parameters (Geometric mean, %CV)	Subjects with Moderate Hepatic impairment	Healthy Subjects	Geometric Mean Ratio (Hepatic vs. Healthy)
C_{max} (µg/mL)	1.78 (17)	1.80 (49)	1.02 [0.754,1.37]
C_{24} (µg/mL)	0.59 (36)	0.57 (44)	1.04 [0.727,1.48]
$AUC_{(0-\infty)}$ (µg.h/mL)	38.5 (30)	37.3 (47)	1.05 [0.745,1.49]
$AUC_{(0-t)}$ (µg.h/mL)	36.7 (27)	35.5 (48)	1.06 [0.753,1.48]
CL/F (L/hr)	1.30 (30)	1.34 (47)	0.950 [0.673,1.34]
Vz/F (L)	29.1 (18)	28.7 (50)	0.986 [0.737,1.32]
$t_{1/2}$ (h)	15.5 (19)	14.9 (24)	1.04 [0.845,1.27]
T_{max} (h) (median, range)	4.00 (2.0-5.0)	3.00 (1.0-4.0)	1.00 [-0.50, 2.50]
Fraction Unbound at 3 hr post dose, (%)	0.50 (43)	0.23 (18)	2.20 [1.62,2.99]
Fraction Unbound at 24 hr post dose, (%)	0.41 (40)	0.23 (11)	1.76 [1.23,2.51]

2.3.2.7 What pregnancy and lactation use information is there in the application?

No information regarding the use of DTG in pregnant or lactating women was included in this submission.

2.3.2.8 Pharmacogenetics

DTG is primarily metabolized by UGT1A1 with some minor contribution from CYP3A. The applicant conducted a meta-analysis to evaluate the effect of the genetic status of UGT1A1 on DTG pharmacokinetics using samples collected in 9 clinical studies (n=89) (ING116265). For UGT1A1, subjects were classified as low (*28/*28, *28/*37, or *37/*37), reduced (*1/*28, *1/*37, *28*/*36,

*36/*37), or normal UGT1A1 activity (*1/*1, *1/*36, *36/*36) and analysis was done to compare normal functioning subjects to those with either low or reduced function.

ANCOVA analysis showed that CL/F decreased, while $AUC_{(0-\tau)}$ and C_{max} increased, in subjects with low and reduced UGT1A1 activity compared to subjects with normal UGT1A1 activity. In subjects with low UGT1A1 activity compared to subjects with normal UGT1A1 activity, the effect was greater. For all UGT1A1 genotype effects the maximum expected increase is less than a doubling of exposure (based on upper limit of 92% CI). As the therapeutic index of DTG is wide and AEs are mild and not associated with higher exposures, the effects of UGT1A1 polymorphism on DTG exposures are not considered clinically significant. No dose adjustment is required for subjects with the UGT1A1 *28/*28 and *28/*37 genotypes.

The sponsor also explored the influence of CYP3A4, CYP3A5 and pregnane X receptor (NR1I2) variants on DTG PK. Polymorphisms in those enzymes were not associated with differences in the PK of DTG.

Table 2.3.2.8 ANCOVA Results for PK Parameters and UGT1A1 Functional Activity

	Geometric LS Mean				
PK Parameter	***Normal Activity (N=41)***	***Reduced Activity (N=40)***	***Low Activity (N=7)***	***Comparison***	***Geometric Mean Ration (92% CI)***
CL/F (L/hr)	1.09	0.936	0.749	Low+Reduce vs. Normal	0.765 (0.659-0.889)
				Low Vs. Normal	0.684 (0.543-0.862)
AUC (0-INF) (ug*hr/mL	45.7	53.4	66.8	Low+Reduce vs. Normal	1.307 (1.125-1.518)
				Low Vs. Normal	1.462 (1.160-1.842)
Cmax (ug/mL)	3.45	3.89	4.57	Low+Reduce vs. Normal	1.221 (1.063-1.402)
				Low Vs. Normal	1.323 (1.068-1.638)

2.3.2.9 Co-infection with Hepatitis B (HBV) or (HCV)

A total of 71 subjects with HCV at baseline and a total of 27 subjects with HBV at baseline participated in phase II/III efficacy trials. Population pharmacokinetic analysis indicated that HCV co-infection had no clinically relevant effect on the exposure of DTG. There are limited PK data in subjects with HBV co-infection.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Smoking: The population PK analyses using pooled data from Phase II/III trials in a HIV-infected population identified smoking status as a statistically significant covariate; following the same dosing regimen, current smokers have 16% (95% CI 10-22%) higher CL/F compared to non-smokers. This is not considered to be clinically significant and no dose adjustment is necessary based on the smoking status. *In vitro* studies indicated that the contribution of CYP1A to DTG metabolism is none to minimum.

The effects of herbal products, diet, and alcohol use on the DTG PK were not evaluated in this submission.

2.4.2 Drug-drug Interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. DTG is primarily metabolized by UGT1A with minor metabolism by CYP3A4. It is also an inhibitor of OCT2. Please refer to section 2.4.2.2-2.4.2.4 for detailed information on *in vitro* drug interaction study results.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

DTG is primarily metabolized by UGT1A1 with CYP3A4 as a minor route. Several *in vivo* drug interaction studies also indicate that the exposures of DTG in the presence of CYP3A and UGT1A inducers (e.g., rifampin or efavirenz) significantly decreased and dose adjustments are recommended. Co-administration of atazanavir (UGT1A1 inhibitor) increased DTG AUC by 91%.

Metabolism via UGT1A1 is also known to be influenced by genetic status. Please refer to 2.3.2.8 for detailed information on the pharmacogenomics analysis for the effects of UGT1A1 variants on the DTG PK.

2.4.2.3 -2.4.2.4 Is the drug an inhibitor and/or an inducer of CYP enzymes or transporters including P-gp?

Potential interaction via enzyme induction or inhibition.
In vitro, DTG showed little or no direct inhibition (IC_{50} > 50 μM) of major metabolizing enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1 or UGT2B7) and major transporters (BCRP, MRP2, OCT1 and P-gp). *In vitro,* DTG did not induce CYP1A2, CYP2B6 or CYP3A4 up to a concentration of 40 μM. *In vivo* drug interaction studies using various substrates (oral contraceptives, rilpivirine, and midazolam) also indicate that DTG has little to no potential for drug interactions as an inhibitor or inducer of CYP metabolism pathways.

Potential interaction via transporter
DTG is not an inhibitor of P-gp, MRP2, OATP1B1 or OATP1B3 but is a substrate of P-gp and BCRP. Therefore, drugs that affect P-gp or BCRP could affect DTG plasma concentration. However, the high

passive membrane permeability appears to minimize the impact of efflux by transporters. The exposure of DTG was not significantly changed in the presence of LPV/rtv or telaprevir (known *in vivo* P-gp inhibitors) although the results may be confounded by CYP3A4 and UGT1A1-mediated interactions.

The DTG glucuronide metabolite, GSK2832500, did not inhibit MRP2, thus inhibition of biliary clearance of bilirubin glucuronides or glucuronide conjugates of coadministered drug is not expected.

In an *in vitro* study, DTG inhibited the renal organic cation transporter 2 (OCT2, IC_{50}=1.9 μM or 0.82 μg/mL). Therefore, DTG may increase the plasma concentrations of drugs (e.g., dofetilide and metformin) or endogenous molecules (e.g., creatinine) for which excretion is dependent upon OCT2 transport. In clinical trials, it was observed that the use of DTG was associated with a modest increase in serum creatinine (10-15%) likely due to OCT2 inhibition by DTG. This suggests that DTG can be an *in vivo* inhibitor of OCT2 and potentially increase the exposures of OCT2 substrates. The applicant did not conduct *in vivo* drug interaction studies determining the effect of DTG on OCT2-mediated excretion (the unbound C_{max}/IC_{50} ratio did not meet the criteria necessitating an *in vivo* study as described in the February 2012 DDI guidance). Instead, the applicant proposed a conservative recommendation of contradindicating dofetilide with DTG and close monitoring of metformin efficacy and safety when it is used with DTG. As dofetilide has a narrow therapeutic index and metformin does not, these proposed recommendations are acceptable, in the absence of *in vivo* drug interaction study results.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

DTG is an OCT2 inhibitor. Some OCT inhibitors are also MATE (Multidrug and Toxin Extrusion)-1 or MATE-2K inhibitors. The sponsor did not evaluate the effects of DTG on MATE-mediated renal transport. The clinical relevance or significance of MATE inhibition is currently unknown and as such, the February 2012 DDI guidance currently does not recommend routine evaluation of MATE inhibition.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

The proposed indication of DTG is to use in combination with other antiretrovirals in the treatment of HIV. There are no specific antiretroviral medications in the proposed DTG label that are to be coadministered with DTG. The sponsor conducted a series of drug interaction studies with anti-retrovirals to be used with DTG. As DTG has little potential to be a perpetrator, most studies only examined DTG as a victim of drug interactions.

The drug interaction study results indicate that DTG can be used without dose adjustments with NRTIs, LPV/rtv, DRV/rtv, rilpivirine (RPV), ATV, or ATV/rtv. Dose adjustment is recommended when DTG is used with moderate to strong inducers (EFV, TPV/rtv or FPV/rtv). Please refer to 2.4.2.8 for magnitude of changes and dosing recommendations. The exposure of DTG is significantly decreased in the presence of etravirine (ETR) which may not be counterbalanced by

50 mg b.i.d dosing. However the effect of ETR was mitigated by co-administration of lopinavir/ritonavir (LPV/rtv) and darunavir/ritonavir (DRV/rtv). Administration of ETR with ATV or ATV/rtv is also expected to mitigate ETR-mediated induction as ATV is a strong UGT1A1 inhibitor. Therefore, coadministration of ETR with DTG is not recommended unless patients also receive concomitant atazanavir/ritonavir (ATV/rtv), LPV/rtv or DRV/rtv. Drug interactions with less commonly used antiretrovirals (e.g., nevirapine or nelfinavir) are not evaluated in this submission.

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

HIV-1 infected patients may receive a variety of medications to treat or prevent comorbidities, including opportunistic infection, hepatitis infection, depression, dyslipidemia, gastrointestinal discomfort and substance abuse. For the female population of childbearing potential, oral contraceptives are also commonly used medication.

2.4.2.8. Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The applicant conducted drug interaction studiess with commonly co-administered drugs in this population (e.g., HIV antiretrovirals, HCV antiretrovirals, methadone, oral contraceptives), a sensitive substrate of CYP3A4 (midazolam), and drugs that can potentially alter DTG exposures based on the DTG ADME profiles (rifampin, rifabutin, high dose of prednisone, drugs containing multivalent cations such as Maalox or multivitamin).

Drug-Drug Interactions

Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In general, DTG has a low potential to cause drug interactions as a perpetrator. *In vitro*, DTG demonstrated little or no direct inhibition on major drug metabolizing enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, UGT1A1 or UGT2B7) or major transporters (BCRP, MRP2, OATP1B1, OATP1B3, OCT1, and P-gp). *In vitro*, DTG did not induce CYP1A2, CYP2B6 or CYP3A4. In in vivo drug interaction studies testing DTG as perpetrator, DTG did not exhibit significant drug interactions with midazolam, tenofovir, methadone, oral contraceptive (Ortho-Cyclen), or rilpivirine. *In vivo* drug interaction studies also demonstrated that DTG did not affect the PK of EFV, LPV/rtv, DRV/rtv, ATV, FPV, RPV, and TVR (telaprevir), by comparing PK data of these agents observed when co-administered with DTG to historical data.

In vitro, DTG inhibited renal organic cation transporter 2. Based on this observation, DTG may increase plasma concentrations of drugs for which excretion is dependent upon OCT2, such as

dofetilide and metformin. The applicant did not conduct *in vivo* drug interaction studies with OCT2 substrates such as metformin.

Table 2.4.2.8-1 Summary of effects of dolutegravir on the pharmacokinetics of coadministered drugs

Coadministered Drug(s) and Dose(s)	Dose of **DTG**	n	Geometric Mean Ratio (90% CI) of Coadministered Drug With/Without Dolutegravir No Effect = 1.00			
			C_{max}	AUC	C_τ or C_{24}	Conclusion
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91, 1.08)	1.03 (0.96, 1.11)	1.02 (0.93, 1.11)	No effects
Methadone 20 to 150 mg Individualized	50 mg twice daily	12	Total methadone 0.99 (0.91, 1.07) R-methadone 0.95 (0.89, 1.02) S-methadone 1.02 (0.93, 1.12)	0.98 (0.91, 1.06)	0.99 (0.91, 1.07)	No effects
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79 to 1.15)	_	No effects
Norgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82, 0.97)	0.98 (0.91, 1.04)	0.93 (0.85, 1.03)	No effects
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99, 1.22)	1.06 (0.98, 1.16)	1.21 (1.07, 1.38)	No effects
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	16	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)	No effects

Effect of Other Agents on the Pharmacokinetics of Dolutegravir and Dose Recommendations

DTG is eliminated mainly through metabolism by UGT1A1 with CYP3A4 as a minor route. Moderate to strong inducers of UGT1A1 and/or CYP3A4 such ETR, EFV, FPV/rtv, TPV/rtv, RIF significantly reduced the plasma concentrations of DTG (Table 2.4.2.8-2). The PopPK analysis using Study ING111762 data (SAILING: 50 mg q.d. DTG in subjects with optimized background regimen) also indicated that subjects receiving DTG 50 mg once daily in combination with TPV/rtv or EFV had significantly lower C_{0h} and lower virologic response. The analysis also indicated that use of fosamprenavir/ritonavir was also associated with significantly lower C_{0h} although the effects on virologic response were inconclusive due to limited number of samples. Please refer to section 2.2.4.1 and Table 2.2.4.1-1 for detailed information.

Based on the results of DDI studies as well as the PopPK analysis, increasing the DTG dose is recommended in treatment-naïve or INI-naïve patients receiving DTG in combination with EFV, FPV/rtv, or TPV/rtv. As rifampin (RIF) reduced DTG exposure to a similar extent as TPV/rtv and EFV (Table 2.4.2.8-2), increasing the DTG dose is also recommended for treatment-naïve or treatment-experienced, INI naïve subjects who require RIF therapy. The proposed dosing recommendation, DTG 50 mg b.i.d, in the presence of moderate to strong inducers is supported by

the following observations. First, there are enough data regarding the safety and pharmacokinetics of DTG 50 mg DTG b.i.d regimen. Increasing the dose from 50 mg q.d. to 50 mg b.i.d did not pose any additional safety issues in phase III trials. Increasing the dose from 50 mg q.d. to 50 mg b.i.d is expected to increase AUC_{24h}, C_{max}, and C_{min} by 66%, 102%, and 193%, respectively (Table 2.2.5.8-2), enough to mitigate the induction effects by EFV, FPV/rtv, TPV/rtv or rifampin shown in the drug interaction studies. The drug interaction study comparing DTG 50 mg q.d. vs. rifampin 600 mg q.d + DTG 50 mg b.i.d also indicated that exposure of DTG 50 mg b.i.d in the presence of rifampin is comparable to that of DTG 50 mg q.d (ING113099). In summary, a dose adjustment from 50 mg q.d. to 50 mg b.i.d of DTG in treatment-naïve or treatment-experienced, INI-naive subjects receiving EFV, FPV/rtv, TPV or rifampin is acceptable. The applicant initially proposed no dose adjustment in the presence of FPV/rtv. However, the review team concluded that dose adjustment is recommended based on the C_0 values in the popPK analysis.

At the time of this submission, adequate safety and pharmacokinetic data are not available when DTG is administered chronically at doses higher than 50 mg b.i.d in the patient population. Thus, increasing the dose beyond 50 mg b.i.d. is not supported at this time. Caution is warranted when moderate to strong inducers are used in INI-experienced patients whose dosing regimen is already 50 mg b.i.d.

Etravirine reduced DTG C_{24} by more than 80%. However the effect of ETR was mitigated by co-administration of lopinavir/ritonavir (LPV/rtv) and darunavir/ritonavir (DRV/rtv). Administration of ETR with ATV or ATV/rtv is also expected to mitigate ETR-mediated induction as ATV is a strong UGT1A1 inhibitor. Therefore, coadministration of ETR with DTG is not recommended unless patients also receive concomitant atazanavir/ritonavir (ATV/rtv), LPV/rtv or DRV/rtv.

DRV/rtv slightly reduced DTG, but the magnitude of the effect is not considered clinically significant. The effect of DRV/rtv was evaluated in the phase III study ING111762. The patients on DRV/rtv exhibited a slightly lower C_0 compared to the overall mean C_0, but no significant difference was observed in efficacy. DTG can be dosed with DRV/rtv (once or twice daily) without dose adjustment (Table 2.4.2.8-2).

ATV (or ATV/rtv) significantly increased the exposure of DTG (Table 2.4.2.8-3). The AUC, C_{max}, and C_{min} are increased by 91%, 50%, 180% in the presence of ATV and by 61%, 33%, and 120% in the presence of ATV/rtv, respectively. The following observations support the use of DTG with atazanavir without a dose adjustment despite the increased exposure of DTG in the presence of ATV ± rtv; DTG adverse reactions are generally mild and well-tolerated. There was no exposure-response relationship for safety in the phase III trials. The major toxicity observed in preclinical species was GI toxicity which is the result of local intolerance rather than a systemic exposure. Therefore, an increase in the systemic exposure of DTG without increasing the dose administered would not change the safety margin. Also, high fat food increases DTG exposure by 67%. Dolutegravir was administered without regard to food in the phase III trials and no significant safety concern was

raised. In sum, it is reasonable to conclude that use of atazanavir (+/-ritonavir) with DTG is acceptable without a dose adjustment.

The exposure of DTG was not significantly altered by co-administration of the following drugs and dose adjustment is not required: Tenofovir, lopinavir/ritonavir, rilpivirine, boceprevir, telaprevir, rifabutin or high dose prednisone.

Table 2.4.2.8-2 Effects of concomitant medications on DTG pharmacokinetics.

Coadministered Drug(s) and Dose(s)	Dose of **TIVICAY**	n	Geometric Mean Ratio (90% CI) of **Dolutegravir** Pharmacokinetic Parameters With/Without Coadministered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Atazanavir 400 mg once daily	30 mg once daily	12	1.49 (1.40 to 1.59)	1.91 (1.80 to 2.02)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.33 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Tenofovir 300 mg once daily	50 mg once daily	16	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.10 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg + 100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Maalox	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Maalox 2 hrs after	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Multivitamin One tablet once daily	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)

Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampin[a] 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampin[b] 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.15 (0.97 to 1.36)	0.95 (0.81 to 1.09)	0.70 (0.57 to 0.86)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.13 (1.06 to 1.21)	1.12 (1.05 to 1.19)	1.22 (1.15 to 1.30)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	13	0.53 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Telaprevir 750 mg every 8 hours	50 mg once daily	15	1.18 (1.11 to 1.26)	1.25 (1.19 to 1.31)	1.40 (1.29 to 1.51)
Bocepravir 800 mg every 8 hours	50 mg once daily	13	1.05 (0.96 to 1.15)	1.07 (0.95 to 1.20)	1.08 (0.91 to 1.28)

[a] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.
[b] Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug- drug interactions, if any?

There are no known pharmacodynamic drug-drug interactions for DTG.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

(b) (4)

Both efavirenz and nevirapine can induce and inhibit multiple CYPs and UGTs, so they can exhibit different drug interaction results depending on the metabolic characteristics of the co-administered drugs. For example, as shown in the following table, nevirapine and efavirenz exhibited differential effects on maraviroc, rifabutine, darunavir, and zidovudine. (b) (4)

Table 2.4.2.10 Comparison of nevirapine and efavirenz drug interactions and clinical recommendations

Coadministered drugs	**Nevirapine (NVP)**			**Efavirenz (EFV)**		
	AUC	Cmax	Cmin	AUC	Cmax	Cmin
ATV/ rtv	↓19% (↓35% -↑2%)	↓2% (↓15%-↑24%)	↓59% (↓73-40%)	↔	↑17% (↑8-27%)	↓42% ↓31-51%
Clinical recommendation	Do not coadminister due to the decreased exposure of ATV and the increased the exposure of NVP			ATV/rtv can be administered with efavirenz		
LPV/ rtv	↓27% (↓47-2%)	↓19% (↓38% -↑5%)	↓51% (↓72-26%)	↓19% (↓36% -↑3%)	↔	↓39% (↓3-62%)
Maraviroc	↑1% (↓35%-↑55%)	↑54% (↓6%-↑151%)	↔	↓45% (↓38-51%)	↓51% (↓37-62%)	↓45% ↓28-57%)
Clinical recommendation	Maraviroc 300 mg twice daily is recommended with NVP			Maraviroc 600 mg twice daily is recommended with EFV		
Indinavir	↓31% (↓39-22%)	↓15% (↓24-4%)	↓44% (↓53-33%)	↓46% (↓37-54%)	↓29% (↓11-43%)	↓57% (↓50-63%)
Nelfinavir	↔	↔	↓32% (↓50% -↑5%)	↑20% (↑8-34%)	↑21% (↑10-33%)	↔
Clinical recommendation	An appropriate dose of nelfinavir with respect to safety and efficacy has not been established			Efavirenz can be used with nelfinavir without dose adjustments		
Clarithromycin	↓31% (↓38-24%)	↓23% (↓31-14%)	↓56% (↓70-36%)	↓39% (↓30-46%)	↓26% (↓15-35%)	↓53% (↓42-63%)
Darunavir/rtv	↑40% (↑14-↑73%)	↑24% (↓3-↑57%)	↔	↓15% (↓28-0%)	↓13% (↓25-↑1%)	↓31% (↓46-↓13%)
Ethinyl Estradiol	↓20% (↓33-3%)	↔	ND	↔	↔	↔
Rifabutin	↑17% (↓2%-↑40%)	↑28% (↑9-51%)	↔	↓38% (↓28-47%)	↓32% (↓15-46%)	↓45% (↓31-56%)
Clinical recommendation	Caution should be used in concomitant administration as some patients may be at higher risk for rifabutin toxicity			Increase daily dose of rifabutin by 50%. Consider doubling the rifabutin dose in regimens where rifabutin is given 2 or 3 times a week		
Zidovudine	↓28% ↓40-4%	↓30% ↓51% -↑14%	ND	↔	↔	↑225% ↑43-640%

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

There are no significant issues relating to dose, dosing regimens, or administration at this time

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

DTG is BCS class II (low solubility, high permeability) drug. Please refer to the Biopharmaceutics review for further details.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial? 2.5.2.1.1. What data support a waiver of in vivo BE data?

The formulation used in pivotal Phase III studies is identical to the commercial formulation with the following exceptions; the Phase III tablet is deep convex round and the commercial tablet is normal convex round. The Phase III tablet is film coated (b) (4) and the commercial tablet is film coated (b) (4) This is a components and composition-SUPAC level 2 change that can be supported with dissolution profile comparison and similarity f2 data. The applicant provided dissolution data using 5 different dissolution media and demonstrated that dissolution is similar between two formulations in all media (f2 > 50 for all media). Please refer to the Biopharmaceutics review for further details.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effects of food are dependent upon the calorie, fat content, dose of DTG (20 mg vs. 50 mg of DTG) and possibly formulation (AW vs. AP). In study ING111322, administration of DTG at a single dose of 20 mg (10 mg tablet x 2) with a moderate fat meal (30% fat/699 Kcal) slightly increased AUC (11%) and C_{max} (11%). In study ING112941, administration of DTG at a single dose of 50 mg (25 mg X 2 tablets, AP formulation) with a high fat meal (53 % fat/869 Kcal) significantly increased the AUC and C_{max} by 84% and 94%, respectively. In ING113674, administration of DTG at a single dose of 50 mg (25 mg X 2 tablets, AW formulation) with a low fat (7% fat/300 Kcal), moderate fat (30% fat/ 600 Kcal) and high fat (53%/870Kcal) meal increased DTG AUC by 33%, 41%, and 66%, respectively. T_{max} was prolonged to 3, 4, or 5 hours from 2 hours under fasted conditions. As the composition of AW formulation used in this study is the same with the to-be-marketed formulation (with the exception of containing 25 mg DTG instead of 50 mg), the study results from ING113674 are considered most clinically relevant among the 3 food effect study results.

The meta-analysis conducted by the applicant using phase I trials also indicated that exposures of DTG are increased approximately 30% under fed conditions compared to the exposures under fasted conditions (Table 2.2.5.2)

The increased exposure with food is not considered clinically significant based on the accumulated safety data in Phase IIb and III studies which permitted DTG dosing without restriction to food or food content. The PK variability for $AUC_{(0-\tau)}$ in the SPRING-1 dose ranging trial was 40-48% across doses, suggesting that dosing without regard to food does not lead to unpredictable high exposures in clinical practice. It is unknown if the increased exposure is beneficial to efficacy when DTG exposure is expected to be low (e.g., co-administration of drugs that can decrease DTG exposure or subjects with severe renal impairment).

Table 2.5.3-1 Summary of DTG PK following a single dose 20 mg under fed vs. fasted conditions (ING111322)

Plasma DTG PK Parameter	20 mg Oral Tablet Fasted (Treatment B) N=12	20 mg Oral Tablet Fed (Treatment C) N=12	Fed Tablet/Fasted Tablet (Treatment B/Treatment A) N=12
AUC(0-∞) (μg.h/mL)	23.5 (38)	26.0 (33)	1.11 [1.02, 1.21]
Cmax (μg/mL)	1.30 (30)	1.44 (16)	1.11 [1.01, 1.22]

Source Data: Study ING111322, Table 11.19 and Table 11.20
geometric mean (CVb%) for PK summary and GLS mean ratio (90% CI) for treatment comparison
Treatment B = 10mg as DTG 10mg tablet x 2 administered under fasted conditions
Treatment C = 10mg as DTG 10mg tablet x 2 administered under fed conditions

Table 2.5.3-2 Summary of DTG PK following a single dose 50 mg under fed vs. fasted conditions (ING112941)

Plasma DTG PK Parameter	50 mg (2x25 mg) Oral Tablet Fasted (Treatment A) N=12	50 mg (2x25 mg) Oral Tablet Fed (Treatment B) N=12	Fed Tablet/Fasted Tablet (Treatment B/Treatment A) N=12
AUC(0-∞) (μg.h/mL)	34.7 (57)	67.2 (24)	1.94 [1.63, 2.30]
Cmax (μg/mL)	1.84 (44)	3.39 (17)	1.84 [1.55, 2.19]

Source Data: Study ING112941, Table 11.3 and 11.4
geometric mean (CVb%) for PK summary and GLS mean ratio (90% CI) for treatment comparison
Treatment A: 50 mg DTG as 25 mg X 2 (AP formulation) administered under fasted conditions
Treatment B: 50 mg DTG as 25 mg X 2 (AP formulation) administered under fed conditions (high fat)

Table 2.5.3-3 Summary of DTG PK following a single dose 50 mg q.d. under various fed conditions (ING113674)

Plasma DTG PK Parameter	50 mg (2x25 mg) Oral Tablet Fasted N=18	50 mg (2x25 mg) Oral Tablet with Low Fat Meal N=18	50 mg (2x25 mg) Oral Tablet with Mod Fat Meal N=18	50 mg (2x25 mg) Oral Tablet with High Fat Meal N=18
AUC(0-∞)	50.3 (27)	66.7 (35)	71.0 (31)	83.6 (35)
Cmax	2.65 (28)	3.88 (21)	4.03 (19)	4.44 (24)

Data Source: ING113674, Table 11.6
geometric mean (CVb%) for PK summary
DTG 50 mg AW = DTG 50 mg using new formulation 1 fasting
DTG 50 mg AW + Low Fat = DTG 50 mg using formulation AW with low fat meal
DTG 50 mg AW + High Fat = DTG 50 mg using formulation AW with high fat meal
DTG 50 mg AW + Mod Fat = DTG 50 mg using formulation AW with moderate fat meal

2.5.4 When would a fed BE study be appropriate and was one conducted?

A fed BE study is not required for the approval.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Please refer to the Biopharmaceutics review for information regarding dissolution conditions and specifications.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

Not applicable to this submission. Only one formulation (50 mg tablet) is proposed for marketing at this time.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable to this submission.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable to this submission.

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed

Threre are no *in vivo* BA and BE issues that need to be addressed at this time. Please refer to the Biopharmaceutics review for *in vitro* dissolution data.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The active moiety (DTG) was identified and plasma samples were analyzed using validated LC/MS/MS assays.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites were routinely analyzed in DTG studies except in the mass balance trial and renal impairment study. The major circulating form is DTG parent drug and metabolites are pharmacologically inactive.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total plasma concentrations were determined for all clinical pharmacology studies with exceptions in renal and hepatic impairment trials where both free concentrations were additionally measured. This is acceptable since it is standard to measure total concentrations and DTG is not a narrow therapeutic index drug.

2.6.4 What bioanalytical methods are used to assess concentrations?

The bioanalytical method for the measurement of dolutegravir (DTG) concentrations in plasma and phosphate buffered saline (PBS, matrix for protein binding assays) was based on extraction by protein precipitation using acetonitrile containing an isotopically labeled internal standard ($[^2H_7{}^{15}N]$-DTG) followed by HPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring.

The following table shows summary of each validation report and clinical studies supported. Please refer to the individual trial reviews in Section 4 for bioanalysis information of an individual study.

Table 2.6.4-1 List of validation methods and clinical studies supported by each method

Validation report	Clinical study supported	Document Number Study Site
DTG human plasma EDTA (original method) Title: Validation of a method for the determination of GSK134952 in human plasma (range 5-5000 ng/mL) using HPLC-MS/MS	ING111207, ING111322 ING111521, ING111602 ING111603, ING111604 ING111853, ING111854 ING111856, ING112276 ING112934, ING112941 ING112961	RD2007/01425 2011N112541 GSK
DTG human plasma EDTA (lower limit of quantitation raised) Title: the validation of a method for the determination of GSK1349752 (range 20 to 20000 ng/mL) using HPLC-MS/MS.	ING113068, ING113096 ING113097, ING113125 ING113674, ING114005 ING114819, ING116070	RD2010/00175 2011N112542 GSK
DTG human plasma (EDTA) (Transfer of original method to (b) (4) Full validation) Title: Validation of a method for the determination of GSK1349572 in Human plasma by LC-MS/MS)	ING111762, ING111855 ING112574, ING113086 ING113099, ING114556 ING114581, ING115381 ING115696, ING115697 ING115698, LAI116181	2011N112453 (b) (4)
DTG Phosphate buffered Saline Title: The validation of a method for the determination of GSK1349572 range 1 to 1000 ng/mL) in phosphate buffered saline using HPLC-MS/MS	ING113097, ING113125 ING116070	2011N112679 GSK
DTG human cerebrospinal fluid	ING116070	2012N145767

Title: Validationn of a method for the determination of GSK1349572 in human cerebrospinal fluid (CSF) by LC-MS/MS		(b) (4)
DTG2832500 (glucuronide of dolutegravire; M3) Human plasma (EDTA)- Original method full validation Title: The validation of a method for the determination of GSK2832500 (range 1 to 1000 ng/mL) in human plasma using HPLC-MS/MS	ING113125	2011N122389 GSK

2.6.4.1- 5.
What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?
What are the lower and upper limits of quantification (LLOQ/ULOQ)?
What are the accuracy, precision, and selectivity at these limits?
What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?
What is the QC sample plan?

Please refer to the following table for information pertaining to questions 2.6.4.1.-2.6.4.5

Table 2.6.5 Summary of bioanalysis method validation

Validation report	LLOQ, validation range, QC levels, precision , accuracy, and stability
DTG human plasma EDTA (original method)	Lower limit of quantitation: 5 ng/mL Validated Range: 5- 5000 ng/mL QC levels: 5, 20, 400, 4000, and 5000 ng/mL Within-run Precision (% CV): ≤ 14.4% Between-run Precision (% CV): ≤ 3.8% Within-run Accuarcy (% Bias): -8.4 ≤ bias ≤-0.7% Stability in Human Plasma: At least 3 freeze-thaw cycles from - 30ºC At least 16 months at - 30ºC At least 24 hours at ambient temperature Processed Extract Stability : At least 3 days at ambient temperature
DTG human plasma EDTA (lower limit of quantitation raised)	Lower limit of quantitation: 20 ng/mL Validated Range: 20- 20000 ng/mL QC levels: 20, 60, 1600, 16000, 20000 ng/mL Within-run Precision (% CV): ≤ 4.5% Between-run Precision (% CV): ≤ 2.7% Within-run Accuarcy (% Bias): -0.3 ≤ bias ≤-9.6% Stability in Human Plasma: At least 3 freeze-thaw cycles from - 20ºC At least 265 days at - 20ºC At least 24 hours at ambient temperature Processed Extract Stability : At least 3 days at ambient temperature
DTG human plasma (EDTA) (Transfer of original method to (b) (4) Full validation)	Lower limit of quantitation: 20 ng/mL Validated Range: 20- 20000 ng/mL QC levels: 20, 60, 1600, 16000, 20000 ng/mL Within-run Precision (% CV): ≤ 8.0% Between-run Precision (% CV): ≤ 7.5% Within-run Accuarcy (% Bias): -1.6 ≤ bias ≤16.9% Stability in Human Plasma: 5 freeze-thaw cycles from - 20ºC and - 70ºC At least 373 days at - 20ºC At least 147 hours at ambient temperature

	Processed Extract Stability : At least 3 days at ambient temperature
DTG Phosphate buffered Saline (PBS)	Lower limit of quantitation: 1ng/mL Validated Range: 1-1000 ng/mL QC levels: 1, 3, 80, 800, 1000 ng/mL Within-run Precision (% CV): ≤ 6.2% Between-run Precision (% CV): ≤ 2.2% Within-run Accuarcy (% Bias): -4.4 ≤ bias ≤4.4% Stability in PBS : At least 3 cycles from 4ºC to ambient At least 17 days at 4ºC At least 24 hours at ambient temperature Processed Extract Stability : At least 1 day at ambient temperature
DTG human cerebrospinal fluid	Lower limit of quantitation: 1ng/mL Validated Range: 1-1000 ng/mL QC levels: 1, 3, 30, 150, 750 ng/mL Within-run Precision (% CV): ≤ 9.0% Between-run Precision (% CV): ≤ 12.7% Within-run Accuarcy (% Bias): -10.0 ≤ bias ≤17.8% Stability in Human Plasma: 5 freeze-thaw cycles from - 20ºC and - 70ºC At least226 days at - 20ºC and - 70ºC in CSF:plasma 1:1 At least 6.5 hours at ambient temperature Processed Extract Stability : At least 109 hours at ambient temperature
DTG2832500 (glucuronide of dolutegravire; M3) Human plasma (EDTA)- Original method full validation	Lower limit of quantitation: 1ng/mL Validated Range: 1-1000 ng/mL QC levels: 1, 3, 80, 800, 1000 ng/mL Within-run Precision (% CV): ≤ 12.6% Between-run Precision (% CV): ≤ 1.4% Within-run Accuarcy (% Bias): -3.9 ≤ bias ≤12.8% Stability in Human Plasma: at3 least freeze-thaw cycles from - 20ºC and - 70ºC At least 127 days at - 20ºC At least 24 hours at ambient temperature Processed Extract Stability : At least 48 hours at ambient temperature Stability in Human Blood : At least 2 hours at 37 ºC : At least 2 hours at ambient temperature

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4. Appendices

4.1. Individual study review

4.1.1 General clinical pharmacology and biopharmaceutics

Individual study review ING111853

Study title An Open Label, Non-Randomized, Single dose, Mass Balance Study to Investigate the Recovery, Excretion, and Pharmacokinetics of 14C-GSK1349572 20 mg, Administered as a Single Oral Suspension Dose to Healthy Adult Subjects (ING111853)

Site of investigation Covance Clinical Research Unit Madison, WI

Study initiation date 17 February 2009

Study completion date 21 April 2009

Objective

Primary

- To determine the total recovery and relative excretion of total radiocarbon in urine and feces after a single, oral suspension dose of [^{14}C]-GSK1349572.
- To describe the pharmacokinetics of total radiocarbon in blood and plasma relative to plasma GSK1349572 pharmacokinetics after a single, oral suspension dose of [^{14}C]-GSK1349572.
- To generate samples (for a separate investigation) with which to define the metabolic profile of GSK1349572 in plasma, urine, and feces and to identify and quantify (where possible) major metabolites in these matrices following administration of a single oral suspension dose of [^{14}C]-GSK1349572.

Secondary

- To evaluate the safety and tolerability of GSK1349572 following single-dose, oral administration in healthy subjects.
- To determine the blood:plasma ratio of [^{14}C]-GSK1349572-related material and the amount of total radiocarbon associated with blood cellular components.

Study Design

This was a Phase I, open-label, single dose, mass balance study in a cohort of 6 healthy adult male subjects. After an overnight fast of at least 10 hours, each subject received a single oral suspension dose of GSK1349572 at 20 mg containing [^{14}C]-GSK1349572 of approximately 80μCi (0.96 mSv) of radioactivity. Following dosing, serial whole blood and plasma samples were collected for a minimum of 72 hours post dose. Urine and fecal samples were collected for a minimum of 120 hours post dose. On-

site measurement of total radiocarbon present in individual samples (plasma, urine, and feces) was performed.

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male subjects between 30 and 55 years of age.
- Body weight ≥50kg and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).
- A history of regular bowl movement (averaging one or more bowel movement per day)

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- Subjects who had received a total body radiation dose of greater than 5.0mSv (upper limit of WHO category II) or exposure to significant radiation (e.g. serial x-ray or computed tomography [CT] scans, barium meal etc) in the 12 months prior to this study. Any condition that could have interfered with the accurate assessment and recovery of radiocarbon
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

Permitted Medications

Acetaminophen, at doses of ≤2 g/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor.

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and

sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Drugs Used in This Study
GSK1349572 (DTG) 20 mg oral suspension administered as a single dose only (batch number: R17450/136/1)

Sample Collection
Plasma sample collection
Collections of whole blood and plasma samples continued to a minimum of 72 hours post dose and until the measured total radiocarbon for two consecutive samples fell below the background radiation count twice or until cessation of both urine and stool collections, whichever occurred first. The actual date and time of each blood sample collection were recorded.

Urine and stool sample collection
After dosing, pooled collections of urine and stool samples during each collection interval continued for up to 10 days post-dosing (minimum of 5 days) or until the total radiocarbon in pooled sample from one collection interval fell to ≤1% (~0.96μCi) of the administered radiocarbon dose for two consecutive 24-hour periods, whichever occurred first. Thus, if the total radiocarbon measured in the 72 to 96 and 96 to 120-hour collections were both ≤1% of the administered radiocarbon dose, further collections were not necessary. Any ongoing collections at the time the radioanalysis report confirmed the end of sample collection may have been discarded.

Bioanalysis assessments
Plasma samples
Human plasma samples were analyzed for GSK1349572 using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. The lower limit of quantification (LLQ) for GSK1349572 was 5 ng/mL using a 25 uL portion of human plasma with a higher limit of quantification (HLQ) of 5000 ng/mL. Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.

Radioanalysis in plasma
A portion (1.0 mL) of each pooled human plasma sample was mixed with 0.5 mL of EDTA disodium salt solution (10 mg/mL in water) prior to initial extraction. The sample was extracted by methanol followed by acetonitrile. The total weight of the combined extract was determined and a portion (240 to 850 μg) was removed for LSC to determine the efficiency of extraction of radiocarbon. The combined supernatant was dried under a stream of nitrogen and reconstituted by adding methanol (200 μL) and water containing

EDTA (2 mg/mL, 1000 µL). The sample extract was centrifuged at 21000 g for 5 minutes and a portion (20 to 50 µg) was removed to determine the recovery of radiocarbon upon reconstitution. A portion of each extract (200 to 1000 µL) was analyzed by using HPLC with radiochemical detection.

Radioanalysis in urine

A pooled urine sample (1500 µL) from each subject was centrifuged and a portion (1000 µL) was analyzed by using HPLC with radiochemical detection. A portion of urine (100 µL) was removed before and after centrifugation and analyzed by using LSC to monitor the recovery of radiocarbon.

Radioanalysis in feces

For each subject, a weighed portion (approximately 0.3 g) of pooled fecal homogenate was mixed with 0.15 mL of EDTA disodium salt solution (10 mg/mL in water) prior to initial extraction. The sample was extracted by adding one volume of methanol and vortex mixing, followed by two times of acetonitrile extraction and acetonitrile water:formic acid (50:50:0.1, v/v) of the residual pellet. The weight of each combined extract was determined and a portion (90 µg) was assayed in duplicate by using LSC to determine the recovery of radiocarbon. The supernatant was dried under a stream of nitrogen and reconstituted by the addition of methanol (200 or 300 µL) and water (1500 or 2500 µL). The sample extract was centrifuged at 21000 g for 5 minutes and duplicate portions (20 to 50 µg) were removed to determine the recovery of radiocarbon upon reconstitution. A portion (1000 µL) was analyzed by using HPLC with radiochemical detection.

Metabolite isolation and identification

LC-MS/MS was used to analyze samples of plasma, urine, and feces homogenate. During the LC separation, a post column split was used to direct 25% of the sample to an LTQ-Orbitrap mass spectrometer implementing data dependent scanning by using a parent mass list. The parent mass list consisted of masses of all known and probable metabolites. A full scan mass spectrum at resolution 30,000 was collected and the data were interrogated in real- time to identify mass peaks (+/- 5 ppm) corresponding to masses in the parent mass list. If present, the parent mass peaks were selected as target peaks for subsequent MS/MS scans under either high or low resolution settings.

The remaining 75% of LC effluent from the post column split was directed into to a LEAP Collect Pal fraction collector and the radioactivity in each well was measured by using a Perkin Elmer Topcount NXT microplate scintillation counter. The reconstructed radiochemical profiles were compared to the LC-MS data and the definitive radiochemical profiles to ensure proper peak assignment. The presence of metabolites in samples from a given matrix not directly analyzed by mass spectrometry was inferred from the presence of components with retention times similar to those in the characterized samples.

Results

Subject Disposition and Demographics

A total of 6 subjects were enrolled and all completed the study as planned. All subjects were healthy. The mean age (range) was 37.5 years (32 to 46 years).

Table 1. Summary of demographic characteristics

Demographics	**All Subjects (n=6)**
Age in Years, Mean (SD)	37.5 (6.28)
Sex, n (%)	
Male:	6 (100%)
BMI (kg/m2), Mean (SD)	26.6 (1.93)
Height (cm), Mean (SD)	180.5 (5.39)
Weight (kg), Mean (SD)	86.9 (10.56)
Ethnicity, n (%)	
Hispanic or Latino:	1 (17%)
Not Hispanic or Latino:	5 (83%)
Race, n (%)	
White – White/Caucasian/European Heritage	6 (100%)

Pharmacokinetic results

Plasma and blood DTG pharmacokinetics

Mean concentration-time profiles for plasma GSK1349572, plasma radiocarbon, and blood radiocarbon are presented in Fig 1. Geometric mean PK parameters of GSK1349572 are shown in Table 2. No plasma GSK1349572 concentrations were excluded from the PK analysis. For plasma radiocarbon, data from Subject 531002 values are not reportable due to out-of-range variation and insufficient sample volume for duplicate sample reanalysis, therefore, this data was excluded from PK analysis. For blood radiocarbon, several samples (Subject 531001: 1 h, 1.5 h, 6 h Subject 531002: 2 h, 12 h Subject 531003: 48 h, Subject 531004: 0.5 h, 1 h, 8 h, Subject 531005: 0.5 h, 5 h, Subject 531006: 0.5 h, 1.5 h, 72 h) are not reportable due to out-of-range variation and insufficient sample volume for duplicate sample reanalysis, and all these data were excluded from PK analysis. Values for the 10-hour samples for all subjects were missing due to oxidizer malfunction and insufficient sample volume for duplicate sample reanalysis.

Reviewer comments: The missing time points may have some impact on t_{max} and C_{max} of blood. Five out of six subjects have at least one missing sample for the first 2 hour window where C_{max} and T_{max} were observed.

The following are key findings based on the plasma pharmacokinetics, plasma radiocarbon, blood radiocarbon of GSK1349572. First, the study results indicated that GSK1349572 is the predominant circulating compound. The individual ratio of the plasma AUC(0-τ) of GSK1349572/the total plasma radiocarbon AUC(0-∞) has a mean of 0.97 with range of 0.95~0.99 (mean 0.97). Second, low mean blood:plasma concentration ratios indicated minimal association of radioactivity with the blood cellular components. The mean blood:plasma concentration ratios of [^{14}C]-GSK1349572-related material from 0.5 hour through 72 hours post-dose ranged from 0.441 to 0.535; association with blood cellular components was <5% at all time points in all subjects. Third, the estimated terminal half-lives were similar among

plasma GSK1349572, plasma radiocarbon and blood radiocarbon, suggesting that there are no metabolite(s) with aprolonged half-life.

Fig 1. Mean concentration-time profiles for plasma GSK1349572, Plasma radiocarbon, and blood radiocarbon.

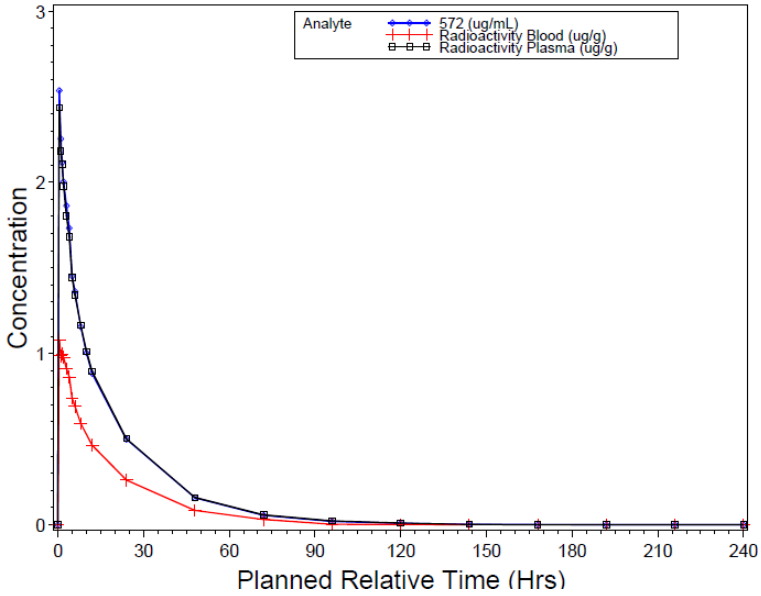


Table 2. Summary of plasma GSK1349572, plasma radiocarbon, and blood radiocarbon pharmacokinetic parameters, following a single oral dose administration of [^{14}C]-GSK13495721 (n=6)

	C_{max} (µg/mL)	T_{max} (h)	$AUC_{(0-t)}$ (µg.h/mL)	$AUC_{(0-\infty)}$ (µg.h/mL)	T1/2 (hr)
Plasma GSK1349572	2.57 (24)	0.50 (0.50-2.00)	35.7 (12)	35.9 (12)	15.6 (16)
plasma radiocarbon	2.46 (24)	0.50 (0.50-1.50)	35.9 (11)	36.1 (11)	15.7 (14)
blood radiocarbon	1.13 (25)	1.25 (0.50-2.00)	17.7 (13)	18.4 (13)	14.6 (12)

Geometric mean (CV%) except T_{max} [median, (range)]

Reviewer comments: The results are comparable with historical data (25 mg single oral dose administration of DTG in suspension (ING112077)

Circulating metabolites of GSK1349752 in plasma

The principal radiolabeled component in the 6, 24 and 48 hour plasma samples was unchanged GSK1349572 which represented 95.2, 96.8 and 99.8% of plasma radiocarbon (1190, 481, and 150 ng eq./g) at these time points, respectively. An ether glucuronide conjugate (M3) represented 2.4 and 1.5% of

the plasma radiocarbon (29.9 and 7.4 ng eq./g) at 6 and 24 hours post dosing, respectively. This metabolite was not detected in the 48 hour post dose plasma sample.

Table 3. Radiochrmatographic analyses of plasma following a single oral dose of [^{14}C]GSK1349572 20 mg

Peak ID	Retention Time (minutes)	% Plasma Radiocarbon (ng equivalents [^{14}C]GSK1349572/g)		
		Male		
		6 h	24 h	48 h
M3	24.6	2.4 (29.9)	1.5 (7.4)	ND
GSK1349572	44.4	95.2 (1190)	96.8 (481)	99.8 (150)
Total [^{14}C]GSK1349572-related Material Assigned		97.6 (1220)	98.3 (488)	99.8 (150)

ND = Not Detected.

Urine

The radiocarbon in the 0 to 72 hour male human urine samples examined represented a mean of 30.2% of the administered dose, which equated to 95.6% of the material excreted by this route. The prinicipal radiolabeled component in human urine was an ether glucuronide conjugate (M3) which represented 62.5% of the urinary radiocarbon (18.9% of the dose). Two other notable products M1 (N-dealkylation) and M7 (oxidation at the benzylic carbon) represented means of 11.8 and 10.1% of the urinary radiocarbon (3.6 and 3.0% of the dose), respectively. Unchanged GSK1349572 represented 2.2% of the urinary radiocarbon (0.7 % of the dose). Other unidentified components present in human urine each represented ≤3.3% of the urine radiocarbon (≤1.0% of the dose).

Feces

The radiocarbon in the pooled male human fecal homogenate samples represented a mean of 59.7% of the administered dose, which equated to 93.3% of the material excreted by this route. The recovery of radiocarbon following solvent extraction of human fecal homogenates ranged from 94.9 to 101.3%. Recovery of radiocarbon upon reconstitution of dried fecal extracts ranged from 84.7 to 98.5%. Recovery of radiocarbon from the column was 99.7%.

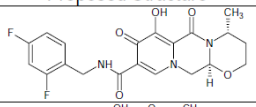
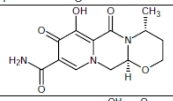
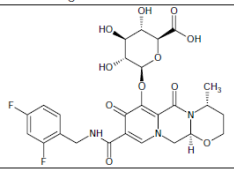
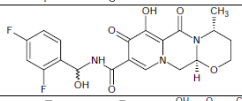
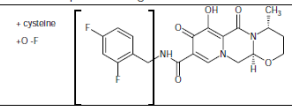
The principal radiolabeled component in male human feces was unchanged GSK1349572 which accounted for a mean of 89.1% of the fecal radiocarbon (53.1% of the dose). It is not clear how much of the unchanged GSK134572 in the feces is due to unabsorbed dose and how much may be due to biliary secretion of the ether glucuronide conjugate with subsequent conversion of the conjugate to parent. Two other identified products, M1 (N-dealkylation) and M13 (fluorine loss; cysteine and oxygen addition), represented a mean of 2.2 and 3.1 % of the fecal radiocarbon (1.3 and 1.8% of the dose), respectively. An additional unidentified component in feces represented 1.7% of the fecal radiocarbon (1.0% of the dose).

Table 3. Summary of the radiochromatographic analyses of urine and feces following a single oral dose of [^{14}C]GSK1349572 20 mg

Peak ID	Retention Time (minutes)	Mean % Matrix Radiocarbon (mean % dose)	
		Urine	Feces
M1	12.2-12.8	11.8 (3.6)	2.2 (1.3)
M13	24.0-24.4	NA	3.1 (1.8)
M3	24.4-24.8	62.5 (18.9)	ND
M7[a]	37.2 + 40.2	10.1 (3.0)	ND
GSK1349572	44.4	2.2 (0.7)	89.1 (53.1)
Total Radioactive Material Assigned		86.6 (26.2)	94.4 (56.3)
% Dose in Matrix Pool Analyzed		30.2	59.7
Total % Dose Excreted in Matrix (all timepoints)[b]		31.6	64.0

a. M7 appeared as two separate chromatographic peaks at 37 and 40 minutes in human urine. These peaks had identical MS spectra, and are thought to be interconverting rotamers (RD2008/00220/00). The reported values for M7 are the sum of both peaks.
b. Data obtained from GSK Study Report RD2009/01002/00.
NA = Not Analyzed. Radioactivity was present at this RT; however, structural identification was not performed due to low concentration.
ND = Not detected, below lower limit of detection (detection limit set to 3 times background).

Table 4. Summary of metabolites of GSK1349572 identified in plasma, urine, and feces of healthy male human subjects

ID	Biotransformation	Proposed Structure	Matrix
GSK1349572	Parent		Plasma, urine, feces
M1	N-dealkylation		Urine, Feces
M3	Glucuronidation		Plasma, urine
M7	Oxidation		Urine
M13	Fluorine loss; cysteine and oxygen addition		Feces

Reviewer comments
In vitro study results indicated that the enzymes responsible for M3 and M1 formation are UGT1A1 and CYP3A4, respectively. At this time, it is unknown what enzyme is responsible for M13 formation.

Safety results
No non-fatal or fatal SAEs were reported during the study. No subjects were withdrawn from the study due to AEs. The most frequently reported drug-related AE was diarrhea (2 subjects; 33%;). All other drug-related AEs were reported in only one subject each (headache, intention tremor, and areflexia). No clinically significant trends in clinical laboratory values, vital signs, or ECGs were observed.

Conclusion
The total mean recovery was 95.6% of the administered dose with a mean recovery of 64.0% in feces and 31.6% in urine. GSK1349572 was the predominant circulating compound in plasma. Low mean blood:plasma concentration ratios indicated minimal association of radioactivity with the blood cellular components.

Individual study review ING113674

Title: Relative Bioavailability Study of three Different Tablet Formulations of GSK1349572 50 mg and the Dose Proportionality of and Effect of Food on the Selected Formulation in healthy male and female volunteers

Purpose of Review: The focus of this review is only on part two (the food effect portion) of this study.

Study Initiation Date: April 13, 2010, Completion Date: July 06, 2010

Objective:
One of the objectives of this study was to evaluate the effect of a low fat meal, moderate fat meal, and high fat meal on the selected new formulation at a selected dose 50 mg (2X25 mg tablet). One of the secondary objectives was to assess the safety and tolerability of GSK1349572 50 mg (2X25mg tablets) given with a low fat meal, moderate fat meal, and high fat meal.

Study Design:
Eighteen subjects who completed the 3 dosing periods in Part A (dose proportionality) continued to participate in Part B (food effect), a randomized, open-label, single dose, 3-way crossover study with 7-day washout period. Based on the PK results from Part A, GSK1349572 50 mg (AW) (2X25 mg) formulation was used.

Treatment Regimen:
A single dose of GSK1349572 50 mg AW (2X25 mg tablets, batch number 101241248 by GSK, Harlow) was administered with the following foods.
Low-fat containing 7% fat (300 kcal)
Moderate-fat containing 30% fat (600 kcal)
High-fat containing 53% fat (870 kcal)

Study Population:
All 18 subjects enrolled in part B of the study completed the study. The demographics of the subjects are shown in the following table.

Table 1: Study Subjects

SUBJECTS DEMOGRAPHICS	
Subjects	9 Male and 9 Female
Age(yr)	41.8 $\pm$ 14.4
Weight(kg)	69.6 $\pm$ 10.3
Height(cm)	168.4 $\pm$ 10.8
BMI ()	24.5 $\pm$ 2.4
Race	17 White/Caucasian, 1 White Arabic-North African

Note: Data presented as mean ± SD

Sample Collection for Pharmacokinetic Measurements:
Blood samples (2 mL each) for the determination of concentrations of dolutegravir were collected at the following specified times during each period: prior to dosing (zero hour) and at 1, 2, 3, 4, 5, 6, 8, 12, 24, and 48 hours post dosing.

Bioanalytical:
A validated bioanalytical method was employed using HPLC-MS/MS for determination of dolutegravir in human plasma. The following table shows the bioassay performance for this study.

Table 2: Assay Performance

Analytical	**Dolutegravir**		
Range µg/mL	**0.02 – 20.00**		
Nominal. µg/mL	**0.06**	**1.66**	**16.00**
QC Conc. µg/mL	**0.06**	**1.70**	**16.02**
Precision %CV	**3.5**	**4.1**	**4.4**
Bias %	**2.1**	**3.9**	**0.2**

Pharmacokinetic and Statistical Analysis:
WinNonlin® version 5.3 was used for calculation of the pharmacokinetic parameter values for dolutegravir. The following table contains the summary of the pharmacokinetic parameters.

Table 3: Summary of Plasma Pharmacokinetic Parameters, Mean ± SD, N=18

PK-Parameter	**Fasting**	**Low Fat**	**Mod. Fat**	**High Fat**
C_{max} (µg/mL)	**2.75 ± 0.82**	**3.95 ± 0.82**	**4.10 ± 0.74**	**4.56 ± 1.14**
C_{24} (µg/mL)	**0.79 ± 0.24**	**1.07 ± 0.37**	**1.15 ± 0.36**	**1.41 ± 0.54**
T_{max} (h)	**2.73 ± 1.27**	**3.23 ± 0.82**	**3.84 ± 0.98**	**4.23 ± 1.63**
AUC_{0-t} (µg•h/mL)	**46.71 ± 13.05**	**63.36 ± 17.95**	**66.52 ± 16.10**	**78.64 ± 22.96**
AUC_{∞} (µg•h/mL)	**52.02 ± 14.43**	**70.19 ± 21.29**	**73.83 ± 19.26**	**88.02 ± 28.20**
$T_{1/2}$ (hr)	**14.35 ± 2.79**	**13.64 ± 2.40**	**13.71 ± 2.26**	**13.66 ± 2.50**
CL/F (L/hr)	**1.03 ± 0.26**	**0.79 ± 0.30**	**0.74 ± 0.27**	**0.63 ± 0.23**
V_{dz}/F (L)	**20.92 ± 5.55**	**14.88 ± 3.42**	**14.01 ± 3.04**	**11.83 ± 2.58**

SAS® software for Windows release 9.1 was used for the statistical analysis of this study. The PROC MIXED procedure with model being treatment, and period with subject as random effect was used for the analysis of the variance. The results of the statistical analysis i.e. geometric least squares means, the point estimates (ratio of test divided by the reference), and 90% confidence intervals are shown in the following table.

Table 4: Statistical Summary, N=18

Test & Reference	C_{max}		C_{24}		$AUC_{(0-t)}$		$AUC_{(0-\infty)}$	
	Ratio	**90%CI**	**Ratio**	**90%CI**	**Ratio**	**90%CI**	**Ratio**	**90%CI**
Low-fat vs fasting	**146.2**	**133.7 – 159.8**	**133.0**	**119.9 – 147.5**	**134.3**	**122.9 – 146.8**	**132.7**	**121.4 – 145.2**
Modrate-fat vs fasting	**152.1**	**139.1 – 166.3**	**145.1**	**130.8 – 161.0**	**142.5**	**130.4 – 155.7**	**141.2**	**129.1 – 154.5**
High-fat vs fasting	**167.4**	**153.1 – 183.1**	**172.9**	**155.8 – 191.8**	**167.0**	**152.8 – 182.5**	**152.1**	**152.1 – 182.0**

Based on the results reported by the sponsor for this study the exposure to dolutegravir increased as the fat content of the food increased. Dolutegravir AUCt increased by 34%, 43%, and 67% when administered with a low-fat, medium-fat, and high-fat meal, respectively, as compared with fasting. Similar increases were observed for Cmax and C24 for all three fed conditions. It has been shown that this increase in exposure is not considered clinically significant.

Protocol Deviations:
There was no protocol deviation reported.

Safety and Tolerability:
One subject complained of feeling hot when dolutegravir was administered with moderate fat meal. This was the only AE reported in part B which was not considered to be related to the study medication. The treatments were tolerated well by the study subjects.

Conclusion:
There was an increase in exposure when dolutegravir AW was administered with low-fat, moderate-fat, and high-fat food. Based on $AUC_{(0-t),}$ the exposure to dolutegravir increased by 34%, 42% and 67% when dolutegravir was administered with a low, moderate, and high fat meal, respectively, as compared with fasting.

Dolutegravir has a favorable safety profile and a 67% increase in exposures is not considered clinically significant. Furthermore, subjects were instructed to take dolutegravir without regard to food (or content of food) in the pivotal phase 3 trials. Thus, it is acceptable to recommend that dolutegravir be administered without regard to food in the label.

Individual study review ING114005

Title: A Phase 1, Open Label, Single Sequence, Three Period Study to Evaluate the Single Dose Pharmacokinetics of GSK1349572 100 mg versus 50 mg and the Effect of Efavirenz 600 mg Once Daily on the Pharmacokinetics, Safety and Tolerability of GSK1349572 50 mg Once Daily in Healthy Adult Subjects

Purpose of Review: The focus of this review is only on period one and two (the dose proportionality) of this study.

Study Initiation Date: Mar 16, 2010
Study Completion Date: May 26, 2010

Objective:
One of the primary PK objectives of this study was to evaluate the dose proportionality of single dose GSK1349572 (dolutegravir) 50 mg (2X25 mg) and 100 mg (4X25 mg) oral tablets under fasted conditions.

Study Design:
The study was an open-label, single-sequence, three-period, study. Twenty-five milligram (25 mg) tablets manufactured by Shionogi Japan batch number 091213013 were used for this dose proportionality assessment. In the first treatment period, subjects received treatment A, a single dose 100 mg (4X25 mg) of GSK1349572, as the test treatment. In Period 2 subjects received treatment B, 50 mg (2X25 mg) of GSK1349572 q24h in the morning for 5 days, the reference treatment. Data from period 1 and day one of period 2 were used for the assessment of dose proportionality between single-dose 50 mg and 100 mg treatments. The study medications were administered under fasted conditions (with 240 mL of water following an over-night fast). There was a 6-day wash-out between period one and two.

Study Population:
All twelve subjects enrolled in this study completed the study. The demographics of the subjects are shown in the following table.

Table 1: Study Subjects

Subjects Demographics	
Subjects	All Male
Age(yr)	38.7 $\pm$ 15.2
Weight(kg)	83.3 $\pm$ 12.6
Height(cm)	176.8 $\pm$ 8.1
BMI (kg/m^2)	26.6 $\pm$ 3.2
Note: Data presented as mean ± SD	

Sample Collection for Pharmacokinetic Measurements:

Blood samples (2 mL each) for the determination of concentrations of dolutegravir were collected at the following specified times during period 1 and day one of period 2: prior to dosing (zero hour) and at 1, 2, 3, 4, 8, 12, and 24 hours post dosing.

Bioanalytical:
A validated bioanalytical method was employed using HPLC/MS/MS for determination of dolutegravir in human plasma. The following table shows the bioassay performance for this study.

Table 2: Assay Performance

Parameter	**Dolutegravir**		
Analytical Range (µg/mL)	**0.02 – 20.00**		
Nominal. µg/mL	**0.06**	**1.60**	**16.00**
QC Conc. µg/mL	**0.63**	**1.71**	**16.89**
Precision %CV	**3.0**	**4.7**	**5.3**
Bias %	**4.7**	**6.6**	**5.5**

Results
Pharmacokinetic and Statistical Analysis:
There was no carryover effect as the zero hour plasma concentrations for none of the subjects were quantifiable. WinNonlin® version 5.3 was used for calculation of the pharmacokinetic parameter values for dolutegravir. The following table contains the summary of the pharmacokinetic parameters.

Table 3: Summary of Plasma Pharmacokinetic Parameters, Mean ± SD, N=12

PK-Parameter	**Trt. A**	**Trt. B**
C_{max} (µg/mL)	**2.91 ± 0.89**	**1.93 ± 0.63**
C_{24} (µg/mL)	**0.89 ± 0.41**	**0.61 ± 0.35**
AUC_{0-24} (µg•h/mL)	**36.51 ± 6.29**	**26.28 ± 10.89**
T_{max} (h)	**2.25 ± 1.29**	**2.17 ± 1.27**

SAS® software for Windows release 9.2 was used for the statistical analysis. The PK parameters for 100 mg dose were dose normalized to the lowest dose, 50 mg, by dividing the PK parameter values by 2. The geometric means for dose normalized PK parameters, the point estimate (ratio of test divided by the reference), and 90% confidence intervals are shown in the following table.

Table 4. Summary statistics, (N=12)

PK-Parameter	**Treatment A**	**Treatment B**	**Point Estimate (%)**	**90% CI**
C_{max} (µg/mL)	**1.38**	**1.83**	**75.6**	**64.8 – 88.3**
C_{24} (µg/mL)	**0.40**	**0.53**	**75.0**	**63.9 – 88.1**

$AUC_{(0-24)}$ (µg•h/mL)	**17.13**	**24.30**	**70.5**	**59.7 – 83.3**

Based on the results for AUC, C_{max}, and C_{24} the exposure was less than dose proportional as the dose increased from 50 to 100 mg.

Protocol Deviations:
There was no protocol deviation reported.

Safety and Tolerability:
There were no serious adverse events reported due to single dose of 50 mg or 100 mg DTG in this study. The DTG treatments were tolerated well by the study subjects.

Conclusion:
The exposures to GSK1349572 were less than dose proportional as the dose increased from 50 mg to 100 mg when given as a single dose of 2X25 mg tablets versus 4X25 mg tablets under fasted conditions.

Individual study review ING114556

Title: Relative bioavailability study of a tablet formulation vs. pediatric granule formulation of dolutegravir 50 mg and effect of different types of water plus infant formula on the pediatric granule formulation in healthy male and female volunteers

Study Initiation Date: June 21, 2011
Study Completion Date: August 22, 2011

Objective:
The primary objective of this study was to evaluate relative bioavailability of a single 50 mg oral dose of dolutegravir (DTG) granule formulation given without liquid or with 30 mL of purified water, Contrex mineral water, or a milk-based infant formula to the tablet formulation administered with 240 mL water under fasting conditions.

The secondary objectives were to evaluate relative bioavailability of an oral DTG granule formulation given as single 50 mg dose in the fasted state administered directly to mouth, in mineral water (Contrex), or in infant formula (milk-based) compared to DTG granule administered in purified water (treatment C). Additionally the safety and tolerability as well as the palatability were evaluated.

Study Design:
This was a single-center, randomized, open-label, 5-period, crossover study in healthy adult subjects. This study evaluated the single dose PK of a new oral granule formulation of dolutegravir to the tablet formulation.
Reference Treatment:

Treatment A: 50 mg tablet, administered with 240 mL of water
(Batch number 101258084, GSK)
Note: this formulation was selected for use in phase 3 clinical trial

Test treatments:
Treatment B: 50 mg granules, administered directly to mouth without liquid
Treatment C: 50 mg granules, administered with 30 mL of purified water
Treatment D: 50 mg granules, administered with 30 mL of Contrex mineral water
Treatment E: 50 mg granules, administered with 30 mL of infant formula
(Granules batch number S11010, Shionogi)
Note: Treatments C, D, and E were dispersed in 15 ml plus 15 ml of rinse.

Subjects fasted overnight prior to each treatment. There was a 7-day wash-out between treatment periods. This 7-day wash-out period was adequate to assure no carryover effect.

Study Population:
All twenty subjects enrolled in this study completed the study. The demographics of the subjects are shown in the following table.

Table 1: Study Subjects

SUBJECTS DEMOGRAPHICS	
Subjects	10 Male and 10 Female
Age(yr)	41.9 ± 11.9
Weight(kg)	72.9 ± 16.9
Height(cm)	168.2 ± 12.6
Race	19 Caucasian, 1 African-American
Note: Data presented as mean ± SD	

Sample Collection for Pharmacokinetic Measurements:
Blood samples (2 mL each) for the determination of concentrations of dolutegravir were collected at the following specified times during each period: prior to dosing (zero hour) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, and 48 hours post dosing.

Bioanalytical Method Validation:
The concentrations of dolutegravir in human plasma were determined by using liquid chromatography (HPLC/MS/MS) using a TurbolonSpray™ method. Validation of the bioanalytical methods performance used for the determination of concentrations of dolutegravir in plasma are presented in the following table.

Table 2: Bioanalytical Method Validation

Analytical Parameters	**Dolutegravir**

Analytical Range µg/ml	**0.02 – 20.00**
Inter-day Precision (%CV)	**3.6 – 7.5**
Inter-day Accuracy (%RE)	**2.3 – 10.1**
Intra-day Precision (%CV)	**1.1 – 8.0**
Intra-day Accuracy (%RE)	**-1.7 – 16.9**
Recovery (%)	**94.7**
Freeze-thaw Stability LQC (three cycles) (% Difference)	**-4.6**
Freeze-thaw Stability HQC (three cycles) (%Difference)	**-0.8**

The bioanalytical method is acceptable for the analysis of dolutegravir from the plasma samples.

Within Study Bioanalytical Assay:
A validated bioanalytical method was employed using HPLC/MS/MS for determination of dolutegravir in human plasma. The following table shows the bioassay performance for this study.

Table 3: Assay Performance

Analytical	**Dolutegravir**			
Range µg/mL	**0.02 – 20.00**			
Nominal. µg/mL	**0.06**	**1.60**	**16.00**	**20.00**
QC Conc. µg/mL	**0.06**	**1.61**	**16.67**	**20.70**
Precision %CV	**8.4**	**4.7**	**4.6**	**3.7**
Accuracy %	**98.7**	**99.3**	**95.8**	**96.5**

Pharmacokinetic and Statistical Analysis:
WinNonlin® version 5.3 was used for calculation of the pharmacokinetic parameter values for dolutegravir. The following table contains the summary of the pharmacokinetic parameters.

Table 4: Summary of Plasma Pharmacokinetic Parameters, Mean ± SD, N=20

PK-PARAMETER	**TRT. A**	**TRT. B**	**TRT. C**	**TRT. D**	**TRT. E**
C_{max} (µg/mL)	**2.95 ± 0.96**	**4.65 ± 1.08**	**4.77 ± 1.23**	**4.78 ± 1.32**	**5.80 ± 1.35**
C_{24} (µg/mL)	**0.86 ± 0.37**	**1.32 ± 0.46**	**1.31 ± 0.46**	**1.27 ± 0.40**	**1.52 ± 0.41**
T_{max} (h)	**2.00 ± 1.03**	**2.63 ± 1.22**	**2.30 ± 1.50**	**1.87 ± 1.07**	**2.18 ± 0.78**
AUC_{0-t} (µg•h/mL)	**50.70 ± 18.56**	**77.54 ± 20.55**	**77.37 ± 20.75**	**77.23 ± 22.16**	**89.23 ± 19.82**
AUC_{∞} (µg•h/mL)	**57.09 ± 21.75**	**87.27 ± 24.95**	**86.70 ± 25.40**	**86.18 ± 26.38**	**99.78 ± 23.46**

$T_{1/2}$ (hr)	**14.71 ± 3.19**	**14.61 ± 2.82**	**14.37 ± 2.81**	**14.22 ± 2.80**	**14.46 ± 3.28**
CL/F (L/hr)	**1.03 ± 0.45**	**0.62 ± 0.20**	**0.63 ± 0.22**	**0.65 ± 0.28**	**0.53 ± 0.16**

The reviewer-calculated statistics (using SAS® software for Windows release 9.2) are in agreement with the results reported by the sponsor. The GLM procedure with model being sequence, subject within sequence, treatment, and period was used for the analysis of the variance. The results of the statistical analysis for bioequivalence i.e. geometric means, the point estimate (ratio of test divided by the reference), and 90% confidence intervals are shown in the following table.

Table 5: Statistical Summary, N=20

Test & Ref.	**C_{max}**		**C_{24}**		**$AUC_{(0-t)}$**		**$AUC_{(0-\infty)}$**	
	Ratio	**90%CI**	**Ratio**	**90%CI**	**Ratio**	**90%CI**	**Ratio**	**90%CI**
B vs A	162.30	149.11 – 176.65	160.67	147.55 – 174.89	158.23	146.26 – 171.26	158.24	142.23 – 171.17
C vs A	165.88	152.41 – 180.58	158.16	145.21 – 172.29	157.60	145.67 – 170.49	156.71	144.92 – 169.55
D vs A	164.63	151.26 – 179.14	139.39	139.82 – 165.86	155.96	144.20 – 168.71	154.57	142.89 – 167.20
E vs A	202.47	186.08 – 220.38	187.60	172.29 – 204.42	183.66	169.72 – 198.77	182.94	169.13 – 197.90
B vs C	97.84	89.88 – 106.48	101.63	93.30 – 110.65	100.40	92.77 – 108.62	100.97	93.33 – 109.20
D vs C	99.25	91.18 – 108.00	96.26	88.42 – 104.87	98.96	91.48 – 107.04	98.63	91.18 – 106.70
E vs C	122.06	112.13 – 132.84	118.62	108.95 – 129.21	116.54	107.74 – 126.09	116.72	107.92 – 126.28

Based on these results for AUC, C_{max}, and C_{24} the bioavailability of granules is approximately 50% higher than the tablet formulation under fasted conditions. The bioavailability of the dolutegravir granules administered with Cortex mineral water or administered directly to mouth are similar to granules administered with pure water.

The bioavailability of dolutegravir granules administered with infant formula is approximately 16% higher than granules administered with pure water (treatment C). When dolutegravir tablets were administered under fed conditions, the AUCs were increased by 33%, 41% and 66% when dolutegravir was administered with low fat, moderate fat and high fat food, respectively, compared to fasting conditions (study ING113674).

Protocol Deviations:
There was no protocol deviation reported.

Safety and Tolerability:
There were no serious adverse events reported in this study. The fifteen adverse events reported were mild and were not considered to be related to DTG. The treatments were tolerated well by the study subjects.

Conclusion:
The 90% confidence intervals for dolutegravir are not contained within 80% - 125% for both AUC and C_{max} indicating that dolutegravir granule 50 mg is not bioequivalent to the tablet formulation administered under fasting conditions. The granule administered with or without liquids provide approximately 50%

higher dolutegravir exposures compared to the tablet formulation under fasting conditions. The granules administered with or without liquid showed similar exposure compared to granules administered with pure water; however, bioavailability was ~16% higher when the granules were administered in infant formula as compared to granules administered with pure water. These study results indicate that although both formulation differences and food can affect the bioavailability of dolutegravir, the granule formulation is not as susceptible to food effects as are the tablets.

Individual study review ING116070

Study title A single-arm study of the safety, efficacy and central nervous system and plasma PK of GSK1349572 (dolutegravir, DTG) 50 mg once daily in combination with the abacavir/lamivudine fixed dose combination tablet over 96 weeks in HIV-1 infected antiretroviral naïve adult subjects (ING116070)

Study initiation date 24 Jan 2012- ongoing

Objective

Primary

- To determine plasma (total and unbound) DTG concentration and evaluate the relationship between DTG concentration in plasma and cerebrospinal fluid (CSF).

Secondary

- To determine the effect of DTG + abacavir/lamivudine (ABC/3TC) on CSF and plasma human immunodeficiency virus type 1 (HIV-1) viral load
- To determine the tolerability, long-term safety, incidence of HIV-associated conditions, antiviral and immunologic activity of DTG in combination with ABC/3TC over time
- To assess the relationship between DTG concentration in CSF and HIV-1 ribonucleic acid (RNA) in CSF at Week 2 and Week 16
- To assess the relationship between HIV-1 RNA suppression in plasma and CSF at Week 2 and Week 16
- To assess the development of viral resistance in subjects experiencing virologic failure.

Study Design

ING116070 is a Phase IIIb single-arm, open-label, multicenter study conducted in HIV-1 infected antiretroviral therapy (ART)-naïve subjects. Subjects fulfilling eligibility requirements received DTG 50 mg once daily in combination with ABC/3TC for 96 weeks. One pair of pharmacokinetic (PK) samples in plasma and CSF (matching time) for determination of DTG concentration were collected at Week 2 and Week 16.

Samples for plasma HIV-1 RNA were collected at baseline and various time points throughout the study and samples for HIV-1 RNA levels in the CSF were collected at Baseline, Week 2 and Week 16. The primary analysis will take place after the last subject completes 16 weeks on therapy; additional analyses will be conducted after the last subject completes Week 2 (subject of this report) and Week 96 (end of study).

Key Inclusion Criteria

- HIV-1 infected adults ≥ 18 years of age
- HIV-1 infection as documented by Screening plasma HIV-1 RNA ≥5000 c/mL
- CD4+ cell count ≥200 cells/mm^3

- Antiretroviral-naïve (≤ 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection)
- Documentation that the subject has been screened for, and is negative for the *HLA- B*5701* allele
- Is willing to undergo serial lumbar punctures as outlined in study evaluations.

Key Exclusion Criteria

- Relative or absolute contraindication to lumbar puncture, such as current coagulopathy, thrombocytopenia (platelets<50,000/μL), hemophilia, or use of anticoagulant medication
- Moderate or severe cognitive impairment
- Women who are pregnant or breastfeeding
- Any evidence of an active Centers for Disease Control and Prevention (CDC) Category C disease except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic CD4+ cell levels <200 cells/mm^3
- Subjects with any degree of hepatic impairment
- Positive for Hepatitis B at screening (+HbsAg), or an anticipated need for Hepatitis C virus (HCV) therapy during the study
- History or presence of allergy or intolerance to the study drugs or their components or drugs of their class
- History of malignancy within the past 5 years or ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma;other localized malignancies require agreement between the investigator and the Study medical monitor for inclusion of the subject
- Recent history (≤ 3 months) of any upper or lower gastrointestinal bleed, with the exception of anal or rectal bleeding
- Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening
- Treatment with radiation therapy, cytotoxic chemotherapeutic agents or any immunomodulators that alter immune responses within 28 days of Screening
- Treatment with any agent, except recognized ART as allowed in inclusion criteria above, with documented activity against HIV-1 in vitro within 28 days of first dose of investigational product (IP)
- Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP
- Any evidence of primary viral resistance based on the presence of any major resistance-associated mutation in the Screening result or, if known, any historical resistance test result. Note: retests of Screening genotypes are not allowed
- Any verified Grade 4 laboratory abnormality (a single repeat test is allowed during the Screening period to verify a result). Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, would preclude the subject's participation in the study of an investigational compound is exclusionary Alanine aminotransferase (ALT) >5 times the upper limit of normal (ULN) ALT ≥ 3xULN and bilirubin ≥ 1.5xULN (with >35% direct bilirubin)
- Subject has creatinine clearance of <50 mL/min via Cockroft-Gault method.

Pharmacokinetic assessments

Bioanalysis

Total plasma DTG

DTG was extracted by protein precipitation using acetonitrile containing [$^{2}H_{7}$,^{15}N]-DTG as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method.

Unbound plasma DTG

The unbound DTG concentrations were measured in phosphate buffered saline (PBS) following equilibrium dialysis of plasma collected from patients. DTG was extracted from PBS using acetonitrile containing [$^{2}H_{7}$,^{15}N]-DTG as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method.

DTG concentrations in CSF

DTG in CSF was mixed 1:1 with blank human plasma and extracted by protein precipitation using acetonitrile containing [$^{2}H_{7}$,^{15}N]-DTG as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method.

For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria. The standard curve and QC data indicated that assay methods of DTG in CSF, PBS, or plasma in this study were precise and accurate as shown in the table 1.

Table 1. Bioanalysis quality control

Matrix	Linear range	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples	Sample range
CSF	1 to 1000 ng/mL $R^2 = 0.993$	1.6% to 6.0%	-3.5% to 0.7%	3, 30, 150, 750 ng/mL	40 to 232 ng/mL
PBS	1 to 1000 ng/mL $R^2 = 0.997$	1.7% to 2.1%	-5.0% to 2.5%	3, 80, 800 ng/mL	10.3 to 23.96 ng/mL
Plasma	20 to 20000 ng/mL $R^2 = 0.996$	2.4% to 4.5%	-2.8% to 1.8%	60, 1600, 16000 ng/mL	2029 to 6013 ng/mL

Results

Study population results

All subjects were white males, 23% were of Hispanic ethnicity and the mean age was 40 years (ranging from 28 to 52 years). All subjects had negative test results for hepatitis C and hepatitis B infection and approximately half were CDC Class A (54%) at entry. All subjects initially received ABC/3TC as their background NRTI therapy at Day 1. Switch of NRTI therapy to an alternative approved NRTI therapy for toxicity management is allowed once during the first 96 weeks of the study.

Pharmacokinetic results

Eleven subjects provided evaluable plasma PK data and CSF PK data at week 2. The summary of sampling time was provided in Table 2. The plasma and CSF DTG concentrations are summarized in Table 3.

Plasma and CSF samples were obtained 2-6 hours post dose. The total plasma concentrations of DTG ranged from 2.09 to 5.28 µg/mL. The CSF concentrations ranged from 0.004 to 0.0232 µg/mL, similar to the unbound concentration in plasma (ranged from 0.0103 to 0.0240 µg/mL). The unbound fraction ranged from 0.33% to 0.65%. There was no significant correlation between CSF and total plasma concentrations or between CSF and unbound plasma DTG concentrations.

Table 2. Summary of subjects providing PK data at week 2

	Hours Post-Dose Sample was Collected				
	2 to <3 hrs	3 to <4 hrs	4 to <5 hrs	5 to <6 hrs	>= 6 hrs
Subjects providing Plasma PK[a]	5	4	1	0	1[b]
Subjects providing CSF PK[a]	6	4	0	1[b]	0

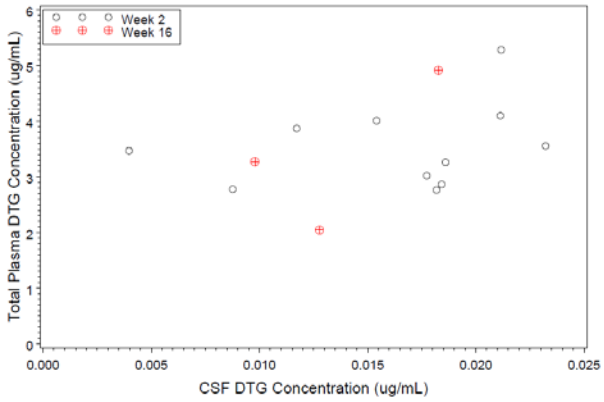
a. Subjects providing at least 1 evaluable PK sample.
b. Subject 21 had plasma and CSF PK samples collected at 6.13 hrs and 5.88 hrs post dose. These samples were determined to be evaluable.

Table 3. Summary of DTG concentration in CSF and plasma at Week 2

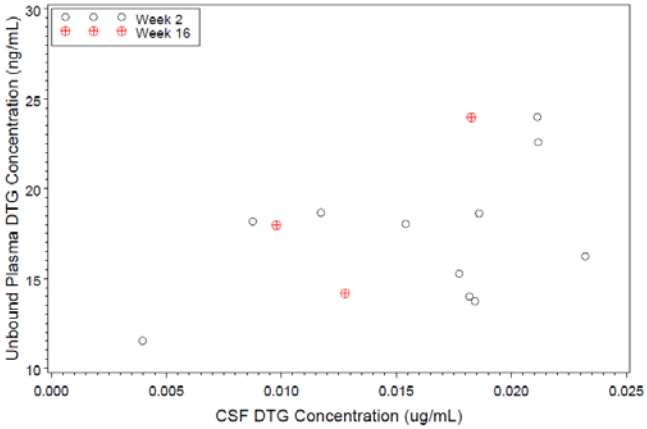
PK Variable, n	**Week 2 Result median (range)**
CSF (µg/mL), n=11	0.0182 (0.0040 – 0.0232)
Total Plasma (µg/mL), n=12	3.36 (2.09 – 5.28)
Unbound Plasma (µg/mL),n=12	0.0171 (0.0103 – 0.0240)
Unbound Fraction (%), N=12	0.49 (0.33 – 0.65)
CSF/Plasma Ratio (%)	0.52 (0.11 – 0.66)

Fig 1. Scatter plots of CSF DTG concentrations and total plasma DTG concentrations (a) or unbound plasma DTG concentrations (b)

(a)



(b)



*Week 16 data from 3 subjects are presented in Fig 3, but not included in the analysis.

Pharmacodynamic results

A regimen of DTG+ABC/3TC decreased CSF HIV-1 RNA levels with a median decrease of -2.18 log c/mL (ranging from -1.29 to -3.11) at week 2. The plasma HIV-1 RNA levels were decreased by -2.53 log c/mL at week 2. There was no statistically significant correlation between CSF DTG concentrations and CSF HIV-1 RNA levels at week 2 or changes from baseline of HIV-1 RNA.

Reviewer comments

In the study report (b) (4) *the CSF concentrations were above the in vitro IC_{50} against wild type viruses (0.0002 µg/mL), supporting the median reduction from baseline in CSF HIV-1 RNA of 2.1 log after 2 weeks of therapy. However, caution should be used in interpreting the results as the sponsor did not obtain the full pharmacokinetic profiles of CSF concentrations. In particular, we do not have information on C_{min} or C_τ and whether the concentrations in CSF are above IC_{50} throughout the dosing interval. In the phase II study (ING111521), plasma C_τ was the PK parameter that best predicted antiviral activity. In addition, the clinical significance of week 2 CSF viral load (i.e. whether this is correlated to a better outcome in HIV associated neurocognitive disorder) is unknown at this time. Overall, the PK results as well as PD results in this study are considered as descriptive/exploratory and no definitive conclusion should be made.*

4.1.2 Pediatrics

Individual study review ING112578 (P1093)

Study title P1093: Phase I/II, multicenter, open-label pharmacokinetic, safety, tolerability, and antiviral activity of GSK1349572, a novel integrase inhibitor, in combination regimens in HIV-1 infected infants, children and adolescents (ING112578)

Site of investigation

Chicago Childrens CRS, IL (2 subjects)
Childrens Hospital of Boston CRS, MA (1 subject)
Jacobi medical center, Bronx NICHD CRS, NY (4 subjects)
University of California, San Francisco NICHD CRS, CA (3 subjects)

Study initiation date 20Apr 2011

Study completion date Ongoing

Objective

Primary

- To select a DTG dose for chronic dosing in infants, children and adolescents, that achieves similar exposure to the DTG adult dose selected from the Phase IIb clinical trial in ART-naïve adult subjects.
- To determine the safety and tolerability of DTG in HIV-1 infected infants, children and adolescents at 24 and 48 weeks.
- To evaluate the steady-state PK of DTG in combination with other antiretrovirals (OBT) in treatment-experienced HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves a targeted AUC24

Secondary

- To evaluate the antiviral activity of DTG in combination with an OBT, by measuring virologic response in infants, children and adolescents at 24 and 48 weeks
- To evaluate the effect on immunologic response from baseline to 24 and 48 weeks
- To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in subjects experiencing virologic failure
- To determine DTG exposure, its variability and clinical covariates that impact DTG disposition (e.g. age, weight) using intensive and sparse sampling and population PK analysis.
- To determine the extended long term (≥48 weeks) safety and tolerability of DTG in HIV-1 infected infants, children and adolescents.
- To explore the relationship between DTG exposure and the antiviral activity

Study Rationale

Younger children, who are infected despite exposure to ARVs in utero and after birth for prevention of mother to child transmission (PMTCT) may have virus that is resistant to currently available medications and also need new options. The purpose of this pediatric study is to determine the appropriate dose for the pediatric DTG formulations and acquire short and long term safety data, intensive and population PK data, and efficacy experience with DTG in HIV-1 infected children with which to guide potential use in children ages 6 weeks through adolescence. Initially, only treatment experienced children will be considered for this study; as more data becomes available, the team will consider adding recruitment of treatment naïve infants and children.

Rationale for Dose Selection

The goal of this study is to determine pediatric dose(s) that approximates adult exposure (AUC_{24} and C_{24h}) observed at the 50 mg once daily dose from Phase I and II trials of DTG. Steady state pharmacokinetic data was collected in real time for dose adjustments. As it is expected that AUC_{24} should have much lower variability than C_{24h} and there has been good correlation between AUC_{24} and C_{24h} after once daily dosing, the primary PK endpoint is AUC_{24}, with C_{24h} as secondary endpoint. Two sets of exposure parameter criteria were developed: the minimal and maximal exposure and the target population exposure. The minimal and maximal exposure is developed for individual patient management in the case of extreme exposure which could prevent the subject from being considered evaluable. The target population exposure (range) is developed for dose selection for the population.

Individual Subject PK Targets

Since pediatric PK tend to be more variable than adults, a lower target for both the AUC_{24} and C_{24h} was used for this study. Using maximum effect (E_{max}) models, the estimated AUC_{24} required to produce 95% of the maximum virologic response (EC_{95}) is 25µg·h/mL, and the EC_{95} for the C_{24h} is 0.5µg/ml. Therefore, all subjects must meet these minimum exposure targets. These are to be considered the lowest exposures acceptable in this study. Similarly, the maximal exposure (upper threshold) is defined to ensure subjects are not exposed to extremely high drug concentrations which may cause safety concerns. Based on accumulated data in adults (in Phase I and IIB) to date, DTG is generally well tolerated with no significant safety issues identified. A dose of DTG 50 mg BID was being studied (at the time of the adolescent portion of this pediatric trial) in ING112961 (VIKING) and ING112574 (VIKING-3) in adult HIV-infected subjects with resistance to raltegravir (RAL), and exposures up to 2-fold higher are expected with co-administration of atazanavir (ATV) with DTG, which is allowed in adult Phase III studies. Therefore, the maximal exposure target is 92 µg·h/mL for AUC_{24}, which is 2 times the geometric mean value at 50 mg once daily in adults (46 µg·h/mL) and is comparable to exposures anticipated with 50 mg BID or co-administration of DTG 50 mg once daily with ATV. Accroding to the applicant, this upper threshold may be adjusted upon availability of further clinical data. A dose limiting toxicity has not been identified to date.

Group Mean PK Targets

The 50 mg adult dose AUC_{24} target value is 46 µg·h/mL and the C_{24h} is 0.96 µg/mL. However, there will be variability around these targets which are acceptable. Therefore, the target mean range was as follows: the lower limits are 80% of the geometric means (GM) (37 µg·h/mL for AUC_{24} and 0.77 µg/mL for

C24h); the upper limits are the 90th percentiles around the AUC_{24} and C_{24h} (67 µg·h/mL for AUC_{24} and 2.26 µg/mL for C_{24h}) observed in adult subjects in SPRING-1. Thus, the target mean AUC_{24} is 46 µg·h/mL with an acceptable range of 37-67 µg·h/mL. The target mean for C_{24h} is 960 ng/mL with an acceptable range of 770-2260 ng·h/mL. The first 4 subjects (mini cohort) as well as all subjects in Stage 1 must have a GM AUC_{24} and C_{24h} within this range. Subjects falling below these ranges but above the minimum individual threshold will be discussed by the team on an individual basis.

Table 1. P1093 Pharmacokinetic targets

Protocol Defined Targets		
	AUC24 (µg*h/mL)	**C24 (ng /mL)**
Targets:	46	960
Target Range	37-67	770-2260
Max Lower Limit	25	500
Max Upper Limit	92	-

Reviewer comments: The target exposures are based on results from the Phase IIb study (ING112276 and ING111521). The exposures of DTG from these studies were slightly lower than those observed in the pivotal phase III trials. The AUC_{24} and C_{max} of DTG at steady state obtained from phase III trials are 53.5 µg·h/mL (CV: 26%) and 1.11 µg/mL (CV: 44%) respectively. The study results of this study are compared to the phase III data as well as the applicant-proposed targets.

Study Design

P1093 is an ongoing Phase I/II multi-center, open-label non-comparative study of approximately 160 HIV-1 infected infants, children and adolescents aged 6 weeks to <18 years, evaluating the PK parameters, safety, tolerability and efficacy of DTG when administered both prior to starting, and in combination with OBT (optimized background therapy). Dolutegravir will initially be administered orally as tablets of 10 mg, 25 mg and 50 mg. A pediatric formulation was developed for the younger children unable to swallow tablets. There will be six cohorts of HIV-1 infected children in this study:

Cohort I: Adolescents ≥ 12 to <18 years of age (Tablet formulation)
Cohort IIA: Children ≥6 to <12 years of age (Tablet formulation)
Cohort IIB: Children ≥ 6 to <12 years of age (Pediatric formulation)
Cohort III: Children ≥ 2 to < 6 years of age (Pediatric formulation)
Cohort IV: Children ≥ 6 months to < 2 years (Pediatric formulation)
Cohort V: Infants ≥ 6 weeks to < 6 months

Enrollment began with Cohort I and to date has progressed to Cohort IIA once a preliminary dose of DTG for Cohort I had been determined based upon successfully meeting the PK and 4 week safety criteria in Stage 1. If preliminary PK and safety metrics (see Stage 1) are met for Cohort IIB, Cohort III will open. When safety and PK criteria are met for this cohort, the protocol will sequentially enroll Cohort IV and finally Cohort V. Subjects in Cohort IIB that are taking the pediatric formulation will be allowed to switch to the tablet formulation after the Week 4 study visit, if they request to do so.

Each age cohort consists of two sequential stages: Stage 1 and 2. The objectives of Stage 1 were to examine pharmacokinetic parameters after intense sampling and evaluate the short term tolerability and safety of DTG in approximately ten subjects allowing the selection of a dose for further study in Stage 1. Those enrolled into Stage 1 remain in Stage 1 for the duration of the study. Longer term safety and antiviral activity of DTG will be assessed from data obtained from those enrolled in Stage 1 as well as those in Stage 2 who initiated treatment at the chosen dose for the cohort and remained on this dose. Subjects in Stage 1 or Stage 2 will progress to the Long Term Safety Follow-up once 48 weeks of drug is completed and if they are deriving benefit from the study drug.

STAGE 1

For those enrolled in Stage 1, DTG treatment was added to a stable, failing ARV regimen or started as monotherapy for those not taking ARV. Intensive PK assessments were performed over a single day starting with an observed dose between Days 5-10. The HIV-1 genotype obtained at screening, as well as historical virologic and medication tolerance, were used to determine an appropriate OBT that must include at least two ARV drugs, of which one must be a fully active drug, in addition to DTG. To minimize the impact of drug-drug interactions on PK variability, use of ATV, nevirapine (NVP), ATV/ritonavir (ATV/r), efavirenz (EFV), fosamprenavir (FPV), FPV/ritonavir (FPV/r), and tipranavir/ritonavir (TPV/r) was not allowed prior to the initial PK evaluation but may have been added as part of OBT. After obtaining the 24 hour PK sample, the background ARV regimen was to be immediately optimized.

Mini-Cohort

Stage 1 of each cohort began with enrollment of an initial mini-cohort of 4 subjects. After the fourth subject is enrolled, enrollment into this cohort temporarily paused to allow for the evaluation of the obtained intensive PK parameters and 4 week safety reports.

Full Cohort

If upon review of all PK and safety data from the full cohort, the PK and safety criteria have been met, subjects will continue their treatment in the Stage 1 group. Additionally, Stage 2 for that cohort will then open for enrollment of additional subjects at the selected dose. If upon review of the mini-cohort data, the dose is still not acceptable, the dose selection process will repeat until the PK and safety evaluations result in an acceptable dose for that cohort.

Individual Dose Adjustment

Subjects undergoing intensive PK assessments who have extremes in PK parameters will be considered for a dose modification if they choose to continue DTG treatment or may need to go off study drug, as these values may represent a safety or efficacy concern

Stage 2

At the completion of the Stage 1 full cohort, the recommended dose must be approved by the P1093 protocol team. Once a dose is approved, Stage 2 opened for enrollment. Stage 2 was intended to provide

long-term safety, tolerability and efficacy data for DTG given in combination with an optimized background ARV regimen.

Treatment Assignment
This was an open-label study. For those subjects enrolling in Stage 1, DTG treatment was added to a stable, failing ARV regimen or started as monotherapy for those not taking ARV. Intensive PK was performed between Days 5-10; after obtaining the 24 hour PK sample, the background ARV regimen was immediately optimized. All ARV regimens must have contained at least one fully active drug AND one additional drug in their OBT, in addition to DTG. An initial starting DTG dose was approximately 1 mg/kg once daily, with a maximum daily dose of 50 mg (Table 2).

Table 2. Initial Dosing Table for Subjects Enrolled in P1093 in all cohorts

Weight Range (kg)	Dose (mg)	Tablets taken	Dose in mg/kg for lower weight subjects	Dose in mg/kg for upper weight subjects
15 - <20	20	Two 10mg tablets	1.33	1.00
20 - <30	25	One 25mg tablet	1.25	0.83
30 - <40	35	One 10mg tablet and one 25mg tablet	1.17	0.88
≥40	50	One 50mg tablet	1.25	≤1.25

Reviewer comments
The dose in each cohort is subject to change depending on the results from the previous cohorts.

Drugs used in this study
Investigational product (IP) in this protocol referred to the investigational study drug DTG. Antiretroviral administered as part of the OBT were not considered to be investigational products. Optimized background therapy was recorded.

Table 3. Description of investigation product

Investigational Product	Strength and Packaging	Batch Numbers from CofA	Lot Number
Dolutegravir	**10 mg tablets** 30 tablets per bottle	101276423	111277992
	25 mg tablets 30 tablets per bottle	101271002	101275522
	50 mg tablets 30 tablets per bottle	101258083 111287795	101257683 111288487

Selection of Study population
Key Inclusion Criteria

Key inclusion criteria include ART treatment experienced, IN naive infants, children and adolescents age: ≥ 6 weeks to <18 years at study entry, confirmed HIV-1 infection and an optimized background regimen that contained at least one fully active drug.

Key exclusion criteria include known resistance to an integrase inhibitor, presence of any active AIDS defining opportunistic infection, known ≥Grade 3 and Grade 4 lab toxicities, evidence of pancreatitis, liver toxicity and known exposure to an integrase inhibitor.

Criteria for study discontinuation

- The subject or legal guardian refuses further treatment and/or follow-up evaluations.
- The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results.
- The subject requires treatment with medications that are disallowed while on this study.
- Virologic failure and subject does not meet the criteria for continuation of study treatment.
- Non-adherence of study medications.

Criteria for treatment discontinuation

- Pregnancy
- Drug toxicity that requires permanent study drug discontinuation
- Liver toxicities
- The investigator determines that further participation would be detrimental to the subject's health or well-being.

Concomitant medication

Table 4. Summary of allowed/disallowed ARV medications

	STAGE I		STAGE II	Notes
	Allowed Prior to Intensive PK	Allowed After Intensive PK (OBT)		
Efavirenz (EFV)	No	Yes*	Yes*	*May NOT be given as part of OBT if it is in combination with TPV/r
Atazanavir (ATV)	No	Yes	Yes	
Atazanavir /Ritonavir (ATV/r)	No	Yes	Yes	
Tipranavir / Ritonavir (TPV/r)	No	Yes*	Yes*	*May NOT be given as part of OBT if it is in combination with ETR, NVP or EFV
Nevirapine (NVP)	No	Yes*	Yes*	*May NOT be given as part of OBT if it is in combination with TPV/r
Fosamprenavir / Ritonavir	No	Yes	Yes	
Fosamprenavir (FPV)	No	Yes	Yes	
Etravirine (ETR)	No	No	No	
Etravirine with Lopinavir / Ritonavir	Yes	Yes	Yes	

Etravirine with Darunavir / Ritonavir	Yes	Yes	Yes	
Raltegravir (RAL)	No	No	No	
Elvitegravir (EVG)	No	No	No	

The following medications are also prohibited: dofetilide, medications for HCV therapy, chronic use of oral glucocorticoids, enzyme inducers (barbiturates, modafinil, oxacarbamazepine, pioglitazone, rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine, ST. John's wort). DTG should be administered 2 hours before or 6 hours after taking antacid products containing divalent cations (e.g. aluminum and magnesium) or iron supplements.

Pharmacokinetic assessments

Blood sample collection

Pharmacokinetic samples were collected at time-points outlined in Table 5. Samples were to be collected at nominal times relative to the proposed time of DTG dosing. The actual date and time of each blood sample collection were recorded.

The pharmacokinetic evaluation was scheduled so that observed dosing of DTG was as close as possible to 24 hours (generally 22-26 hours) after the previous dosing. Subjects were to be compliant in taking their medications for 3 days prior to the intensive PK visit; otherwise the intensive PK visit was re-scheduled. Subjects were fasted for 6 hours prior to dosing. Liquids including milk and juice could be consumed up to 4 hours prior to dosing. Water was consumed as desired. Subjects could consume a light meal of their choice four hours after dosing on the intensive PK day. For subjects who vomit within 4 hours after dosing; PK was cancelled and rescheduled. Two mL of whole blood was collected at the following time points: pre-dose, 1, 2, 3, 4, 6, 8 and 24 hours post dosing. The 24 hour sample was collected prior to the next dose. All intensive PK samples were shipped to the bioanalysis site (b) (4) for real-time quantification (< 2 week turnaround).

Table 5. Sample Collection Times for Stages I and II in P1093

Stage 1	**Sample Times Relative to Dose**
Days 5-10	Pre-dose, 1, 2,3, 4, 6, 8, and 24
Week 4	Pre-dose, 2-4h post dose
Week 12	Any time post dose
Week 24	2 samples of 2h apart between 12 and 26 hours post dose
Stage 2	
Week 4	Pre-dose, 2-4h post dose
Week 12	Any time post dose
Week 24	2 samples of 2h apart between 12 and 26 hours post dose

Bioanalysis assessments

Human plasma samples were analyzed (b) (4) for DTG concentration using a validated analytical method based on protein precipitation, followed by

HPLC/MS/MS analysis. The lower limit of quantification (LLQ) for DTG was 5 ng/mL with a higher limit of quantification (HLQ) of 10000 ng/mL. Quality Control (QC) samples, prepared at 3 different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria. The summary of bioanalysis methods and quality control is shown in Table 6.

Table 6. Summary of Bioanlaysis methods and quality control

Sample preparation and detection method	Extraction of DTG from 20 µL of human plasma is achieved in 120 µL of acetonitrile containing internal standard [10 ng/mL, Stable isotope of DTG ($^{15}N^{2}H7$)]. Separation is achieved on an XBridge C18 analytical column (3.5 µm, 50 x 2.1 mm). The mobile phase consists of 0.1 % formic acid in H2O:0.1% formic acid in AcN (60:40, v/v). The detection is accomplished by multiple reaction monitoring (MRM), and DTG and DTG-IS were detected using the following transitions for protonated products [M+H]+: *m/z* DTG, 420.1→ 136.0; *m/z* DTG-IS 428.1→ 283.1.
Quantitation range Calibration standard for each run Regression method information	5 -10,000 ng/mL 5,10, 50, 100, 500, 1000, 5000, 10,000 ng/mL Linear regression with $1/(conc)^2$ weighting
Observed concentrations from samples	LLOQ (lower limit of quantitation - 6083.3 ng/mL
QC samples	15, 450, 9000 ng/mL, blank plasma, blank
Stability Maximum sample storage duration from collection to analysis	At least 15 months at – 80 ºC At least 72 hours at 15 ºC in injection matrix 13 months
Analysis date	Start May 2011, complete November 2011
Detection method	LC/MS/MS
Anticoagulant	K2 EDTA and K3-EDTA Equivalence of K2 and K3-EDTA was demonstrated by comparing intra-day precision and accuracy for three replicates of each quality control concentration, low (15 ng/mL), mid (450 ng/mL), and high (9000 ng/mL).
Between run precision (%CV range)	5.0% to 5.8%
Between run accuracy (% bias range)	-6.4% to 3.7%

Reviewer comments
The bioanalysis site inspection is scheduled, but has not been performed at the time of this review.

Pharmacokinetic Endpoints and analysis
Steady-state PK parameters were determined from plasma concentration-time profiles using non-compartmental methods (WinNonlin version 5.2.1, Pharsight Corp., Mountain View, CA). Calculated PK parameters will be: area-under-the-curve (AUC_{0-24}), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), plasma concentration observed at end of 24 hour dosing interval (C_{24h}), plasma concentration observed immediately prior to dosing of 24 hour dosing interval (C_0), minimum plasma concentration (C_{min}), apparent clearance (CL/F), apparent volume of distribution (Vz/F), and terminal half-life ($t_{1/2}$).

AUC_{0-24} will be determined using the linear-log trapezoidal rule. C_{max}, T_{max}, C_0, C_{24h}, and C_{min} will be taken directly from the observed concentration-time data. Per standard practice for samples collected at steady state, half the lower assay limit for BLQ result was used. Samples collected following first dose that were BLQ were zero.

Safety Assessments

Safety assessments included monitoring and recording all AEs and SAEs, laboratory parameters including hematology, fasting lipid profile and blood chemistry. Toxicity through Week 24 was a primary endpoint and included all AEs or lab toxicities of Grade 3 or higher severity, AEs or lab toxicities of Grade 3 or higher judged to be at least possibly attributable to the study medication, termination from treatment due to a suspected adverse drug reaction (SADR) and Death. Laboratory samples were analyzed using certified local laboratories, and sites were notified of subjects with abnormal results.

Efficacy Assessments

Key secondary efficacy analyses included virologic outcomes based on HIV-1 RNA (c/mL) at Week 24 and Week 48. At both of these time points the primary definition of virologic outcome will be calculated according to a Missing, Switch or Discontinuation = Failure (MSDF) algorithm – as codified by the FDA's snapshot algorithm. Subjects will be classified as virologic failures if they have missing HIV-1 RNA data throughout the window surrounding the time point of interest.

Results

Study population results

A total of 10 subjects were enrolled in Cohort I, Stage 1 and received DTG once daily. Of the subjects in Cohort I, Stage 1, all 10 subjects received at least one dose of study medication. All 10 adolescents are included in the PK analyses and safety evaluations. All 10 subjects are through Week 24 and all 10 subjects are continuing on study. Baseline demographics and characteristics are found in Table 7.

Table 7. Summary of demographic characteristics

Demographics (n=10)	**DTG Once Daily Cohort I, Stage 1**
Age in Years, median (range)	13.5 (12 – 17)
Sex, n (%)	
Male/ Female	3 (30) / 7 (70)
Ethnicity, n (%)	
Hispanic or Latino:	2 (20)
Race, n (%)	
African American/African Heritage	6 (60)
White – White/Caucasian/European Heritage	4 (40)
Median Baseline HIV-1 RNA (log10 c/mL)	4.5 (3.9 – 5.4)
Median Baseline CD4+ (cells/mm^3)	543 (266 – 827)
Median Baseline CD4+ Percent	21.5 (14 – 29.2)

CDC Category C, n (%)	(40)

Concomitant medication

Concomitant HIV ARVs

The following subjects received background ARVs at the study entry.

- Subject 290207H: lamivudine, zidovudine, and nelfinavir
- Subject 400412G: zidovudine, emtricitabine, lopinavir/ritonavir
- Subject 8503342I: lamivudine, didanosine, nelfinavir
- Subject 8503351J: emtricitabine

The following lists are ARVs administered with DTG after optimization

- Darunavir/ritonavir (n=7)
- Atripla (n=2)
- Atazanavir (n=1)

Reviewer comments

DTG is not expected to interact with NRTIs (lamivudine, zidovudine, emtricitabine, and didanosine). The drug interaction study indicated that there is no significant interaction between lopinavir/ritonavir and DTG (ING111405). The interaction between nelfinavir and DTG is unknown. Subject 290207H was receiving nelfinavir at the time of DTG PK assessments. Therefore, there is a possibility of a drug interaction between DTG and nelfinavir although the direction and magnitude of the interaction is unknown. Subject 8503342I was receiving nelfinavir at study entry, but did not take nelfinavir at least 5 days prior to DTG PK assessments.

Of note, two subjects (400535I and 290207H) are on Atripla as an OBT without a dose adjustment of DTG. The proposed dosing recommendation of DTG with efavirenz is 50 mg b.i.d in treatment-naïve or treatment-experience INI-naïve adult patients. However, these two subjects achieved the virologic goals (HIV-1 RNA <50 copies/mL) at week 24.

Concomitant non-ARVs

Most subjects (70%) used at least 1 concomitant medication during the study. The following is the list of concomitant medications: albuterol, alclometasone, trimethoprim-sulfamethoxazole, cholecalficerol, esomeprazole, fluticasone, loratadone, Ovrette® (oral contraceptive), methylphenidate, Patanol® (eyedrop), albuterol inhaler, topical triamcinolone acetonide, multivitamin, Zyrtec ®.

Reviewer comments

None of the drugs (non-ARVs) are expected to have a significant drug interaction with DTG.

Pharmacokinetic results

Plasma DTG time-concentration profiles from Cohort I (age ≥12 to < 18 HIV-1 infected subjects) are shown in Fig 1. The individual concentration-time data from cohort I are listed in Table 8. A DTG dose of approximately 1 mg/kg using weight- based dosing (50 mg for children > 40 kg and 35 mg for children

>30 -40 kg) achieved exposures within the pre-defined $AUC_{(0-24)}$ and C_{24} targets (46 µg·h/mL and 0.96 µg/mL, respectively) and is comparable to the exposure in adults supporting DTG 50mg once daily in children 12 to <18 years of age who weigh > 40 kg.

Subject 290207H had an unexpectedly low AUC_{24} of only 13 µg·h/mL and C_{24h} of 0.2 µg/mL. The protocol team thoroughly researched possible explanations as to why this subject's exposure was so low, including non-adherence, food interactions, and potential interactions with other non-HIV related medications and herbal products. No suitable reason for the low exposure could be found so the team allowed inclusion of this subject's results in the mini-cohort. This subject also underwent a second intensive PK assessment (after optimization of the background regimen) to determine if the results would be the same. Following the repeat PK, the AUC_{24} and C_{24h} were 13.6 µg·h/mL and 0.2 µg/mL, respectively. This subject was receiving concomitant EFV during the second PK assessment. The investigator allowed the subject to remain on DTG with no dose adjustment as she was previously failing and is now responding virologically (HIV-1 RNA 39 copies/mL at Week 48) and tolerating the regimen well.

Fig 1. Mean ±standard error plot of cohort I, stage 1 concentration-time

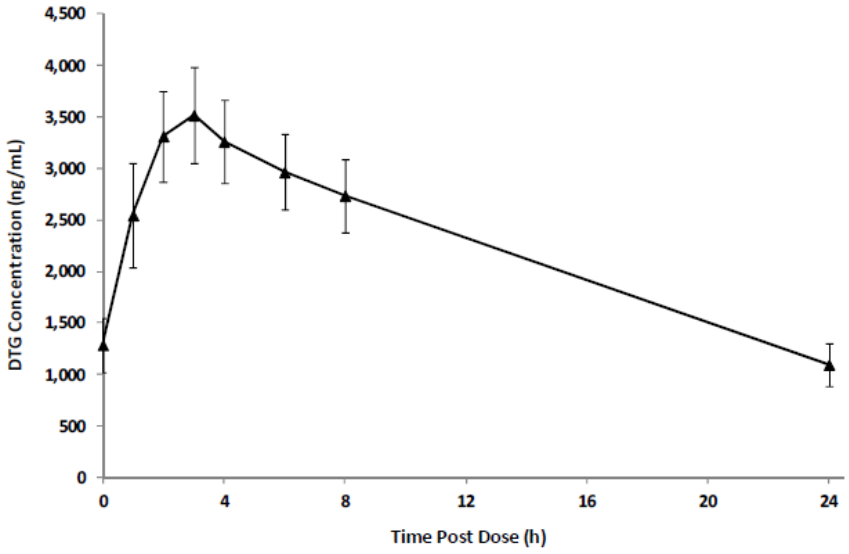


Table 8. Pharmacokinetic parameters for Cohort I (age ≥12 to < 18) subjects receiving 1 mg/kg of the tablet formulation once daily

Cohort	PID	Age (yr)	Sex	Weight (kg)	Dose (mg)	Dose (mg/kg)	K_e (1/hr)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	T_{last} (hr)	C_{24h} (ng/mL)	AUC_{last} (hr*mg/L)	C_{0h} (ng/mL)	C_{min} (ng/mL)	CL_{ss}/F (L/hr)	V_z/F (L)	AUC_{24} (hr*mg/L)
I	8503351J	12.23	F	37.1	35.0	0.94	0.08	8.24	4.08	2714.10	22.92	642.50	38.20	2.50	2.50	0.90	10.70	38.86
	8503340A	12.41	F	48.9	50.0	1.02	0.07	9.90	6.00	4106.80	24.00	1180.30	61.28	997.50	997.50	0.82	11.65	61.28
	290207H	12.94	F	56.8	50.0	0.88	0.08	8.82	3.00	1153.00	24.00	208.10	13.05	27.50	27.50	3.83	48.78	13.05
	400412G	13.19	F	91.4	50.0	0.55	0.04	16.95	3.03	4481.70	23.82	2096.50	77.93	1976.60	1976.60	0.64	15.62	78.31
	8503342I	13.55	F	51.7	50.0	0.97	0.04	17.97	3.00	6083.30	23.83	2125.80	84.60	2218.30	2125.80	0.59	15.26	84.96
	450364B	14.67	M	45.7	50.0	1.09	0.08	8.70	2.00	3786.60	24.33	656.10	45.69	1227.70	1227.70	1.10	13.81	45.47
	450367G	15.80	F	46.0	50.0	1.09	0.06	11.06	3.00	4959.50	24.20	1218.00	62.50	1567.00	1567.00	0.80	12.82	62.25
	8500394C	16.57	M	50.0	50.0	1.00	0.06	10.98	1.00	4898.30	23.83	1106.50	60.19	1996.00	1106.50	0.83	13.12	60.37
	400535I	16.98	F	56.6	50.0	0.88	0.07	9.71	3.00	2117.70	24.00	455.50	27.15	750.70	455.50	1.84	25.79	27.15
	450527G	17.86	M	87.4	50.0	0.57	0.03	24.80	2.00	3926.80	22.38	1261.40	41.98	2100.50	1261.40	1.14	40.67	43.98
	N	10		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Mean	14.62		57.16	48.50	0.90	0.06	12.71	3.01	3822.78	23.73	1095.07	51.26	1286.43	1074.80	1.25	20.82	51.57
	SD	2.05		17.93	4.74	0.19	0.02	5.43	1.34	1466.29	0.61	641.93	22.26	829.79	734.51	0.97	13.41	22.24
	CV	14.03		31.38	9.78	21.50	31.50	42.73	44.51	38.36	2.55	58.62	43.43	64.50	68.34	78.03	64.38	43.13
	Min	12.23		37.10	35.00	0.55	0.03	8.24	1.00	1153.00	22.38	208.10	13.05	2.50	2.50	0.59	10.70	13.05
	Median	14.11		50.85	50.00	0.96	0.07	10.44	3.00	4016.80	23.92	1143.40	52.94	1397.35	1167.10	0.87	14.53	52.92
	Max	17.86		91.40	50.00	1.09	0.08	24.80	6.00	6083.30	24.33	2125.80	84.60	2218.30	2125.80	3.83	48.78	84.96
	GM	14.49		55.00	48.25	0.88	0.06	11.87	2.74	3489.94	23.72	902.21	45.67	532.14	451.55	1.05	17.98	45.97

NOTES: Predose conc for PID 8503351J was BLQ (<5 ng/mL)

Reviewer comments

When PK results from all subjects were included in the analysis, AUC_{24} and C_{24} were 46 µg·h/mL and 0.90 µg/mL. This is comparable with the predefined targets by the applicant, but slightly lower (yet acceptable) than the phase III adult data (Table 9). One subject received 35 mg once daily due to her lower body weight (37.1 kg, subject 8503351J). The PK parameters of subject 8503351 were lower than the average observed in this study, but within the predefined target. Excluding this subject's data did not change the study results or conclusion.

Subject 290207H had an unexpectedly low AUC_{24} of 13 µg·h/mL and C_{24h} of 0.2 µg/mL. The investigational team could not identify a suitable reason for the low exposure. However, the subject was receiving nelfinavir as a part of a background ARV regimen at the time of PK assessments. Nelfinavir is known to be a CYP3A4 inhibitor, thus it increases the exposure of some CYP3A substrates (e.g., saquinavir, indinavur, azithromycin). However, nelfinavir can also decrease exposures of other CYP3A substrates (e.g., ethinylestraidol, methadone, and phenytoin), suggesting nelfinavir may induce drug metabolizing enzymes, too. The effect of nelfinavir on UGT1A1 induction/inhibition is currently unknown. Of note, in the second PK assessments in the same subject, the AUC_{24} and C_{24h} were 13.6 µg·h/mL and 0.2 µg/mL, respectively, in the presence of efavirenz. When the results from 290207H were excluded from the statistical analysis, the geometric means of AUC_{24} and C_{24} were increased to 52.9 µg·h/mL and 1.06 µg/mL, respectively. This is slightly higher than the pre-defined target, but similar with data from the adult phase III studies.

Overall, it is agreed that the desired exposure target was achieved. Reanalysis by excluding the outliers (subject 290207 or subject 85033851) did not change the conclusion. Other pharmacokinetic parameters (e.g., half-life, T_{max}, C_{max}, and volume of distribution) are also comparable with historical data of adult patients.

There are many typos in the concentration units throughout the study report. The average C_{max} is ~3500 ng/mL and C_{min} is ~900 ng/mL. In some text, units are mistakenly written as µg/mL.

Table 9. Comparison of pharmacokinetic parameters in Cohort I and historical data from adult trials.

	AUC24 µg·h/mL	*C24 (µg /mL)*
Applicant pre-defined target based on phase IIb studies (ING111521, 112276)	*46 (37-67)*	*0.96 (0.7-2.26)*
Pivotal phase III trial results	*53.5 (26)*	*1.11 (44)*
P1093 all subjects	*46.0 (43)*	*0.90 (58)*
P1093 290207 excluded	*52.6 (34)*	*1.06 (50)*
P1093 853351 excluded	*46.8 (44)*	*0.94 (58)*
Ratio pediatric/adult	*0.86-0.99*	*0.81-0.95*

Geometric mean (%CV)

Safety results

Adverse events

The safety data presented in this section support the primary objective of determining the safety and tolerability of DTG at Week 24. Overall, in this small population of adolescent subjects, DTG dosed at 35 mg and/or 50 mg once daily was safe and well tolerated as part of their OBT. Clinical AEs were reported by 90% of the subjects and many were related to common childhood illnesses (e.g., impetigo, ear congestion, etc) or pre-existing secondary baseline diagnoses. There were no cases of Grade 3 or Grade 4 clinical AEs reported. There were no cases of drug-related AEs reported. There were no AEs leading to withdrawal or discontinuation.

Laboratory events

Laboratory events were reported by 9/10 (90%) subjects; none were serious or clinically significant or considered related to DTG by the investigator. One Grade 3 asymptomatic elevated lipase was reported (Subject 8500394, a 17 yo African American male) at Day 344 (Week 48) which was not considered related to DTG. An increase in total bilirubin was noted in one subject and was considered related to atazanavir used in the OBT.

Similar to observations in adult subjects, adolescent subjects had small increases in creatinine that appeared at Week 2 and remained stable to Week 24. The small, non- progressive increases in serum creatinine recorded across DTG doses are consistent with pharmacological inhibition of tubular creatinine secretion via the organic cation transporter OCT2. There was one treatment emergent urine laboratory event: one subject had trace amounts of urine protein at Week 24, with a baseline urine dipstick that was negative.

Efficacy results

The majority of subjects (80%) experienced virologic success, (plasma HIV-1 RNA < 400 c/mL) a key secondary analysis at Week 24. Seven (70%) of the subjects have Plasma HIV-1 RNA <50 c/mL at Week 24. Nine out of 10 subjects (90%) had > 1 log10 drop from Baseline in HIV-1 RNA or HIV-1 RNA < 400 c/mL at Week 24. The efficacy analyses were designed using the missing, switch or discontinuation = failure (MSDF) Snapshot approach, however, there was no missing data at the key time points of baseline and Week 24. The rate of virologic failure was low (n=2 with 400c/mL cutoff, n=3 with 50c/mL cutoff),

particularly for a study in adolescents (≥ 12 to <18 yrs) who tend to have greater compliance issues than adults. Neither subject with virologic failure had INI resistance-associated mutations identified at the time of virologic failure.

CD4+ absolute cell count and CD4 % increases were observed in Cohort I, Stage 1 through Week 24 based on the majority of observed subjects (median increase of 118 cells/mm3 in CD4+ count and 5.85 in CD4 % at Week 24).

Reviewer comment
Please refer to the clinical reviewer's assessments for safety and efficacy. It is of note that the applicant did not submit the sparse PK data in this study report, thus accurate adherence assessments are not available at this time.

Conclusion
DTG exposure, $AUC_{(0-24)}$ and C_{24}, at doses evaluated in Cohort I, Stage 1 subjects (adolescents ≥12 to <18 yr) fell within the predefined target range and are similar to adult exposure at 50 mg once daily. DTG plus OBT was well tolerated through Week 24. A rapid and sustained antiviral response was observed, with 80% of subjects achieving HIV-1 RNA <400 c/mL and 70% achieving HIV-1 RNA <50 c/mL by Week 24. The PK/safety/tolerability data support dose selection of 50 mg QD in ≥12 to <18 yr weighing ≥ 40kg. Data from Cohort I, Stage 1 support further DTG initiation and evaluation in the next younger pediatric cohort, i.e., 6-12 year olds.

4.1.3 Intrinsic factors
Individual study review ING113097

Study title A Phase I, Open-Label, Parallel-Group, Two-Part, Adaptive Study to Evaluate the Pharmacokinetics and Safety of Dolutegravir in Subjects with Hepatic Impairment and Healthy Matched Control Subjects (ING113097)

Site of investigation DaVita Clinical Research, Minneapolis, MN 55404

Study initiation date 11/19/2010

Study completion date 06/04/2011

Objective

- Primary: To compare plasma pharmacokinetic (PK) parameters of dolutegravir (DTG) in subjects with hepatic impairment to healthy controls matched for gender, age, and body mass index (BMI).
- Secondary: To determine safety and tolerability of a single dose of DTG in subjects with hepatic insufficiency and healthy subjects and to evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of DTG

Study Design
This was a single-dose, open-label, parallel group, two-part, adaptive study in adult males and females with mild or moderate hepatic impairment and matched, healthy control subjects. Control subjects were matched for gender, age (± 10 years), and BMI (± 20%) to the subjects in the mild or moderate hepatic impairment category. In Part 1, moderately impaired subjects defined by a Child-Pugh score of 7 to 9 (n=8) and matched controls (n=8) were dosed. Subjects received a single oral dose of DTG 50 mg in the morning followed by 72 hour serial PK Sampling. Part 2 of the study would have been conducted, in which subjects with mild hepatic impairment (a Child-Pugh score of 5 to 6 and matched control subjects) would have received a single oral dose of DTG 50 mg. Since the DTG PK were not affected in the moderate hepatically impaired group in Part 1, subjects with mild hepatic impairment and matched controls, Part 2, were not evaluated.

Drugs used in this study
DTG 50 mg tablet, administered as an oral single dose (batch number: 101258084)
Reviewer comments
The dosage form used in this study (50 mg tablet (b) (4)) is also used in all pivotal phase III studies.

Key Inclusion Criteria
For all subjects

- Male or female between 18 and 70 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) or agreed use contraception
- Body weight $\geq$ 50 kg for men and women and BMI within the range 19– 41 kg/m^2 for hepatically impaired subjects; healthy matched control subjects were matched to BMI $\pm$ 20%.

For Hepatically Impaired Subjects

- Moderate hepatic insufficiency of any etiology (a Child-Pugh score of 7-9 and previous confirmation of liver cirrhosis) and had been clinically stable for at least 1 month prior to screening.

For healthy subjects

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.

Key Exclusion Criteria

For all subjects

- Subjects with a pre-existing condition (except hepatic impairment) interfering with normal gastrointestinal anatomy or motility, renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive HIV antibody at screening.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

For healthy subjects

- A positive Hepatitis B surface antigen or positive Hepatitis C antibody result at screening.
- AST or ALT >1.5xULN; alkaline phosphatase or bilirubin $\geq$ 1.5xULN (isolated bilirubin >1.5xULN was acceptable if bilirubin is fractionated and direct bilirubin <35%).

For hepatically impaired subjects

- Evidence of recent infection with Hepatitis B and/or Hepatitis C within preceding 6 months. Subjects with chronic Hepatitis B or C (duration > 6 months) were eligible for enrolment.
- Subjects with advanced ascites (Grade 3)
- Subjects with creatinine clearance $\leq$ 50 mL/min
- Subjects with fluctuating or rapidly deteriorating hepatic function determined by the investigator

Permitted Medications
Acetaminophen at doses of ≤ 2 grams/day was permitted in healthy volunteer subjects only. Ibuprofen 200-400 mg could have been administered, not to exceed 800 mg in a 12 hour period, to hepatically impaired subjects. Other concomitant medications were considered on a case by case basis. Subjects with hepatic impairment were permitted to use the following concomitant mediations during the study if necessary and after consultation with the GSK Medical Monitor:

Prohibited Medications
Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the dose of study medication until the collection of the last PK sample. Subjects receiving DTG must not have concurrently taken strong enzyme inducers.

Pharmacokinetic assessment
Pharmacokinetic Endpoints
After a single dose (50 mg) of DTG, AUC_t, AUC_∞, C_{max}, C_{24}, apparent $t_{1/2}$, CL/F and Vz/F of DTG were estimated. At 3 and 24 hours post dose blood was collected for the protein binding determination.

Plasma protein binding assay
Plasma protein binding of DTG was conducted by equilibrium dialysis. The pH of each plasma sample was adjusted to 7.4, then added to a 96-well Rapid Equilibrium Dialysis (RED) Device (ThermoScientific, Rockford, IL), with a molecular weight cut-off 8,000 daltons, and dialyzed for 5 hours against isotonic phosphate buffered saline (PBS).

Bioanalytial Methods
Blood (2 mL) for plasma (K_3EDTA anticoagulant) was collected at scheduled times for the measurement of DTG concentration. Following centrifugation, plasma was isolated within one hour of sample collection and stored at -20°C or colder. DTG was extracted by protein precipitation using acetonitrile containing [$^2H_7$,^{15}N]-DTG as an internal standard. Extracts were analyzed by HPLC/MS/MS analysis. For the protein binding assay, DTG was extracted from 50 µL of phosphate buffered saline (PBS) using acetonitrile containing [$^2H_7$,^{15}N]-DTG as an internal standard. Extracts were analyzed by HPLC/MS/MS analysis. The standard curve and QC data indicated that the plasma assay methods of DTG in this study were precise and accurate as shown in the table 1.

Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.

Table 1. Summary of bioanalysis quality control

Analyte	Linear range (lower limit of quantitation- upper limit of quantitation)	Overall precision (%CV)	Overall Bias (% deviation)	QC samples (ng/mL)
DTG in plasma	20-20000 ng/mL $R^2 > 0.997$	1.5% to 4.4%	2.7% to 12.5%	60, 1600, 16000
DTG in PBS	1-1000 ng/mL $R^2 > 0.997$	3.4% to 8.0%	3.7% to 8.6%	3, 80, 800

Results

Study population results

A total of 8 hepatic impaired and 8 healthy matched subjects enrolled in the study and all completed the study as planned. There were 6 females and 10 males with a mean age of 56.3 years. Since hepatic impaired and healthy matched subjects were required to be matched by sex, age and BMI there are no significant differences between the two groups in terms of baseline demographics. All 8 of the subjects with hepatic impairment had alcoholic liver disease. Four of the 8 hepatic impaired subjects also had chronic hepatitis C infection.

Table 2. Summary of subject disposition and demographic characteristics

Demographics	**Moderate Hepatic Impaired N=8**	**Healthy Matched Controls N=8**	**Overall N=16**
Age in Years, Mean (SD)	55.5 (3.89)	57.0 (8.72)	56.3 (6.57)
Sex, n (%)			
Female:	3 (38%)	3 (38%)	6 (38%)
Male:	5 (63%)	5 (63%)	10 (63%)
BMI, Mean (SD)	31.74 (3.389)	31.53 (3.674)	31.63 (3.416)
Height, Mean (SD)	174.14 (9.114)	174.56 (10.064)	174.35 (9.278)
Weight, Mean (SD)	96.58 (15.492)	97.15 (22.687)	96.86 (18.769)
Ethnicity, n (%)			
Hispanic or Latino:	0	0	0
Not Hispanic or Latino:	8 (100%)	8 (100%)	16 (100%)
Race, n (%)			
African American/African Heritage	1 (13%)	1 (13%)	2 (13%)
American Indian or Alaskan Native	2 (25%)	0	2 (13%)
White	5 (63%)	6 (75%)	11 (69%)
Mixed Race	0	1 (13%)	1 (6%)

Concomitant Medication

Eight hepatic impaired subjects and 3 healthy subjects reported using concomitant medications during the study. No subjects were reported to have taken a prohibited medication while on study. All concomitant medications taken by hepatic impaired subjects were reviewed and approved by the medical monitor prior to dosing.

Reviewer comments: The following is the list of concominant medication. amiloride, amitriptyline, amlodipine, bupropion, ciprofloxacin, colecalciferol, cyclobenzaprine, darbepoetin alfa, dicycloverine, docusate, fluticasone, propionate, folic acid, furosemide, gabapentin, glipizide, hydrocortisone, acetate, hydromorphone, ibuprofen, insulin aspart, insulin glargine, lactulose, levothyroxine, lidocaine, metoprolol tartrate, morphine sulfate, nadolol, omeprazole, oxycodone, pancrelipase, pantoprazole, paracetamol, potassium chloride, propranolol, quetiapine, rifaximin, sertraline, spironolactone, thiamine, tramadol, trolamine salicylate, vitamin D, zinc sulfate. None of those drugs are a strong inducer or inhibitor of CYP3A4 or UGT1A1.

Pharmacokinetic results

Plasma pharmacokinetics of DTG

Mean plasma DTG concentrations are shown in linear concentration versus time plots in Fig 1. Mean DTG PK parameters and the results of statistical analysis to compare plasma PK parameters of DTG in subjects with hepatic impairment to healthy controls are summarized in table 3. Overall, C_{24h}, C_{max}, T_{max}, and AUC are comparable between the groups except Cmax appears to be slightly lower and Tmax appears to be slightly delayed in subjects with hepatic impairment.

Reviewer comments: The Cmax values in some hepatically impaired subjects were lower than healthy subjects. The sponsor concluded that this is likely due to compromised bile flow or low bile salt concentrations (suggested by the higher direct bilirubin in these hepatically impaired subjects) resulting in less solubilization and a lower dissolution rate. There was no statistical difference between the groups based on the geometric mean ratio.

Fig 1. Mean plasma concentration of DTG-time plot

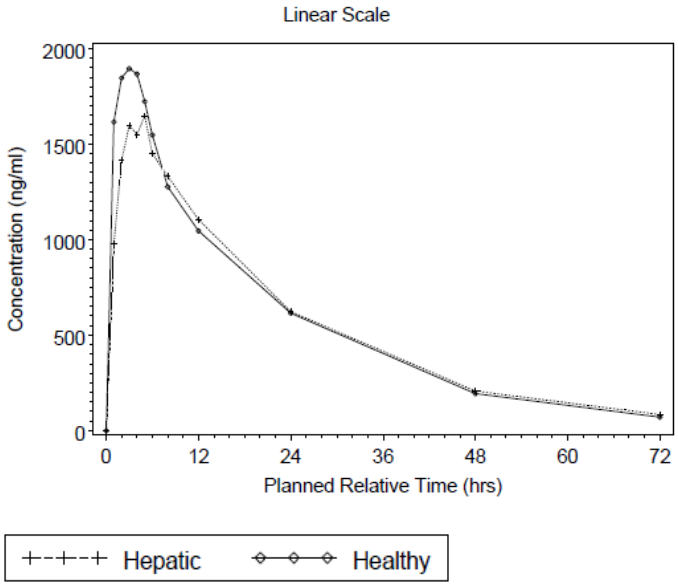


Table 3. Summary of plasma DTG pharmacokinetic parameters and statistical analysis

Cohort	Hepatic impaired	Healthy	Ratio of GLS Means [90% CI] (Hepatic Impaired vs Healthy)
Cmax (µg/mL)	1.78 (17)	1.80 (49)	1.02 [0.754,1.37]
C24 (µg/mL)	0.59 (36)	0.57 (44)	1.04 [0.727,1.48]
AUC(0-∞) (µg h/mL)	38.5 (30)	37.3 (47)	1.05 [0.745,1.49]
AUC(0-t) (µg.h/mL)	36.7 (27)	35.5 (48)	1.06 [0.753,1.48]
CL/F (L/hr)	1.30 (30)	1.34 (47)	0.950 [0.673,1.34]
Vz/F (L)	29.1 (18)	28.7 (50)	0.986 [0.737,1.32]
t1/2 (h)	15.5 (19)	14.9 (24)	1.04 [0.845,1.27]
Tmax (h)*	4.00 (2.0-5.0)	3.00 (1.0-4.0)	1.00 [-0.50, 2.50]

Data expressed are geometric mean (%CV) except * [median (range)]

Unbound DTG in plasma

Unbound plasma DTG concentrations, fraction unbound, and statistical comparison are summarized in table 4. Unbound plasma DTG concentrations in moderate hepatic impaired subjects are 106% and 48% higher than those in healthy subjects, at 3hr and 24hr post dose, respectively. Free fraction (%) of DTG in moderate hepatic impaired subjects was 76%-120% higher than those in healthy subjects

Table 4. Summary and comparison of unbound plasma DTG concentration

Cohort	Hepatically impaired	Healthy

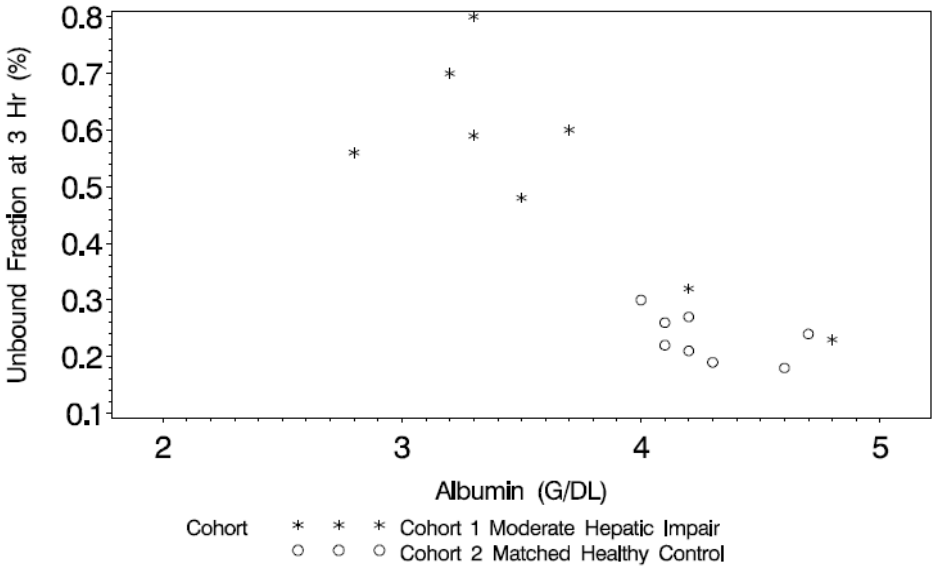
Unbound DTG concentration (ng/mL)		
At 3hr post-dose Median (range)	8. 44 (4.77-13.5)	4.09 (1.85-9.45)
Unbound DTG at 3hr post-dose Median (range)	2.40 (1.35-3.26)	1.62 (LLOQ-1.75)
GLS mean ratios (90% CI) Hepatic impaired vs. healthy	2.062 (1.404-3.029)	1.483 (1.217-1.807)
Unbound fraction of DTG (%)		
Fraction unbound at 3hr post-dose (%) GM (CV%)	0.50 (43)	0.23 (18)
Fraction unbound at 24hr post-dose (%) GM (CV%)	0.41 (40)	0.23 (11)
GLS mean ratios (90% CI) Hepatic impaired vs. healthy	2.20 (1.62-2.99)	1.76 (1.23-2.51)

Reviewer comments
The specific type of proteins to which DTG is bound have not been characterized. However, according to the sponsor, the DTG unbound fraction appears to better correlate with albumin than AAG. In this study, hepatically impaired subjects have lower albumin levels than the healthy subjects (albumin median at day 2 was 3.25 g/dL [ranging from 2.7 to 4.6 g/dL]) for the impaired group and 4.25 g/dL (ranging from 3.8 to 4.7 g/dL) for the healthy group. This may explain the higher DTG unbound fraction observed in hepatic impaired subjects. Two hepatically impaired subjects who had normal albumin concentrations had similar unbound fractions to the healthy controls as shown in the following figure (Figure 2).

The sponsor concluded that doubling of the DTG unbound concentration in hepatic impaired subjects is not considered to be a safety concern as the unbound DTG concentrations are very low in the single digit ng/mL range and doses of 50 mg BID have been studied in VIKING 1 (ING112961), where a doubling of unbound DTG concentrations would be anticipated. This regimen was well-tolerated through 24 weeks.

DTG is highly protein bound (> 99%) and exhibits a low extraction ratio. Usually, for a highly protein bound drug with a low extraction ratio, the increased unbound faction leads to an increased oral clearance. However, in this study, plasma total DTG concentrations and clearances were similar despite an increased unbound fraction. Such a discrepancy is likely due to multifactorial changes (yet to be identified) resulting from hepatic impairment.

Fig 2. Scatter plot of percent unbound plasma DTG concentration vs. albumin



Safety Results

DTG, at a single dose of 50 mg, was generally well tolerated in both hepatic impaired and healthy subjects in this study. No SAEs or deaths were reported. There were no withdrawals due to adverse events. There were more AEs in the hepatic impaired group but overall the number of AEs was low and of mild intensity. The only adverse event experienced by more than one subject was headache in the healthy group.

As many of the subjects in this study had existing liver dysfunction, clinical laboratory values of potential clinical importance observed in the study included (as expected): elevated AST, alkaline phosphatase, glucose and decreased albumin, calcium, and hemoglobin. No clinically significant treatment emergent laboratory abnormalities, vital signs, or ECGs were reported during this study.

Conclusion

The pharmacokinetics of total plasma DTG was not affected by moderate hepatic impairment. DTG can be taken without dose adjustment in subjects with mild to moderate hepatic impairment. The fraction unbound (%) of DTG in moderate hepatic impaired subjects was 76%-120% higher than those in healthy subjects primarily due to lower albumin concentrations.

Individual study review ING113125

Study title A Phase I, Open-Label, Parallel-Group Study to Evaluate the Pharmacokinetics and Safety of Dolutegravir in Subjects with Renal Impairment and Healthy Matched Control Subjects. (ING113125)

Site of investigation DaVita Clinical Research, Minneapolis MN, U.S.A

Study initiation date 28 June 2011

Study completion date 20 April 2012

Objective

Primary

- To compare plasma pharmacokinetic (PK) parameters of dolutegravir (DTG) in subjects with renal impairment to healthy controls matched for gender, age, and body mass index (BMI) following oral dosing

Secondary

- To evaluate the impact of severe renal impairment on the plasma protein binding and unbound concentration of DTG
- To assess the effects of severe renal impairment on the plasma exposure of an ether glucuronide conjugate of DTG (GSK2832500)
- To assess the safety and tolerability from 50 mg single dose administration of DTG.

Study Rationale

Dolutegravir is the predominant circulating compound in plasma and renal elimination of unchanged drug is very low (<1% of the dose). The current Renal Impairment Draft Guidance suggests that a PK study should be conducted in patients with impaired renal function when there is a reasonable likelihood that the drug will be used in this patient population and when the renal impairment may alter the PK of the drug or its active metabolites. In addition to drugs eliminated predominantly by renal excretion, drugs primarily metabolized or secreted in bile may be subject to altered PK in renal impairment because renal impairment can inhibit some pathways of hepatic and gut drug metabolism and transport. Therefore, a PK study in patients with renal impairment should be conducted for most drugs intended for chronic use.

Study Design

This was a single-center, Phase I, single-dose, open-label, PK study in human subjects with severely impaired renal function and not on renal replacement therapy, in comparison to a matched group of healthy subjects with normal renal function. Severe renal impairment was defined as a creatinine clearance [CLcr] <30 mL/min based on 24-hour urine creatinine clearance within 30 days of the treatment period. Healthy subjects were matched to severely renally impaired subjects for gender, age (±5 years) and body mass index (±25%). On Day 1, all subjects (independent of the renal function) were

administered a single dose of dolutegravir. The drug was administered with 240 mL of water in the fasted state.

Drugs used in this study
DTG 50 mg tablet (1X 50 mg) as a single dose administration (batch number 10127684)

Reviewer comments
The formulation used in this study (50 mg tablet, (b) (4)) is also used in all pivotal phase III studies.

Key Inclusion Criteria
For all subjects

- Male or female between 18 and 70 years of age.
- A female of non-childbearing potential or childbearing potential and agreed to use contraceptive methods with a failure rate of < 1%
- Body weight ≥50 kg for men and women and BMI within the range 19 to 38 kg/m^2

For healthy subjects

- Creatinine clearance >90 mL/min as determined by a 24-hour urine creatinine clearance done at screening and who were free from clinically significant illness or disease as determined by their medical history, physical examination, laboratory studies, and other tests.

For renally impaired subjects

- Creatinine clearance of <30 mL/min as determined by a 24-hour urine creatinine clearance done at screening. Renally impaired subjects with clinical laboratory test results that were considered clinically stable in the opinion of the principal investigator

Key Exclusion Criteria
For all subjects

- A positive test for HIV antibody at screening
- Pregnant or lactating females
- Subjects with a pre-existing condition interfering with normal gastrointestinal (GI) anatomy or motility, hepatic and/or renal function (except renal impairment), that would have interfered with the absorption, metabolism, and/or excretion of the study drugs
- Alanine aminotransferase >1.5xULN; alkaline phosphatase or bilirubin ≥1.5xULN (isolated bilirubin >1.5xULN was acceptable if bilirubin was fractionated and direct bilirubin <35%).
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol/tobacco product consumption.
- History of sensitivity to any of the study medication.

For healthy subjects

- A positive Hepatitis B surface antigen, or positive Hepatitis C antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the dose of study medication, unless in the opinion of the investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.

For renally impaired subjects

- Evidence of recent infection with Hepatitis B within preceding 6 months. Subjects with chronic Hepatitis B (duration> 6 months) were eligible for enrolment.
- Subjects receiving hemodialysis, peritoneal dialysis, or any other renal replacement therapy or other medical procedure that served as a surrogate for renal function.
- Subjects with fluctuating or rapidly deteriorating renal function.
- Subjects with any other medical condition which, in the judgment of the investigator and medical monitor, would jeopardize the integrity of the data derived from that subject or the safety of the subject

Permitted Medications

Acetaminophen, at doses of ≤2grams/day was permitted. Other concomitant medications may have been considered on a case by case basis by the GSK Medical Monitor.

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Drugs such as trimethoprim and cimetidine were also strictly prohibited from use in this study as they would have interfered with the analysis of the study endpoints.

***** Severe Renal Impairment Subjects: Antacids, vitamins, and iron supplements were held the day of study dosing. Subjects were prohibited from taking prescription or non-prescription drugs within 14 days or 5 half-lives (whichever was longer) prior to dosing of study medication if the drug was a potential enzyme inducer of CYP3A4.

Pharmacokinetic assessments

The single dose pharmacokinetic parameters of DTG and DTG glucuronide were determined from the plasma concentration-time data. The pharmacokinetic parameters were calculated by standard non-compartmental analysis using WinNonlin Professional Edition V5.3. Actual elapsed time from dosing was used to obtain all PK parameters.

Bioanalytical methods

DTG was extracted by protein precipitation using acetonitrile containing [$^{2}H_{7}$,^{15}N]-DTG as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method. For the protein binding

assay, DTG was extracted from 50 µL of phosphate buffered saline (PBS) using acetonitrile containing [$^{2}H_{7}$,^{15}N]-DTG as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method. The standard curve and QC data indicated that the plasma assay methods of DTG in this study were precise and accurate as shown in the table 1.

Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.

Table 1. Summary of bioanalysis quality control

Analyte	Linear range (Lower limit of quantitation-upper limit of quantitation)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples
DTG in plasma	2-20000 ng/mL R^2>0.997	7.3% to 7.7%	0.2 % to 3.1%	30, 1600, 16000 ng/mL
DTG glucuronide (M3) in plasma	1-1000 ng/mL R^2> 0.996	2.9% to 7.7%	-2.7% to 2.3%	3, 80, 800 ng/mL
DTG in PBS (protein binding assay)	1-1000 ng/mL R^2> 0.998	1.7% to 7.7%	-6.2% to 2.7%	3, 80, 800 ng/mL

Plasma protein binding assay

DTG unbound concentrations were determined in plasma samples following adjustment of the plasma sample pH to 7.4. The adjusted samples were, then added to a 96-well Rapid Equilibrium Dialysis (RED) Device (ThermoScientific, Rockford, IL; molecular weight cut-off 8,000 daltons), and dialyzed at 37°C for 5 hours against isotonic phosphate buffered saline (PBS) at pH 7.4.

Results

Study population results

All 16 subjects completed the study as planned. The overall mean age was 56.4 years (SD=7.62). The majority of subjects were male (63%) and White (56%). Screening 24-hour urine creatinine clearance values in the renally-impaired subjects ranged from 16.3 to 27.9 mL/min/1.73m^2. In the healthy subjects, screening 24-hour creatinine clearance values ranged from 95.0 to 160.8 mL/min/1.73m^2.

Table 2.Baseline demographic characteristics

Demographics	Renal (n=8)	Healthy (n=8)	Overall (n=8)
Age in Years, Mean (SD)	56.8 (7.42)	56.1 (8.32)	56.4 (7.62)
Sex, n (%)			

Female:	3 (38)	3 (38)	6 (38)
Male:	5 (63)	5 (63)	10 (63)
BMI, kg/m^2, Mean (SD)	31.34 (6.23)	29.36 (4.08)	30.35 (5.19)
Height, cm, Mean (SD)	174.19 (10.09)	171.21 (9.06)	172.70 (9.39)
Weight, kg, Mean (SD)	94.48 (17.09)	86.59 (17.05)	90.53 (16.98)
Ethnicity, n (%)			
Hispanic or Latino:	0	0	0
Not Hispanic or Latino:	8 (100)	8 (100)	16 (100)
Race, n (%)			
African American/African Heritage	5 (63)	2 (25)	7 (44)
White – White/Caucasian/European Heritage	3 (38)	6 (75)	9 (56)

Concomitant medication

Reviewer comments

Most of the concomitant drugs that were used were in subjects with renal impairment for the purpose of managing their underlying chronic conditions. None of those drugs were strong inducers or inhibitors of CYP3A4 or UGT1A1. The following is the list of concomitant medications; acetylsalicylic acid, allopurinol, amitriptyline, amlodipine, ammonium lactate, atenolol, Benadryl, bumetanide, calcitriol, calcium acetate, carvedilol, cefazolin, chlortalidone, clonidine, darbepoetin alfa, dexamethasone, droperidol, ergocalciferol, fentanyl, ferrous sulphate, fish oil, furosemide, gemfibrozil, glimepiride, glucose injection, heparin, hepatitis B vaccine, hydralazine, hydromorphone, insulin aspart, insulin glagine, labetalol, levothyroxine, lisinopril, losartan, lovastatin, metoprolol, midazolam, minoxodil, nicotinic acid, omeprazole, ondansetron, oxycodone, paracetamol, paricalcitrol, pethidine, pioglitazone, potassium chloride, pravastatin, rosuvastatin, simvastatin, sitagliptin, sodium bicarbonate, sodium chloride, sodium olystyrene sulfonate, vitamin D, Multivitamine, Novolog 70/30, losartan/ hydrochlorothiazide, lactated lingers, aceta minophen/oxycodone.

Pharmacokinetic results

Plasma pharmacokinetics of DTG

Plasma DTG time-concentration profiles are shown in Fig 1. Pharmacokinetic parameters and the results of statistical analysis to compare plasma PK parameters of DTG in renally impaired subjects to healthy subjects are summarized in table 2. Subjects with severe renal impairment had on average a 40% lower plasma DTG AUC and a 23% lower C_{max} than subjects with normal renal function. However, there was considerable overlap in DTG concentrations between the groups. Values for $AUC_{(0-\infty)}$ ranged from 13.6 to 46.7 µg*h/ml in renal impairment subjects and from 14.1 to 60.9 µg*h/ml in matched healthy subjects. C_{max} ranged from 0.79 to 2.1 µg/ml in renal impairment subjects and from 0.82 to 3.2 µg/ml in matched healthy subjects (Fig 2). No statistically significant correlation or relationship was identified between DTG PK parameters and creatinine clearance.

Fig 1. Mean plasma concentration of DTG-time plot

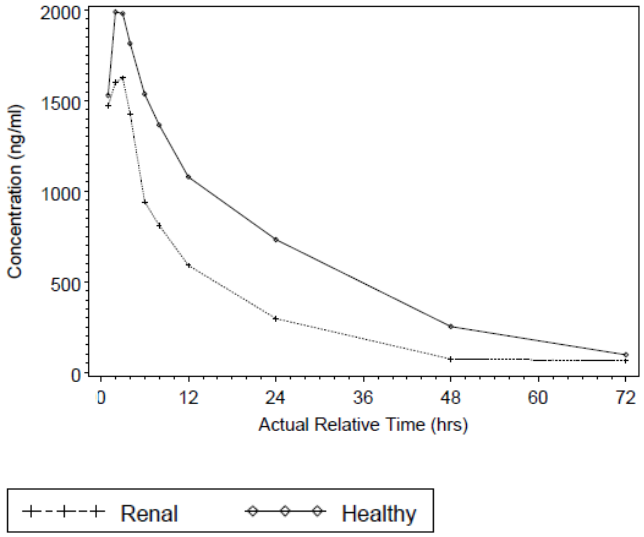
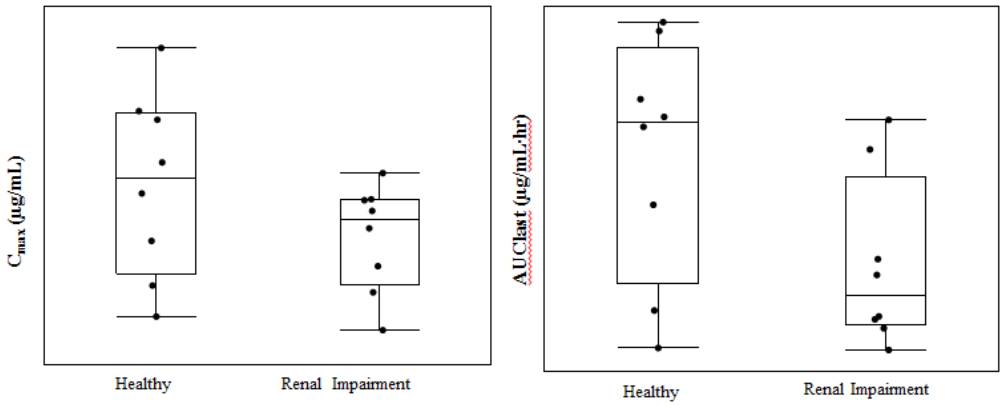


Table 3. Summary of Plasma DTG pharmacokinetic parameters and statistical comparison

DTG PK parameters	**Renal Impaired (n=8)**	**Healthy (n=8)**	**Ratio of GLS Menas (90%) CI Renal impairment vs. Healthy**
$AUC_{(0-\infty)}$ (µg.h/mL)	23.5 (48)	37.1 (58)	0.601 (0.370, 0.975)
$AUC_{(0-t)}$ (µg.h/mL)	22.6 (47)	35.3 (58)	0.606 (0.375, 0.978)
C_{max} (µg/mL)	1.50 (34)	1.86 (45)	0.774 (0.532, 1.13)
$t_{1/2}$ (hr)	12.7 (31)	15.4 (15)	0.818 (0.639, 1.05)
t_{max} (hr)	2.00 (1.0, 3.0)	2.00 (1.0, 4.0)	No difference
CL/F (L/hr)	2.12 (48)	1.35 (58)	1.67 (1.03, 2.70)
Vz/F (L)	38.8 (43)	29.9 (44)	1.36 (0.918, 2.02)

Fig 2. Comparative plot of plasma AUC and C_{max} of DTG (subjects with severe renal impairment vs. matched healthy subjects)



Reviewer comments

As urinary excretion of unchanged DTG is less than 1% of a total oral dose, it was expected that DTG exposure would not be significantly different between healthy subjects and subjects with severe renal impairment. However, the results showed that DTG exposure was unexpectedly lower in subjects with severe renal impairment (CLcr <30 mL/min) compared to healthy, matched subjects: $AUC_{(0-\infty)}$ and C_{max} were 40% and 23% lower, respectively. C_{24} was also significantly decreased in subjects with renal impairment compared to healthy subjects (geometric mean 0.318 ng/mL vs. 0.563 ng/mL with a geometric mean ratio of 0.566 (90% CI: 0.352-0.908).

It is unknown what caused decreased exposures of DTG in subjects with severe renal impairment. It is unlikely due to the decreased renal function itself. No statistically significant relationship was identified between DTG PK parameters and creatinine clearance. While renal impairment can have a multitude of effects on drug-metabolizing enzymes and transporters, the possible explanations (e.g., impaired hepatic metabolism in subjects with renal impairment) would suggest a higher exposure in the renal impairment group and do not support the findings in this study. Previous studies have demonstrated reduced exposure of acidic drugs such as phenytoin, and eltrombopag in subjects with severe renal impairment. However, these findings are usually accompanied by a higher free fraction in renally impaired subjects . The free fraction of DTG in both groups were overall comparable, indicating that changes in plasma protein binding is unlikely the sole cause of such decreases in exposure in subjects with renal impairment. It is of note that 3 subjects in the renal impairment group have a higher fraction unbound (FU) than the highest FU in the healthy subjects. For those outliers, a higher FU might be a contributing factor to a higher clearance. Another explanation is that there are changes in absorption or volume of distribution in subjects with severe renal impairment. In fact, 5 out of 8 subjects in the renal impairment group were on furosemide, indicating potential fluid overload and an altered volume of distribution in these subjects.

While it is unclear what caused such decreased exposures in DTG, the sponsor concluded that the moderate reduction in DTG exposure in subjects with severe renal impairment is not considered clinically significant and no dose adjustment of DTG is needed in subjects with mild to severe renal impairment (not on renal replacement therapy). This is an acceptable conclusion in INI-naïve patients as the exposure-response relationship is relatively flat in this population. However, in subjects with INI-resistance, such decreases may affect efficacy depending on the baseline virologic characteristics. The PopPK analysis indicated that subjects with mild and moderate renal impairment (creatinine clearance 30 to < 60, and 60 to < 90 mL/min) showed no difference in DTG exposure compared to subjects with normal creatinine clearance. This supports use of DTG in subjects with mild and moderate renal impairment without dose adjustment.

<u>Unbound DTG in plasma</u>

Unbound plasma DTG at 3 hr and 24 hr post dose and **t**he results of statistical analysis to compare plasma PK parameters of DTG in renally impaired subjects to healthy subjects are summarized in table 4. The fraction unbound (FU%) was similar between the severe renal impairment and normal renal function groups; the FU% at 3 hr post dose were 0.87 in the healthy cohort and 0.84 in the renally impaired cohort, respectively. The FU% at 24 hr post dose were 1.1% in the health cohort and 1.01% in the renally

impaired cohort. The unbound plasma DTG concentrations of the renally impaired cohort were 14% lower at 3 hr post dose and 49% lower at 24 hr post dose compared to the healthy cohort. There was no apparent correlation between the DTG unbound fraction and the DTG total concentration in plasma, suggesting that protein binding is independent of drug concentration over the range of concentrations observed in this study.

Table 4. Summary of unbound plasma DTG at 3 hr and 24 hr post-dose

Cohort	**DTG unbound concentration (ng/mL)**		**DTG fraction unbound (FU%)**	
	3 hr	**24 hr**	**3 hr**	**24 hr**
Renal Impaired (n=8) Median (range)	12.3 (9.3-16.7)	2.87 (2.11-7.11)	0.84 (0.6, 1.4)	1.01 (0.7, 1.7)
Healthy (n=8) Median (range)	17.7 (5.66-25.1)	7.83 (2.40-10.8)	0.87 (0.8, 0.9)	1.10 (1.0, 1.3)
Geometric LS mean ratio (renal impairment to healthy)	0.857 (0.587, 1.251)	0.510 (0.306, 0.851)	1.051 (0.915, 1.208)	0.957 (0.801, 1.144)

Reviewer comments
Although there was no statistical difference between the groups regarding albumin concentration, unbound DTG fraction, and unbound concentration, the subjects with severe renal impairment exhibited higher inter-individual variability. For some subjects in the renal impairment group, a higher unbound fraction might be a contributing factor to a higher clearance.

Plasma DTG glucuronide pharmacokinetics

Pharmcokinetic parameters of plasma DTG glucuronide and the results of statistical analysis to compare plasma PK parameters of DTG glucuronide in renally impaired subjects to healthy subjects are summarized in table 5. The results of the statistical comparisons showed that plasma exposures of DTG glucuronide in subjects with severe renal impairment were higher than those in healthy subjects. Plasma DTG glucuronide AUC and C_{max} in the subjects with severe renal impairment were approximately 4-fold and 3-fold higher, respectively, than those in the healthy subjects. The median molar DTG glucuronide-to-DTG AUC ratio increased from 0.010 (1%) in healthy subjects to 0.055 (5%) in subjects with severe renal impairment, indicating that DTG is the predominant species in plasma in subjects with renal impairment as well as healthy subjects. There was a statistically significant negative correlation between DTG glucuronide PK parameters including AUC and C_{max}, and renal function variable (creatinine clearance), but not for the $t_{½}$ of DTG glucuronide.

Table 5. Summary of Plasma DTG glucuronide pharmacokinetics and statistical comparison

Cohort	Renal Impaired (n=8)	Healthy (n=8)	Ratio of GLS Means (90% CI) Renal impairment vs. healthy
$AUC_{(0-\infty)}$ (µg h/mL)	2.48 (78)	0.54 (98)	4.30 (2.11, 8.76)
$AUC_{(0-t)}$ (µg.h/mL)	2.40 (79)	0.49 (107)	4.53 (2.16, 9.49)
C_{max} (µg/mL)	0.12 (68)	0.04 (83)	3.07 (1.60, 5.89)
$t_{1/2}$ (hr)	12.9 (30)	13.0 (31)	0.989 (0.724, 1.35)
t_{max} (hr)	3.00 (1.0, 8.0)	1.52 (1.0, 6.0)	Not determined.
$AUC_{(0-t)}$ ratio (Gluc/DTG)	0.055	0.010	
C_{max} ratio (Gluc/DTG)	0.045	0.015	
$t_{1/2}$ ratio (Gluc/DTG)	1.02	0.840	

Reviewer comments
The results are in agreement with the observation that DTG glucuronide is renally eliminated. The Pearson correlation coefficients between AUC and creatinine clearance was -0.59 (p= 0.015), indicating that the increased exposure of DTG-glucuronide is correlated with the decreased renal function (creatinine clearance). This additionally supports the hypothesis that accumulation of DTG glucuronide is due to decreased renal function. As DTG-glucuronide has no antiviral activity, the increased DTG-glucuronide would not contribute to efficacy in subjects with renal impairment.

The safety/toxicity information for DTG-glucuronide is not available. However, the increased concentration of DTG glucuronide in this population would not be expected to be a safety concern; the glucuronide is still about 5% of the exposure of parent DTG based on molar ratios and no significant accumulation is expected based on the comparison of half-lives between the groups (healthy vs. renally impaired). As the glucuronide is present at less than 10% of the circulating parent DTG, the applicant did not conduct safety assessment studies according to FDA's guidance on safety testing for metabolites.

Safety results
No deaths or serious adverse events occurred during this study. No subjects were withdrawn from the study due to AEs. One subject with severe renal impairment and 2 healthy subjects experienced AEs. All AEs were mild in intensity. The only AE considered as a drug-related AE was dizziness. No healthy subjects had Grade 2 or higher laboratory abnormalities. One subject with severe renal impairment (ID 251003) experienced treatment emergent Grade 4 elevated creatinine (increase from Grade 3 elevated creatinine at baseline) and 1 subject with severe renal impairment (ID 251005) experienced treatment emergent Grade 3 elevated creatinine (increase from Grade 2 elevated creatinine at baseline). Creatinine values for both of these subjects returned to normal values at follow-up. Because DTG is an inhibitor of the renal transporter organic cation transporter 2, these transient increases in creatinine are consistent with inhibition of OCT2 tubular secretion of creatinine by DTG in these subjects with compromised GFR. No significant changes in vital signs or ECGs were observed during the study. One subject with severe renal impairment had QTc values >480 msec and 5 subjects with severe renal impairment had QTc values of

potential clinical importance; all occurrences were in subjects with elevated QTc values at baseline with small changes.

Reviewer comments
DTG is an OCT2 inhibitor and increases serum creatinine approximately 0.1 – 0.15 mg/mL upon repeated dosing at 50 mg q.d. or 50 mg b.i.d in healthy subjects (ING114819). In this study, after a single dose administration of DTG 50 mg, some subjects with renal impairment show a significant increase in serum creatinine on day 2 (post-dose) compared to day 1 (pre-dose). It is unclear whether this is solely attributable to DTG-mediated OCT2 inhibition.

Table 6. Summary of changes in serum creatinine after a single oral dose of DTG 50 mg.

Subjects with severe renal impairment Serum Creatinine (mg/dL)					Healthy subjects Serum Creatinine (mg/dL)				
Subject ID	Day -1 (Predose)	Day 2 (Postdose)	Follow-up (Day 7-10)	Changes (Day2 – Day 1)	Subject ID	Day -1 (Predose)	Day 2 (Postdose)	Follow-up (Day 7-10)	Creatinine (Day2 – Day 1)
251001	3.77	3.65	3.71	-0.12	252001	0.80	0.95	0.80	0.15
251002	3.78	3.97	3.82	0.19	252002	0.65	0.66	0.67	0.01
251003	4.81	5.00	4.48	0.19	252003	0.81	0.83	0.82	0.02
251004	3.10	3.57	2.47	0.47	252004	0.52	0.66	0.51	0.14
251005	2.19	2.69	2.30	0.5	252005	0.65	0.73	0.68	0.08
251006	3.78	3.58	3.73	-0.2	252006	1.03	1.04	1.03	0.01
251007	5.10	4.83	5.07	-0.27	252007	0.88	0.93	0.78	0.05
251008	6.05	5.79	7.03	-0.26	252008	1.05	1.04	0.96	-0.01

Conclusion
DTG exposure was lower in subjects with severe renal impairment (CLcr < 30 mL/min) than healthy, matched subjects: $AUC_{(0-\infty)}$, C_{max}, C_{24} were 40%, 23%, and 44% lower, respectively. The fraction unbound (FU%) was similar between the severe renal impairment and normal renal function groups. It is unclear what caused this decrease in DTG exposure in subjects with renal impairment.

DTG can be used without dose adjustment in the treatment naïve and treatment-experienced/INI-naïve population. Caution is warranted when DTG is used in INI-experienced patients with severe renal impairment. Plasma DTG glucuronide AUC and C_{max} in the subjects with severe renal impairment were approximately 4-fold and 3-fold higher, respectively, than those in healthy subjects. The increase of DTG glucuronde in subjects with severe renal impairment would not be expected to be a safety concern.

4.1.4 Drug interactions

Individual study review ING111322

Study title ING111322 A Double-Blind, Randomized, Placebo-Controlled, Repeat Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK1349572 Followed by A Single Dose, Randomized, 3-Period, Balanced, Crossover Study to Assess the Relative Bioavailability of Two Formulations and Food Effect on GSK1349572 in Healthy Male and Female Subjects (ING111322)

Reviewer comments

The study report consists of multiple parts (multiple ascending dose PK assessments, a food effect study, a relative bioavailability study, and a drug interaction study with midazolam). Only the drug interaction with midazolam part is reviewed in this document.

Site of investigation Covance clinical research, Madison, WI

Study initiation date 27 Feb 2008

Study completion date 12 Jun 2008

Objective

To investigate the potential of GSK1349572 to inhibit or induce the cytochrome P4503A (CYP3A) enzymes using midazolam (MDZ) as a probe substrate following repeat dose oral administration of GSK1349572.

Study Design

Table 1. Study design

Day -1	Day 1-10	Day 10
Midazolam 3 mg single dose	GSK1349572 25 mg suspension (n=10) once daily for 10 days	Midazolam 3mg single dose

Reviewer comments

The information on food (whether the study was conducted under fasted or fed conditions) is not available.

Drugs used in this study

Table 2. Identity of investigational products

Product name:	**GSK1349572 Suspension**	**Placebo Suspension**	**Midazolam**
Dosage form:	Oral Suspension	Oral Suspension	Oral Syrup

Unit dose strength(s) Dosage level(s):	Unit dose: N/A Dosage level: 25 mg	Unit dose: N/A Dosage levels: N/A	Unit dose: 2 mg/mL Dosage level: 3mg
Method for individualizing dosage:	Bulk powder in bottle was supplied to the clinical site. Individual doses were weighed and placed in amber bottles for reconstitution by the site pharmacist	Pre-weighed, microcrystalline cellulose were supplied to the clinical site in amber bottles for reconstitution by the site pharmacist.	1.5mL was given for 3mg dose
Batch Number(s)	GSK1349572 – R06001 (b) (4) – 5106020 (b) (4) – CS70640003	Microcrystalline cellulose – 081152977	N/A

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 50 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant)
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

Permitted Medications

Acetaminophen, at doses of ≤2grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor.

Prohibited Medications
Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Bioanalysis
GSK1349572 and midazolam were extracted by protein precipitation using acetonitrile. Extracts were analyzed by a validated HPLC/MS/MS analysis method. The standard curve and QC data indicated that the plasma assay methods of GSK1349572 and midazolam in this study were precise and accurate as shown in the Table 3.

Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.

Table 3. Bioanalysis quality control

Analyte	Linear range (ng/mL)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)
Midazolam	0.35 to 72 ng/mL $R^2 > 0.996$	4.2% to 6.4%	2.8% to 9.4%	1.4, 7, 58 ng/mL
GSK1349572	5-5000 ng/mL $R^2 > 0.993$	2.4% to 7.0%	-1.8% to 0.8%	20,400,4000 ng/mL

Results
Study population results
A total of 12 subjects enrolled in this part of the study. All subjects completed the study as planned.

Table 4. Summary of demographic characteristics.

Demographics	N=12*
Age in Years, Mean (Range)	30.9 (22, 42)
Sex, n (%) Female: Male:	 4 (33) 8 (67)
BMI in kg/m^2, Mean (Range)	25.94 (22.5, 30.0)

Height in cm, Mean (Range)	170.1 (148, 187)
Weight in kg, Mean (Range)	74.75 (58.9, 88.8)
Race, n (%)	
African American/African Heritage	4 (33)
Asian – South East Asian Heritage	1 (8)
White – White/Caucasian/European Heritage	7 (58)
Mixed race	0

* including subjects received placebo (n=2) as a part of multiple ascending dose PK study

Pharmacokinetic results

Plasma midazolam (MDZ) pharmacokinetics

Plasma MDZ PK parameters and statistical analyses with or without GSK1349572 are summarized in Table 5. MDZ concentrations were below detection limit at 8 hours post dose for most subjects. Therefore $AUC_{(0-6)}$ and $AUC_{(0-8)}$ were calculated in addition to $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$. Plasma exposures of midazolam were comparable in the presence of GSK1349572 or without GSK1349572.

Table 5. Summary of midazolam pharmacokinetic parameters and statistical analysis

Treatment	**N**	**$AUC_{(0-\infty)}$ (ng h/mL)**	**$AUC_{(0-t)}$ (ng h/mL)**	**$AUC_{(0-6)hr}$ (ng.h/mL)**	**$AUC_{(0-8)hr}$ (ng h/mL)**
MDZ +GSK1349572	10	17.5 (40)	15.4 (41)	15.0 (33)	16.0 (35)
MDZ	10	18.4 (19)	16.3 (23)	16.2 (18)	17.3 (18)
Geometric Mean Ratio [90% CI] MDZ + GSK1349572 vs. MDZ	10	0.953 [0.790, 1.15]	0.945 [0.815, 1.10]	0.923 [0.806, 1.06]	0.927 [0.798, 1.08]

*Results are expressed as geometric mean (CV%)

Reviewer comments

The sponsor did not specify the reason not to evaluate the effect of GSK1349572 on MDZ Cmax. It may be due to some subjects reaching MDZ Cmax at (or before) the first sampling time (0.5hr).

Plasma GSK1349572 pharmacokinetics

Plasma GSK1349572 PK parameters are summarized in Table 6.

Table 6. Summary of plasma GSK1349572 PK parameters following 10 day administration

Treatment	**N**	**C_{max} (μg/mL)**	**t_{max} (h)**	**$AUC_{(0-\tau)}$ (μg h/mL)**	**$t_{1/2}$ (h)**	**C_{τ} (μg/mL)**
GSK1349572 25 mg	10	3.09 (26)	1.00 (0.50-2.00)	38.4 (23)	15.0 (16)	0.84 (33)

Reviewer comments

As this study was conducted in the early phase of the product development, the dose (25 mg) and formulation (suspension) are not the same as the to-be-marketed drug product or dose (50 mg tablet administered as either 50 mg QD or BID, depending on prior treatment experience). The exposure of GSK1349572 observed in this study was slightly lower than the exposure of GSK1349572 after multiple dose administration of 50 mg tablet once daily ($AUC_{(0-\tau)}$ approximately 53 µg.h/mL). However, GSK1349572 is not expected to cause a significant drug interaction with midazolam (or other CYP3A4 substrates) at clinical doses (50 mg once daily to twice daily) based on the current study results, as well as results from in vitro and in vivo drug interaction studies.

Conclusion

The AUC of midazolam (a sensitive CYP3A4 substrate) was comparable in the presence or absence of GSK1349572. The study confirmed the lack of induction or inhibition effects of GSK1349572 on CYP3A.

Individual study review ING111405

Study title A Phase I, open label, randomized, two period, one-way two sequence crossover study to evaluate the effect of darunavir/ritonavir and lopinavir/ritonavir on GSK1349572 (dolutegravir; DTG) pharmacokinetics in healthy adult subjects (ING111405)

Site of investigation Buffalo clinical research center, Buffalo, NY, 14202

Study initiation date 09 October 2008

Study completion date 12 December 2008

Objective

Primary

- To compare steady-state plasma GSK1349572 pharmacokinetics (PK) following administration of GSK1349572 30mg every 24 hours (q24h) with and without lopinavir (LPV)/ritonavir (RTV) 400/100mg every 12 hours (q12h) or darunavir (DRV)/RTV 600/100mg q12h.

Secondary

- To assess the safety and tolerability of repeat dose co-administration of GSK1349572 30mg q24h with and without LPV/RTV 400/100mg q12h or DRV/RTV 600/100mg q12h.
- To assess plasma LPV, DRV, and RTV PK following co-administration of GSK1349572 30mg q24h and LPV/RTV 400/100mg q12h or DRV/RTV 600/100mg q12h for 14 days.

Study Rationale

Lopinavir/ritonavir (LPV/RTV, Kaletra, Abbott) and darunavir (DRV, Prezista, Tibotec) co-administered with ritonavir (RTV, Norvir, Abbott) are commonly used drugs in treatment-experienced human immunodeficiency virus (HIV)-infected individuals. LPV and RTV are both metabolized by cytochrome P450 (CYP3A) and are inhibitors of CYP3A. RTV is also an inducer of CYP3A and UDP-glucuronosyltransferase (UGTs) and an inhibitor of P-glycoprotein (Pgp). Darunavir ethanolate (DRV; Prezista, Tibotec) is a protease inhibitor (PI) that requires co-administration with RTV for optimal antiviral activity. DRV is metabolized by CYP3A and is an inhibitor of CYP3A. LPV/RTV and DRV/RTV have the potential to induce or inhibit CYPs, UGTs and Pgp, which are involved in the disposition of GSK1349572; therefore, a drug interaction study between GSK1349572 and LPV/RTV or DRV/RTV was warranted.

It is unlikely that GSK1349572 will affect LPV, DRV or RTV exposures given that these PIs are predominantly metabolized by CYP3A and a previous study demonstrated no effect of GSK1349572 on the exposure of the sensitive CYP3A substrate midazolam. Therefore, the study was designed to evaluate the effect of LPV/RTV and DRV/RTV on GSK1349572 PK only. A 30 mg dose of GSK1349572 was selected for this study as a conservative approach to account for the predicted increase in GSK1349572 concentrations caused by LPV/RTV and DRV/RTV.

Reviewer comment
DTG exhibits linearPK between 25 mg to 50 mg. Therefore, the results in this study can be extrapolated to the clinical dose (50 mg). Of note, coadministration of lopinavir/ritonaviror darunavir/ritonavir was allowed in the pivotal phase III studies. Therefore, popPK results from phase III studies are also expected to provide additional information regarding drug interactions.

Study Design

This was a single-center, randomized, open-label, two-period, one-way, two-sequence crossover study in healthy adult subjects. A total of approximately 30 subjects were planned to be enrolled, in order to obtain 24 evaluable subjects (12 per treatment sequence). In the first treatment period, all subjects received GSK1349572 30mg q 24h for 5 days (Treatment A). In period two, subjects received GSK1349572 30mg q 24h in combination with either LPV/RTV 400/100mg q12h (Treatment B) or DRV/RTV 600/100mg q 12h (Treatment C) for 14 days. There was no washout between treatment periods. Day 1 of Period 2 was the day after Day 5 of Period 1. All doses were administered with a moderate fat meal in the morning.

Table 1. Study design

Cohort	Sequence	Sample Size	Period 1; Days 1-5	Period 2; Days 1-14
1	1	15	Treatment A1	Treatment B2
	2	15	Treatment A1	Treatment C3

1. Treatment A = GSK1349572 30mg q24h x 5 days
2. Treatment B = LPV 400mg/RTV 100mg q12h + GSK1349572 30mg q24h x 14 days
3. Treatment C = DRV 600mg/RTV 100mg q12h + GSK1349572 30mg q24h x 14 days

Drugs used in this study

Table 2. Description of investigational products

	Investigational Product			
Product name:	GSK1349572	LPV/RTV	DRV	RTV
Dosage form:	Tablet	Tablet	Tablet	Soft Gelatin Capsule
Unit dose strength(s)/Dosage level(s):	Tablet strength = 10mg Dose level = 30mg	Table strength = 200mg Lopinavir/ 50mg ritonavir Dose level = 400mg Lopinavir/ 100mg ritonavir	Tablet strength = 600mg Dose level = 600mg	Soft gelatin capsule strength = 100mg Dose level = 100mg
Dosing instructions:	Administered with 240mL of water within 30 minutes after the start of a moderate fat meal.			
Batch number	A8302	081169263	8DG417	641872E21

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 50 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant)
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

Permitted Medications

Acetaminophen, at doses of ≤2grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor. Post-menopausal women, if already on HRT prior to the study start, may have continued on HRT during the study at the discretion of the investigator.

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Pharmacokinetic analysis

The pharmacokinetic parameters of DTG, DRV, LPV, and RTV were determined from the plasma concentration-time data. The pharmacokinetic parameters were calculated by standard non-compartmental analysis according to current working practice and using WinNonlin Professional Edition V5.3. Actual elapsed time from dosing was used in the devidation of all PK parameters.

Bioanalysis assessments

Bioanalysis of DTG

DTG was extracted by protein precipitation using acetonitrile containing [$^{2}H_{7}$,^{15}N]-DTG as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method. The standard curve and QC data indicated that the plasma assay methods of DTG in this study were precise and accurate as shown in table 2. Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.

Table 3. Summary of bioanalysis quality control

Analyte	Linear range (ng/mL) Lower Limit of Quantitation-Upper Limit of Quantitation	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)
GSK1349572	5-5000 ng/mL R^2> 0.993	2.5% to 4.3%	-1.1% to 5.2%	20, 400, 4000
Darunavir	10-10000 ng/mL R^2> 0.996	1.8% to 7.8%	-6.2% to 0.6%	40, 800, 8000
Lopinavir	20-20000 ng/mL R^2> 0.994	3.2% to 6.1%	-8.9% to 0.8%	40, 800, 8000
Ritonavir	10-10000 ng/mL R^2> 0.994	2.0% to 3.8%	-5.9% to -3.4%	80, 1600, 16000

Results

Study population results

A total of 31 subjects were enrolled and 30 subjects completed the study. Subject 451002 was withdrawn from the study due to an AE of increased blood pressure that was not considered to be related to study drug. All subjects were male and approximately half of subjects were African American (55%). The median age (range) was 28.0 years (18 to 45 years).

Table 4. Summary of demographic characteristics

Demographics	**GSK1349572 (N=31)**	**GSK1349572 + LPV/RTV (N=15)**	**GSK1349572 + DRV/RTV (N=15)**
Age in Years, Median (Range)	28.0 (18, 50)	25.0 (19, 50)	29.0 (18, 45)
Sex, n (%)			
Male:	31 (100%)	15 (100%)	15 (100%)
BMI (kg/m2), Median (Range)	26.19 (18.8, 30.4)	25.78(18.8, 30.4)	26.60 (21.6, 30.3)
Height (cm), Median (Range)	178.0 (165, 188)	178.0 (165, 183)	178.0 (165, 188)
Weight (kg), Median (Range)	82.10 (60.8, 98.4)	75.80 (60.8, 98.4)	83.00 (62.6, 94.4)
Ethnicity, n (%)			
Hispanic or Latino:	4 (13%)	2 (13%)	2 (13%)
Not Hispanic or Latino:	27 (87%)	13 (87%)	13 (87%)
Race, n (%)			
African American/African Heritage	17 (55%)	9 (60%)	8 (53%)
Asian – East Asian Heritage	1 (3%)	1 (7%)	0
White/Caucasian/European Heritage	12 (39%)	5 (33%)	6 (40%)
Mixed race	1 (3%)	0	1 (7%)

Concomitant medication

Subjects 6 subjects used acetaminophen for the treatment of headache or cold symptoms. One subject used Vaseline lotion for treatment of dry heels.

Pharmacokinetic results

Plasma DTG pharmacokinetics

Plasma DTG time-concentration profiles are shown in Fig 1. Plasma DTG PK parameters following repeat dose administration in each cohort are presented in Table 5. The effect of LPV/ RTV or DRV/ RTV on GSK1349572 PK was primarily evaluated by examining the ratio of GLS means of steady-state plasma GSK1349572 PK with and without LPV/ RTV or DRV/ RTV. The results of the treatment comparison are presented in Table 6.

The results of the comparison showed that co-administration of LPV/RTV had no effect on steady-state pharmacokinetics of GSK1349572. The geometric least-square means for GSK1349752 PK parameters all fell within 80-125%. Co-administration of GSK1349572 with DRV/RTV resulted in a reduction in steady-state plasma GSK1349572 exposures. Plasma GSK1349572 $AUC_{(0-\tau)}$, C_{max}, and C_{τ} decreased by 22%, 11%, and 38%, respectively. Co-administration of GSK1349572 with DRV/RTV resulted in a 28% increase in CL/F and 20% shorter $t_{1/2}$. The effect of DRV/RTV on GSK1349572 is not expected to be clinically significant.

Fig 1. Mean steady-state plasma GSK1349572 concentration-time plots by cohort

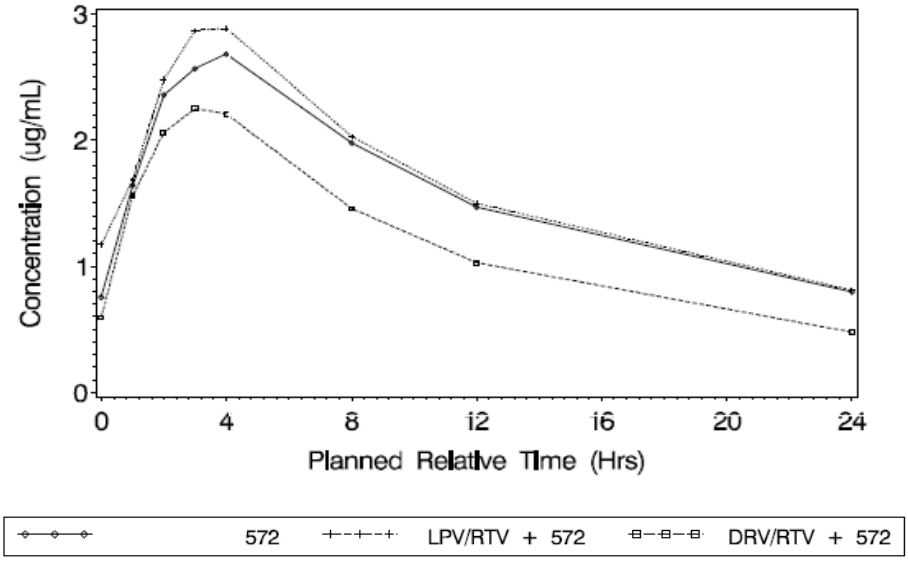


Table 5. Summary of plasma GSK1349572 pharmacokinetic parameters following repeat dose administration in each cohort

Treatment Regimen	N	Cmax (µg/mL)	Cmin (µg/mL)	Cτ (µg/mL)	AUC(0-τ) (µg.h/mL)	t1/2 (h)	CL/F (L/h)
GSK1349572	30	2.80 (15)	0.70 (33)	0.77 (29)	36.9 (19)	12.1 (15)	0.81 (19)
GSK1349572 + LPV/RTV	15	2.94 (21)	0.74 (37)	0.77 (36)	38.0 (25)	12.2 (22)	0.79 (25)
GSK1349572 + DRV/RTV	15	2.38 (20)	0.42 (35)	0.45 (37)	27.3 (23)	9.78 (17)	1.10 (23)

Source Data: Table 11.5
1. geometric mean (CV%)

Table 6. Summary of statistical analysis

Plasma GSK1349572 PK Parameter	GLS Mean			
	GSK1349572 (n=15)	GSK1349572 + LPV/RTV (n=15)	GSK1349572 (n=15)	GSK1349572 + DRV/RTV (n=15)
AUC(0-τ) (hr*ug/mL)	39.0	38.0	34.9	27.3
Cmax (ug/mL)	2.94	2.94	2.67	2.38
Cmin (ug/mL)	0.732	0.745	0.679	0.418
Cτ (ug/mL)	0.812	0.766	0.726	0.451
CL/F (L/h)	0.769	0.790	0.860	1.10
t1/2 (h)	12.1	12.2	12.2	9.78
Plasma GSK1349572 PK Parameter	**GLS Mean Ratio [90% CI]**			
	GSK1349572 + LPV/RTV vs GSK1349572 (n=15)		GSK1349572 + DRV/RTV vs GSK1349572 (n=15)	
AUC(0-τ)	0.973 [0.911, 1.04]		0.782 [0.722, 0.848]	
Cmax	1.00 [0.937, 1.07]		0.892 [0.825, 0.965]	
Cmin	1.02 [0.883, 1.17]		0.617 [0.555, 0.685]	
Cτ	0.944 [0.848, 1.05]		0.620 [0.555, 0.694]	
CL/F	1.03 [0.962, 1.10]		1.28 [1.18, 1.39]	
t1/2	1.01 [0.930, 1.10]		0.804 [0.761, 0.894]	

Reviewer comments

LPV/RTV interaction: Lopinavir is a CYP3A4, P-gp, and OATP1B1/3 inhibitor. Ritonavir is a mixed CYP3A4 inhibitor/inducer and UGT1A1 inducer. Based on in vitro studies, DTG is a substrate of P-gp, UGT1A1 and CYP3A4, but not OATP1B1/1B3. No changes in DTG exposure were observed as a result of interactions with LPV/RTV. When GSK1349572 was co-administered with LPV/RTV, the C_0 of GSK1349572 on Day 5 was ~2 fold of that when GSK1349572 was administered alone. The GSK1349572 C_0 value continued to decrease from Day 5 to Day 9 and did not change from Day 13 to Day 14. This observation indicates that significant CYP3A inhibition by LPV/RTV occurred during the first few days of co-administration, which was later counter-balanced by CYP3A induction, resulting in no net change to steady state GSK1349572 C_0 (pre-dose GSK1349572 concentration at day 5 as the comparator).

<Summary of GSK1349572 pre-dose concentration on Days 5, 9, 13, and 14>

Treatment Regimen	N	Day 5	Day 9	Day 13	Day 14
GSK1349572 alone	30	0.761 (0.246)	NA	NA	NA
GSK1349572 + LPV/RTV	15	1.91 (0.476)	1.07 (0.319)	0.831 (0.218)	0.864 (0.287)
GSK1349572 + DRV/RTV	15	0.880 (0.384)	0.543 (0.225)	0.483 (0.192)	0.467 (0.153)

Source Data: Table 11.1

1. mean (standard deviation [SD])

Darunavir/ritonavir: A decrease in DTG exposure was observed in the presence of DRV/RTV in this trial. The exposure-response analysis using ING111762 (SAILING) data indicated that DTG administration with DRV/RTV was not associated with decreased efficacy. Therefore, the effects of DRV/RTV on DTG PK are not clinically significant and no dose adjustment is required when DTG is used with DRV/RTV.

Plasma lopinavir, darunavir and ritonavir pharmacokinetics

GSK1349572 is not an inhibitor or inducer of CYP enzymes and was not expected to have an impact on LPV, DRV, and RTV PK. The PK parameters for LPV, DRV, and RTV observed in this study are comparable to those observed in published studies and suggest that GSK1349572 has no effect on LPV, DRV, and RTV PK.

Table 7. Observed (in bold) and applicant-provided historical ritonavir, darunavir, and lopinavir pharmacokinetic parameters

Reference	Treatment	AUC(0-12) (ng hr/mL)	Cmax (ng/mL)	Notes
RTV				
ING111405	**400mg/100mg (LPV/RTV) q12h**	**4813 (1529)**	**939 (353)**	**ING111405 (LPV/r), Day 14, with GSK1349572, fed**
ING111405	**600mg/100mg (DRV/ RTV) q12h**	**5,568 (1341)**	**853 (271)**	**ING111405 (DRV/r), Day 14, with GSK1349572, fed**
[Sekar, 2007]	400mg/100mg (DRV/RTV) q12h	11,670 (3,039)	1,906 (560)	Healthy, Day 5, n=6x3, fasted
[Sekar, 2008a]	400mg/100mg (DRV/RTV) q12h	6,838 (2,849)	1,096 (393)	Healthy, Day 7, n=17, fed
[van Heeswijk 2006]	400mg/100mg (LPV/RTV) q12h	2,896 (1939 - 4901)2	543 (431 – 1,085)2	healthy, Day 12, n=8, fasted
[Peng 2006]	400mg/100mg (LPV/RTV) q12h	4,760 (1,910)	710 (266)	HIV-infected, Day 14, n=12, fed, control
DRV				
ING111405	**600mg/100mg (DRV/RTV) q12h**	**48,142 (12,433)**	**5,947 (1,273)**	**ING111405 (DRV/r), Day 14, with GSK1349572, fed**
[Sekar 2007]	400mg/100mg (DRV/RTV) q12h	48,905 (14,352)	5,834 (1,415)	Healthy, Day 5, n=6x3
[Sekar 2008a]	400mg/100mg (DRV/RTV) q12h	32,734 (7,915)	4,108 (874)	Healthy, Day 7, n=17, fed
LPV				
ING111405	**400mg/100mg (LPV/RTV) q12h**	**98,248 (22,246)**	**11,794 (2,629)**	**ING111405 (LPV/r), Day 14, with GSK1349572, fed**
[van Heeswijk 2006]	400mg/100mg (LPV/RTV) q12h	52,405 (40,147-88,629)*	7,286 (5365-10,781)*	Healthy, Day 12, n=8, fasted
[Peng 2006]	400mg/100mg (LPV/RTV) q12h	77,700 (30,300)	9,110 (2,940)	HIV-infected, Day 14, n=12, fed, control

References

Peng J et al. Clin. Pharmacokinet. 2007;46(9):739-756.

Sekar V et al. Antimicrob Agents Chemother, 2007, 51: 958-961.
Sekar V et al. Br. J. clin Pharmacol 2008b, 66: 215-221.
Sekar V et al. J Clin Pharmacol, 2008a, 48: 60-65.
van Heeswijk R et al. J Clin Pharmacol, 2006, 46: 758-767

Reviewer comments

The following steady state DRV/RTV and LPV/RTV PK parameters were obtained from NDA or supplement NDA application study reports. All studies used commercially available DRV/RTV (Prezista) or LPV/RTV (Kaletra) formulations. Overall, it appears that the PK parameters of DRV, LPV and RTV in this study are comparable with historical data.

Reference	*Treatment*	*$AUC_{(0-12h)}$ (ng.hr/mL)*	*C_{max} (ng/mL)*	*Notes*
NDA203093 Application package	*LPV/RTV 400/100 mg BID*	*LPV:150440 RTV:7645*	*LPV:16405 RTV: 1306*	*Study ID: GS-US-183-0116 Healthy subjects (n=14) Under fed condition*
NDA22187 Application package	*LPV/RTV 400/100 mg BID*	*LPV:70848*	*LPV:8605*	*TMC125-C122 Healthy subjects (n=15) Under fed condition*
NDA201917 Application package	*LPV/RTV 400/100 mg BID*	*LPV:109900 RTV:5435*	*LPV:12470 RTV:1063*	*VX-950-TiDP24-C122 Healthy subjects (n=14) Under fed conditions*
NDA203093 Application package	*DRV/RTV 600/100mg BID*	*DRV:47593 RTV:6264*	*DRV:6212 RTV:1332*	*Study ID: GS-US-183-120 Healthy subjects (n=14) Under fed condition*
NDA201917 Application package	*DRV/RTV 600/100mg BID*	*DRV:51940 RTV:6012*	*DRV: 6522 RTV:1080*	*VX-950-TiDP24-C124 Healthy subjects (n=14) Under fed conditions*

Safety Results

GSK1349572 30mg, alone for 5 days or in combination with LPV/RTV or DRV/RTV for 14 days, was well tolerated during this study in healthy adult male subjects. No deaths or serious adverse events occurred during this study. One subject was withdrawn from the study after receiving two doses of GSK1349572 due to an AE of mild increased diastolic blood pressure (104mmHg). The AE was not considered by the investigator to be related to study drug and was not resolved by the end of the study. The most frequently reported drug-related AEs were diarrhea, dizziness, and headache. More AEs were reported during GSK1349572 co-administration with DRV/RTV or LPV/RTV than GSK1349572 administration alone.

Median and mean increases in triglyceride values from baseline (85 and 114mg/dL, respectively) were noted during co-administration of GSK1349572 with DRV/RTV (131 and 151mg/dL, respectively) or LPV/RTV (206 and 246mg/dL, respectively). Lipid elevations have been described with LPV/RTV and DRV/RTV. Otherwise, no consistent, treatment related or clinically significant changes in mean or median hematology, clinical chemistry or urinalysis results were observed in the study.

Additionally, 1 subject was noted to have PR prolongation during co-administration of LPV/RTV and GSK1349572, which resolved after completion of dosing. PR prolongation, including second and third degree heart block, have been described with LPV/RTV.

Conclusions

Co-administration of LPV/RTV had no effect on GSK1349572 pharmacokinetics. However, co-administration of DRV/RTV resulted in decreased plasma GSK1349572 exposures. Plasma GSK1349572 $AUC_{(0-\tau)}$, C_{max}, and C_{τ} decreased by 22%, 11%, and 38%, respectively. These decreases are not considered to be clinically significant based on efficacy analyses of subjects in the pivotal phase 3 trials who received GSK1349572 with DRV/RTV. GSK1349572 can be co-administered with DRV/RTV or LPV/RTV with no dose adjustment. The PK parameters for LPV, DRV, and RTV observed in this study are comparable to those observed in published studies and suggest that GSK1349572 has no effect on LPV, DRV, and RTV PK.

Individual study review ING111602

Study title A Phase I, open label, randomized, four-period crossover study to evaluate the effects of Maalox Advanced Maximum Strength and One A Day Maximum on pharmacokinetics of GSK1349572 in healthy adult subjects

Site of investigation Buffalo Clinical Research Center, Buffalo, NY

Study initiation date 07 January 2009

Study completion date 05 March 2009

Objective

Primary

- To compare single dose plasma GSK1349572 pharmacokinetics (PK) following co-administration of GSK1349572 50mg and Maalox Advanced Maximum Strength to GSK1349572 50mg alone
- To compare single dose plasma GSK1349572 PK following co-administration of GSK1349572 50mg and One A Day Maximum multivitamin to GSK1349572 50mg alone
- To compare single dose plasma GSK1349572 PK following administration of GSK1349572 50mg alone and 2 hour prior to administration of Maalox Advanced Maximum Strength

Secondary

- To assess safety and tolerability of a single dose of GSK1349572 alone or co- administered with a single dose of Maalox Advanced Maximum Strength, or with a single dose of Maalox Advanced Maximum Strength separated by 2 hours.
- To assess safety and tolerability of a single dose of GSK1349572 alone or co- administered with a single dose of One A Day Maximum multivitamin.

Study Rationale

Over the counter antacids, such as Maalox Advanced Maximum Strength, are commonly used in human immunodeficiency virus (HIV)-infected patients for relief of gastrointestinal discomfort. These antacids contain metal cations, such as magnesium and aluminum. Multivitamins, such as One-A-Day Maximum, are also widely used nutritional supplements in HIV-infected individuals. These multivitamin supplements also contain various metal cations such as calcium, iron, zinc, manganese and copper. GSK1349572 is a 2-metal-binding integrase inhibitor that is being evaluated for the treatment of HIV-1 infection. Previous studies with integrase inhibitors have shown clinically significant decreases in integrase inhibitor exposures when coadministered with antacids. The effect of antacids on these integrase inhibitors was due to chelation with metal cations contained in the antacid product, which resulted in reduced water solubility and reduced absorption of integrase inhibitors. Due to this metal binding property of GSK1349572, an evaluation of the effects of One A Day Maximum and Maalox Advanced

Maximum Strength on GSK1349572 pharmacokinetics is warranted to provide guidance for concomitant use in future clinical studies.

One A Day Maximum and Maalox Advanced Maximum Strength were selected for this study since they represent products containing high amounts of metal cations. These products provide for the greatest chance to observe an interaction, if one exists.

Study Design

This was an open-label, randomized four period crossover study to evaluate the effects of One A Day Maximum and Maalox Advanced Maximum Strength on the pharmacokinetics of GSK1349572. A description of each regimen is provided in Table 1.

Table 1. Study Treatment and Description in ING111602

Treatment	Description
A	A single dose of GSK1349572 50mg (five 10mg tablets)
B	A single dose of GSK1349572 50mg co-administered with a single dose of a One A Day Maximum multivitamin
C	A single dose of GSK1349572 50mg co-administered with a single dose of 20mL of Maalox Advanced Maximum Strength
D	A single dose of GSK1349572 50mg administered 2 hours prior to administration of a single dose of 20mL of Maalox Advanced Maximum Strength

Reviewer Comments: The dosing recommendation for Maalox Advanced Maximum Strength is 2-4 teaspoonsful (10-20 mL), two times a day. The dosing regimen used in this study is clinically relevant. Maalox Advanced Maximum Strength contains aluminum hydroxide 400 mg (equiv. to dried gel USP), magnesium hydroxide 400 mg, and simethicone 40 mg in each 5 mL. Once-A-Day-Maximum contains the following multivalent cations per one tablet: calcium (200 mg as elemental), magnesium 100mg, iron 18 mg, zinc 15 mg and trace ions such as copper, manganese, and selenium.

Drugs used in this study

Table 2. Identity of investigational products

	Investigational Product		
Product name:	**GSK1349572**	**One-A-Day Maximum**	**Maalox Advanced Maximum Strength**
Unit dose strength(s)/Dosage level(s):	Tablet strengths = 10mg Dose level = 50mg	1 Tablet	20mL
Route/ Administration/ Duration:	Administered orally, single dose administered in each of the four periods	Administered orally, single dose administered orally in regimen B	Administered orally, single dose administered orally in regimen C and D

Dosing instructions:	Administered with 240 mL of water after an overnight fast of at least 6 hours	Administered with 240 mL of water after an overnight fast of at least 6 hours.	Administered after an overnight fast of at least 6 hours. Administered with 240mL of water during Treatment D. During Treatment C, this drug was co-administered with GSK1349572, therefore no additional water was provided.
Batch/ Lot Number:	A8302	8KA0404	10055826

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant)
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive hepatitis B surface antigen, positive hepatitis C antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

Permitted Medications

Acetaminophen, at doses of ≤2grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor. Post-menopausal women, if already on HRT prior to the study start, may have continued on HRT during the study at the discretion of the investigator.

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Pharmacokinetic assessments

The pharmacokinetic parameters were calculated by standard non-compartmental analysis according to current working practices and using WinNonlin Pro 4.1 or higher. All calculations of non-compartmental parameters were based on actual sampling times. The following pharmacokinetic parameters were determined from the plasma concentration-time data for GSK1349572: $AUC_{(0-\infty)}$, C_{max}, C_{24}, $AUC_{(0-t)}$, t_{lag}, t_{max}, CL/F, and $t_{1/2}$. Additional PK parameters may have been calculated. Pharmacokinetic data were presented in graphical and/or tabular form and were summarized descriptively.

Bioanalysis assessments

Human plasma samples were analyzed for GSK1349572 using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis. The lower limit of quantification (LLQ) for GSK1349572 was 5ng/mL using a 25-uL aliquot of human plasma with a higher limit of quantification (HLQ) of 5000ng/mL.Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.The standard curve and QC data indicated that the plasma assay methods of DTG in this study were precise and accurate (Table 3).

Table 3. Summary of bioanalysis quality control

Analyte	Linear range (ng/mL) Lower Limit of Quantitation-Upper Limit of Quantitation	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)
Dolutegravir	5-5000 ng/mL R^2> 0.995	3.5% to 5.4%	-2.5% to -1.7%	20,400,4000 ng/mL

Results

Study population results
A total of 16 subjects were enrolled and all completed the study as planned. All subjects were male and most were White (69%). The mean age (SD) was 30.8 years (18 to 53 years).

Table 4. Summary of demographic characteristics

Demographics	**Overall N=16**
Age in Years, Mean (SD)	30.8 (11.51)
Sex, n (%)	
Male:	16 (100%)
BMI, Mean (SD)	25.79 (2.754)
Height, Mean (SD)	175.50 (6.909)
Weight, Mean (SD)	79.64 (11.258)
Ethnicity, n (%)	
Hispanic or Latino:	3 (19%)
Not Hispanic or Latino:	13 (81%)
Race, n (%)	
African American/African Heritage	5 (31%)
White – White/Caucasian/European Heritage	11 (69%)

Concomitant medication
Subject 621015 received acetaminophen for treatment of a headache during Period 4 (GSK1349572 2 hours prior + Maalox)

Pharmacokinetic results
Plasma GSK1349572 concentration-time profiles in each treatment are shown in Fig 1. Plasma GSK1349572 PK parameters following a single dose of GSK1349572 in each treatment are presented in Table 5. The effect of Maalox and multivitamin on GSK1349572 PK was primarily evaluated by examining the ratio of GLS means of GSK1349572 exposure parameters. The results of the treatment comparisons are presented in Table 6.

Concurrent administration of Maalox significantly decreased mean GSK1349572 AUC, C_{max}, and C_{24} by 74%, 72%, and 74%, respectively. Administration of Maalox 2 hr after the GSK1349572 dose decreased mean GSK1349572 AUC, C_{max}, and C_{24} by 26%, 18%, and 30%, respectively. Concurrent administration of a multivitamin decreased mean GSK1349572 AUC, C_{max}, and C_{24} by 33%, 35%, and 32%, respectively. Plasma half-life values ($t_{1/2}$) were not affected by the co-administration of either a multivitamin or Maalox and were similar among the four treatment groups.

Reviewer comments
The significant decrease in DTG exposure caused by both antacids appears to be solely attributable to the chelation effects. No change in DTG half-life and a significant decrease in the extent of absorption support the explanation that the interaction is due to decreased absorption. The effects of antacids are not

likely to be due to changes in pH. Of note, no significant drug interaction was observed when DTG was co-administered with omeprazole (ING112941).

The applicant did not evaluate when DTG can be administered if DTG is administered after Maalox. However, based on previous experience with other drugs forming a chelating complex with antacids (e.g., quinolones), administration of DTG at least 6 hours after administration of antacids is considered to be adequate to avoid significant interactions.

The review team suggests using the same recommendation when DTG is administered with any medication containing a significant amount of polyvalent cations, such as oral iron or calcium supplements, milk of magnesia, or buffered tablets. The applicant did not conduct a specific DTG PK study with foods containing calcium (e.g., milk). In Phase I studies conducted under various fed conditions, where subjects received milk as part of their breakfast, DTG exposures were increased overall. Therefore, the effects of milk on DTG exposure appear to be minimal when it is given with other food. However, the effect of milk on DTG PK when milk is given alone is unknown.

Fig 1. Mean plasma GSK1349572 concentration-time plot in each treatment

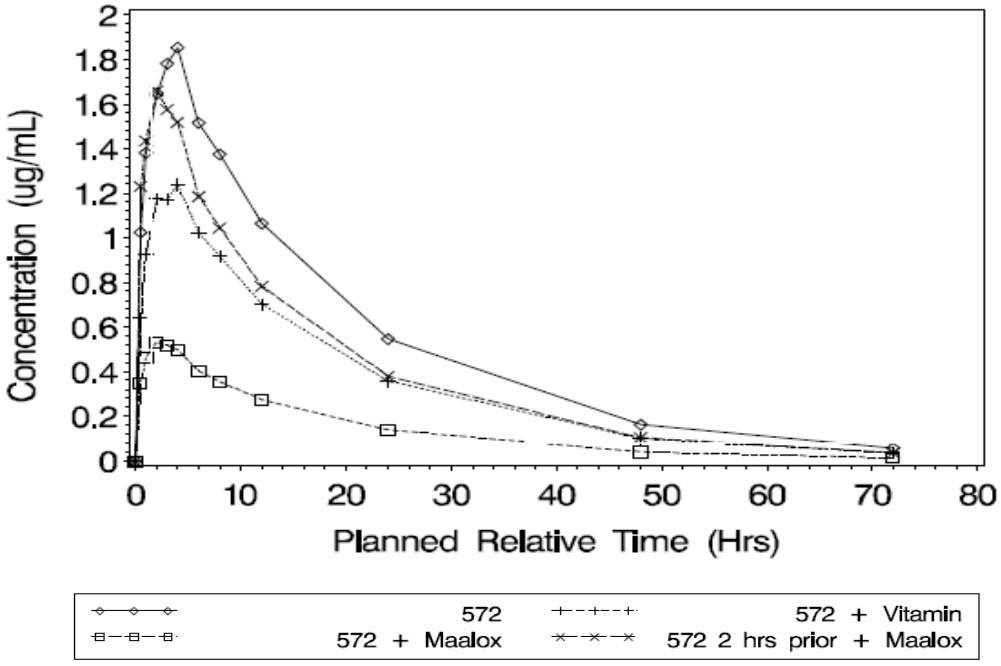


Table 5. Summary of plasma GSK1349572 PK parameters following a single oral 50 mg dose in each treatment

Treatment Regimen	N	AUC(0-t) (hr*µg/mL)	AUC(0-∞) (hr*µg/mL)	CL/F (L/hr)	Cmax (µg/mL)	C24 (µg/mL)	t1/2 (hr)	tlag (hr)	tmax[2] (hr)
GSK1349572	16	34.55 (31)	35.6 (33)	1.40 (33)	2.03 (25)	0.51 (38)	13.7 (15)	0.00	2.50 (0.50-8.00)
GSK1349572 + Multivitamin	16	23.07 (29)	23.74 (30)	2.11 (30)	1.31 (25)	0.34 (33)	13.52 (12)	0.00	2.50 (0.50-8.00)
GSK1349572 + Maalox	16	9.11 (36)	9.40 (36)	5.32 (36)	0.56 (29)	0.13 (41)	13.8 (15)	0.00	2.50 (0.50-8.00)
GSK1349572 2 hours prior + Maalox	16	25.66 (44)	26.33 (45)	1.90 (45)	1.67 (51)	0.36 (42)	13.31 (13)	0.00	2.50 (0.50-8.00)

Source Data: Table 11.3

1. geometric mean (CV% geometric mean)
2. median (range)

Table 6. Summary of GSK1349572 treatment comparison

Plasma GSK1349572 PK Parameter	GLS Mean Ratio [90% CI]		
	GSK1349572+ Multivitamin vs. GSK1349572 alone	GSK1349572 + Maalox vs. GSK1349572 alone	GSK1349572 2 hours prior + Maalox vs. GSK1349572 alone
AUC(0-t)	0.668 [0.553, 0.806]	0.264 [0.218, 0.318]	0.743 [0.615, 0.897]
AUC(0-∞)	0.667 [0.552, 0.805]	0.264 [0.219, 0.319]	0.740 [0.613, 0.893]
Cmax	0.646 [0.540, 0.774]	0.276 [0.231, 0.331]	0.821 [0.686, 0.984]
C24	0.679 [0.560, 0.824]	0.256 [0.211, 0.311]	0.703 [0.579, 0.853]

Source Data: Table 11.4

Safety results

A single dose of GSK1349572 50mg, administered alone or in combination with a single dose of One A Day Maximum Multivitamin, a single dose of Maalox Advanced Maximum Strength or taken 2 hours prior to Maalox Advanced Maximum Strength, was well tolerated during this study in healthy adult males. No deaths, SAEs, or withdrawals due to AEs were reported.

A total of 8 of 16 subjects (50%) reported at least one AE during the study. The most frequently reported AEs were nausea (4 subjects; 25%) and headache (2 subjects; 13%). Nausea was most frequently reported in subjects receiving GSK1349572 + Mulitvitamin (3 subjects 19%). Headache was most frequently reported in subjects receiving GSK1349572 2 hours prior + Maalox (2 subjects; 13%). All AEs were mild (Grade 1) in intensity. The most commonly reported drug-related AE was nausea, reported in 4 subjects (25%) overall and in 3 subjects (19%) in subjects receiving GSK1349572 + Mulitvitamin. Both nausea and headache have been noted in prior studies with GSK1349572 .No clinically significant trends in clinical laboratory values, vital signs, or ECGs were observed.

Conclusion

Concurrent administration of Maalox decreased GSK1349572 AUC, C_{max}, and C_{24} by

74%, 72%, and 74%, respectively, on average; administration of Maalox 2 hr after GSK1349572 decreased mean GSK1349572 AUC, C_{max}, and C_{24} by 26%, 18%, and 30%, respectively. Concurrent administration of a multivitamin decreased mean GSK1349572 AUC, C_{max}, and C_{24} by 33%, 35%, and 32%, respectively. Concomitant administration of GSK1349572 and drugs containing polyvalent cations such as cation-based antacids, multivitamins, oral iron or calcium supplements, milk of magnesia, or buffered tablets should be avoided. It is recommended that GSK1349572 should be administered 2 hours before or 6 hours after those drugs.

Individual study review ING111603

Study title
A Phase I, open label, two period, single fixed-sequence crossover study to evaluate the effect of etravirine on GSK1349572 pharmacokinetics in healthy adult subjects (ING111603)

Site of investigation Buffalo Clinical Research Center, Buffalo, NY, U.S,A

Study initiation date 10/16/2008

Study completion date 12/12/2008

Objective
Primary

- To compare steady-state plasma GSK1349572 pharmacokinetics (PK) following administration of GSK1349572 50mg every 24 hours (q24h) with and without etravirine (ETV) 200mg every 12 hours (q12h).

Secondary

- To assess the safety and tolerability of repeat dose co-administration of GSK1349572 50mg q24h with and without ETV 200mg q12h.
- To assess the steady state plasma ETV PK following co-administration of GSK1349572 50mg q24h and ETV 200mg q12h.

Study Rationale
ETV is a non-nucleoside that inhibits HIV reverse transcriptase. DTG may be coadministered with ETV in the treatment-experienced population. ETV is metabolized by CYP3A4, CYP2C9, and CYP2C19 and eliminated primarily as unchanged drug in the feces. ETV has the potential to induce uridine 5'-diphospho-glucuronosyltransferases (UDP- UGTs) and CYP3A enzymes, which are involved in the disposition of GSK1349572; therefore, a drug interaction study between GSK1349572 and ETV is warranted. It is unlikely that GSK1349572 will affect ETV PK given that ETV is predominantly metabolized by CYP enzymes, on which GSK1349572 has no induction or inhibition effects. Therefore, this one-way drug interaction study was designed to evaluate the effect of ETV on GSK1349572 PK only.

Study Design
This was a single-center, open-label, two-period, fixed-sequence cross over study in healthy adult subjects. A total of approximately 16 healthy subjects were planned to be enrolled to provide data from 12 evaluable subjects.

Period 1:

Subjects received GSK1349572 50mg q24h (Treatment A) from Day 1 to Day 5. All doses were administered following a moderate fat meal. Subjects were housed in the unit for the entire duration of the period. Serial PK sampling was performed on Day 5.

Period 2:
There was no washout between Periods 1 and 2. Subjects received GSK1349572 50mg q24h and ETV 200mg q12h (Treatment B) from Day 1 to Day 14. GSK1349572 was dosed in the morning. The morning ETV dose was given together with the GSK1349572 dose while the evening ETV dose was given 12 hours later. All doses were administered following a moderate fat meal. The first dose of Treatment B was given after the 24-hour PK sample for Period 1 Day 5 was collected. Subjects were housed in the unit for the entire duration of the period. Pre-dose PK concentrations were drawn in the morning on Days 8, 11, and 13, and serial PK sampling on Day 14. On Day 14, the evening ETV dose was given immediately after the 12-hour PK sample was collected.

Drugs used in this study
DTG: 50 mg q.d. as 10 mg X 5 tablets (batch number: A8302)
Etravirine: 200 mg b.i.d as 100 mg X 2 tablets (batch number 8DL5E00)

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant)
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.

- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

Permitted Medications
Acetaminophen, at doses of ≤2grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor.

Prohibited Medications
Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Pharmacokinetic assessments
PK analyses of plasma GSK1349572 and ETV concentration-time data were conducted using noncompartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 5.2. Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable subjects

Bioanalytical assessments
Human plasma samples were analyzed for GSK1349572 and etravirine using a validated analytical method based on protein precipitation, followed by high performance liquid chromatography with tandem mass spectroscopy (HPLC/MS/MS) analysis. Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.

Table 1. Summary of bioanalysis quality control

Analyte	**Linear range** (Upper Limit of Qantitation-Lower Limit of Quantitation)	**Between Run Precision (%CV)**	**Between Run Bias (% Deviation)**	**QC samples (ng/mL)**
Etravirine	5-4500 ng/mL R^2> 0.993	2.3% to 6.5%	-1.3% to 4.6%	20, 500, 3600
DTG	5-5000 ng/mL R^2> 0.996	1.7% to 4.0%	0.5% to 4.0%	20, 400, 4000

Reviewer comments
The method was validated and performed with a linear range of 5-5000 ng/mL in plasma. Some subjects in this study had C_{max} values higher than 5000 ng/mL. According to the method validation report, the

ability to dilute samples containing DTG at concentrations above the upper limit of quantitation was demonstrated by performing 6 replicate 10-fold dilutions of human plasma samples at 10000 ng/mL. However, a detailed method of dilution (e.g., dilution ratio) or the list of samples reanalyzed due to being above the upper limit of quantitation is not available in the bioanalysis study report.

Results

Study population results

A total of 16 subjects were enrolled and 15 subjects completed the study (Table 3). Subject 631012 was withdrawn from the study at the investigator's discretion (the subject was called back to work and had to leave the study. All subjects were male and roughly half were White (56%) and half were African American (44%). The median age (range) was 41.5 years (19 to 64 years).

Table 2. Summary of demographic characteristics

Demographics	**All Subjects (N=16)**
Age in Years, Median (Range)	41.5 (19, 64)
Sex, n (%)	
Male:	16 (100%)
BMI (kg/m2), Median (Range)	26.8 (22.1, 30.1)
Height (cm), Median (Range)	178.0 (163.0, 193.0)
Weight (kg), Median (Range)	84.8 (68.9, 110.7)
Ethnicity, n (%)	
Hispanic or Latino:	2 (13%)
Not Hispanic or Latino:	14 (88%)
Race, n (%)	
African American/African Heritage	7 (44%)
White – White/Caucasian/European Heritage	9 (56%)

Concomitant Medication

Three subjects used concomitant medications during the study No dosing with a concomitant medication was ongoing at the end of the study. Subjects 631005 and 631011 used acetaminophen for the treatment of headache. Subject 631012 used Nyquil (combination of acetaminophen, dextromethorphan hydrobromide and doxylamine succinate) for the treatment of influenza-like symptoms.

Reviewer comments: The concomitant medications are not expected to interfere with the study procedures or results.

Pharmacokinetic results

DTG Pharmacokinetics

Plasma DTG PK parameters following repeat dose administration on Day 5 (Period 1; without etravirine) and Day 14 (in the presence of etravirine) are presented in Table 3 and Fig 1. The effect of etravirine on GSK1349572 PK was primarily evaluated by examining the ratio of GLS means of steady-state plasma GSK1349572 PK with and without ETV. The results of the treatment comparison are also presented in Table 3.

The results of the study showed that co-administration of GSK1349572 and ETV resulted in decreased steady-state plasma GSK1349572 exposures. Plasma GSK1349572 $AUC_{(0\text{-}t)}$, C_{max}, and C_{τ} decreased by 71%, 52%, and 88%, respectively. The ad-hoc analysis showed no correlation between ETV exposure and treatment ratio of GSK1349572 exposure (Table 4). As CYP–mediated metabolism is thought to play a minor role in the metabolism of GSK1349572, a significant drug interaction was not expected; however, a significant decrease was observed and the magnitude of this interaction was larger than anticipated. Due to the large magnitude of reduction in GSK1349572 exposure, especially on Cτ, the effect of ETV is likely clinically significant.

Fig 1. Mean plasma concentration-time curves of GSK1349572 with or without etravirine (ETV)

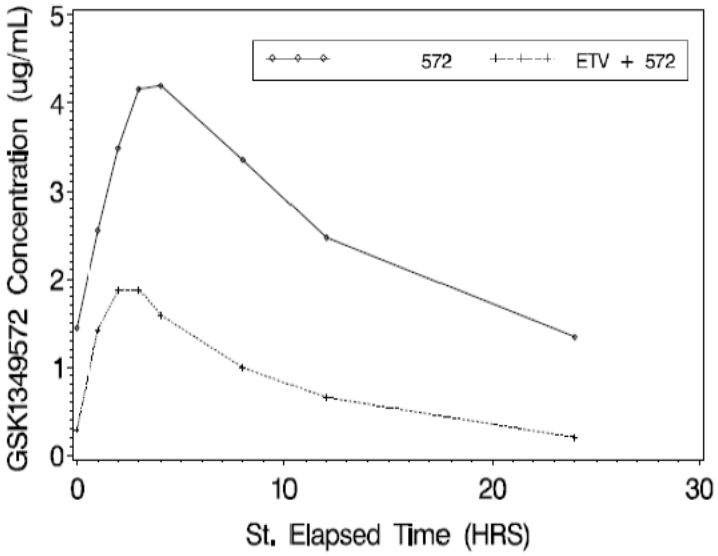


Table 3. Summary of plasma GSK1349572 pharmacokinetic parameters following repeat dose administration and statistical comparison.

PK parameters	GSK1349572	GSK1349572 + ETV	GLS Mean Ratio [90% CI] GSK1349572 + ETV vs GSK1349572 (N=15)
C_{max} (µg/mL)	4.34 (19)	2.10 (24)	0.484 [0.433, 0.542]
C_{min} (µg/mL)	1.25 (32)	0.16 (84)	0.124 [0.096, 0.160]
C_{τ} (µg/mL)	1.29 (29)	0.16 (84)	0.121 [0.093, 0.157]
$AUC_{(0\text{-}\tau)}$ (µg.h/mL)	60.4 (22)	17.8 (39)	0.294 [0.257, 0.337]
$t_{1/2}$ (h)	12.4 (21)	6.39 (22)	0.516 [0.471, 0.565]
t_{max} (hr)	3.00 (1.00-4.07)	2.00 (1.00-3.00)	No difference
CL/F (L/h)	0.83 (22)	2.81 (39)	3.40 [2.97, 3.89]

Table 4. Correlation coefficient (p-value) of etravirine AUC vs. treatment ratio of GSK1349572 pharmacokinetic parameters

	GSK1349572 Pharmacokinetic Parameter		
	$AUC_{(0-\tau)}$ Treatment Ratio	C_{max} Treatment Ratio	C_{τ} Treatment Ratio
Etravirine $AUC_{(0-\tau)}$	-0.217 (0.438)	-0.201 (0.473)	-0.317 (0.249)

Reviewer Comments
Etravirine is a CYP3A4 inducer. While the exposures of known CYP3A4 substrates (e.g., norethindrone, voriconazole, and methadone) are not significantly decreased by etravirine, the exposures of other CYP3A4 substrates (e.g., maraviroc, sildenafil, or clarithromycin) are significantly decreased (more than 40% decrease in AUC). It is uncertain why some drugs are more sensitive to etravirine-mediated metabolic induction. Furthermore, there is no in vitro or in vivo data indicating that etravirine is a UGT1A1 inducer. The exposures of raltegravir and ethinylestradiol, of which metabolism is mainly dependent on UGT1A1, are not significantly decreased by etravirine (20% increase in ethinylestradiol AUC, 10% decrease in raltegravir AUC). Therefore, strong UGT1A1 induction is not likely the sole cause of a significant decrease in DTG exposure. The exposure of digoxin, a sensitive P-gp substrate, was not changed in the presence of etravirine. This indicates that etravirine is not expected to interact with other drugs via P-gp induction or inhibition. Thus, the exact mechanism by which etravirine decreases DTG exposures is unknown. Due to the large magnitude of reduction in GSK1349572 exposure, especially on Cτ, the effect of ETV is likely clinically significant.
The clinical effects of this drug interaction (etravirine and DTG) was not evaluated in phase III trials as use of etravirine alone without a ritonavir-boosted PI were not allowed in the trials. Of note, the etravirine effects on DTG exposure were mitigated in the presence of a ritonavir-boosted PI. Dose adjustment to 50 mg b.i.d may not be sufficient to mitigate 88% decrease in Cτ, thus, coadministration with ETV (without a ritonavir-boosted PI) is not recommended.

Etravirine Pharmacokinetics

Plasma etravirine PK parameters following repeat dose administration on Day 14 (in the presence of etravirine) are presented in Table 5. Because GSK1349572 is not an inhibitor or inducer of CYP enzymes, which governs the primary route of elimination of ETV, co-administration of GSK1349572 and ETV was not expected to have an impact on the pharmacokinetics of ETV. ETV exposure observed in this study is higher compared to published historical ETV PK data provided by the applicant.

Table 5. Observed and historical etravirine pharmacokinetic parameters

Reference	ETV Treatment	AUC(0-12) (ng.hr/mL)	Cmax (ng/mL)	Notes
ING111603	200 mg q12h	10,578 (2,662)[1]	1,168 (351)[1]	Healthy subjects, Day 14, with GSK1349572 and a moderate fat meal, n=15
Anderson, 2007	200 mg q12h	6,216 (5,139 – 7,518)[2]	734 (607 – 888)[2]	Healthy subjects, Day 8, moderate fat meal, n=19
Boffito, 2007	200 mg q12h	4,921 (2,982)[1]	569 (381)[1]	HIV infected, Day 28, with DRV/r, n=10

1. Mean (SD)
2. Geometric mean (95% CI)

Reviewer comments

The following table shows steady-state etravirine PK parameters from the etravirine NDA application and other drug interaction studies. Overall it appears that etravirine PK parameters observed in this study are about 10-20 % higher than historical data. This is likely due to inter-study variability rather than the effects of DTG on etravirine PK.

Study ID	*C_{max} (ng/mL)*	*$AUC_{(0-\tau)}$ (ng.h/mL)*	*C_{τ} (ng/mL)*
TMC125-C178	*958.8 (278.1)*	*8195 (2428)*	*529.5 (172.5)*
TMC125-C171	*1015 (243.8)*	*9008 (2392)*	*529.1 (162.1)*
TMC125-C177	*875.7 (232.8)*	*7638 (2254)*	*426.1 (154.6)*
TMC125IFD1001	*1057 (310.3)*	*9391 (4152)*	*579.9 (191.2)*

Data expressed as mean (SD)

For all studies: etravirine 200 mg b.i.d repeated dosing

Safety Results

GSK1349572 50mg q24h for 5 days, administered alone or in combination with etravirine 200mg q12h for 14 days, was well tolerated during this study in healthy adult males. No deaths, SAEs, or withdrawals due to AEs were reported. Overall, 6 subjects reported at least one AE. The most frequently reported AE was headache (4 subjects). All other AEs, including abdominal pain, influenza-like illness, and acne, were reported by only one subject each. All AEs were mild in intensity. The most commonly reported drug-related AE was headache (4 subjects). Abdominal pain was also considered to be drug-related in one subject. No clinically significant trends in clinical laboratory values, vital signs, or ECGs were observed. Two subjects were noted to have lipase elevations (1 with a Grade 3 lipase elevation at follow-up and 1 with a Grade 2 lipase elevation during co-administration of GSK1349572 and ETV). Infrequent lipase elevations and headache has been described with both DTG and etravirine dosing.

Conclusion

Co-administration of GSK1349572 and ETV resulted in decreased steady-state plasma GSK1349572 $AUC_{(0-\tau)}$, C_{max}, and C_{τ} decreased by 71%, 52%, and 88%, respectively. The effect of ETV is likely clinically significant. GSK1349572 should not be used with etravirine (without a ritonavir-boosted PI).

Individual study review ING111604

Study title A Phase I, Open Label, Single Sequence, Drug Interaction Study Evaluating Plasma GSK1349572 and Tenofovir Pharmacokinetics in Healthy Adult Subjects (ING111604)

Site of investigation: Buffalo Clinical Research Center, Buffalo, NY 14202

Study initiation date 11 Aug 2008

Study completion date 01 Oct 2008

Objective

Primary

- To compare steady-state plasma GSK1349572 pharmacokinetics (PK) following administration of GSK1349572 50mg once every 24 hours (q24h) with and without tenofovir (TDF) 300mg q24h.

Secondary

- To compare steady-state plasma TDF PK following administration of TDF 300mg q24h with and without GSK1349572 50 mg q24h.
- To assess the safety and tolerability of repeat dose co-administration of GSK1349572 50mg q24h with and without TDF 300mg q24h.

Study Rationale

Tenofovir disoproxil fumarate (TDF, Viread) is a commonly used drug in both treatment- naïve and experienced human immunodeficiency virus type 1 (HIV-1)-infected individuals. When coadministered with other integrase inhibitors, tenofovir had no impact on elvitegravir (ELV) exposure but increased raltegravir (RAL) exposure by ~50-60%. Raltegravir increased tenofovir exposure by ~10%. The mechanism(s) for these interactions are unknown. A drug interaction between TDF and GSK1349572 is not expected based on the differing routes of elimination as described in the protocol. However, given the unpredictable nature of drug interactions reported with TDF, a drug interaction study between GSK1349572 and TDF was warranted.

Study Design

This study was an open-label, repeat-dose, single sequence, three- period, drug-drug interaction study conducted in approximately 16 healthy subjects. In Period 1, subjects received GSK1349572 50mg q24h from Day 1 to Day 5. The serial PK sampling was conducted on day 5. In Period 2, subjects received TDF 300mg q24h from Day 1 to Day 7. The serial PK sampling was conducted on day 5. In Period 3, received GSK1349572 50mg q24h and TDF 300mg q24h from Day 1 to Day 5.

All doses were to be administered in the fasting state. There was a ≥6- day washout between the first and second periods and no washout between Period 2 and Period 3. Day 1 of Period 3 was the day after Day 7 of Period 2.

Table 1. Study design

Sample Size	Period 1; Days 1-5	Washout ≥6 days	Period 2; Days 1-7	Period 3; Days 1-5
16	GSK1349572 50mg q24h x 5 days		TDF 300mg q24h x 7 days	TDF 300mg q24h + GSK1349572 50mg q24h x 5 days

Drugs used in this study

DTG 50 mg q. d as 10 mg tablet X 5 (batch/lot number: A8302)
Tenofovir: 300 mg q.d as 300 mg tablet X 1 (batch/lot number: C7L0078A)

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant)
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption or tobacco products.
- History of sensitivity to any of the study medication.
- History/evidence of significant cardiovascular or pulmonary disease

Permitted Medications

Acetaminophen, at doses of ≤2grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor.

Prohibited Medications
Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Pharmacokinetic assessments
The following pharmacokinetic parameters were determined from the plasma concentration-time data for GSK1349572 and TDF: $AUC_{(0-\tau)}$, C_{τ}, C_{max} and time of first occurrence of C_{max} (t_{max}). The PK parameters were calculated by standard non-compartmental analysis according to current working practices and using Win Nonlin Pro 4.1 or higher. All calculations of non-compartmental parameters were based on actual sampling times.

Bioanalysis assessments
Sample Collection

Dolutegravir (GSK1349572) blood samples were obtained on day 5 (Period 1 and Period 3) at predose and up to 24 hours postdose. Tenofovir blood samples were obtained on day 7 (Period 2) and day 5 (Period 3) at predose and up to 24 hours postdose. Trough dolutegravir blood samples were obtained on days 3 and 4 (Period 1 and 3), and trough tenofovir blood samples were obtained on days 5 and 6 in Period 2 and on days 3 and 4 in Period 3.

Bioanalysis

The method and bioanalysis of dolutegravir and tenofovir are acceptable. Specific information regarding whether current dolutegravir or tenofovir reference standards were used for either the method validation experiments or the bioanalysis of samples from the ING111604 trial was not provided by the applicant. Dolutegravir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by GlaxoSmithKline (GSK). Tenofovir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by GlaxoSmithKline. Based on the information provided by the applicant, the blood samples for analysis of dolutegravir and tenofovir appears to have been collected in tubes containing EDTA as an anticoagulant.

For the ING111604 plasma samples that were analyzed for dolutegravir, the lower limit of quantification for dolutegravir was 5 ng/mL and the upper limit of quantification was 5000 ng/mL. There were no precision or accuracy issues identified for dolutegravir based on the bioanalytical report. For the ING111604 trial, precision and accuracy were evaluated using plasma dolutegravir QC samples at three

concentration levels: 20 ng/mL, 400 ng/mL, and 4000 ng/mL. The corresponding dolutegravir inter-run accuracy values were 1% for 20 ng/mL, 1.8% for 400 ng/mL, and -1.5% for 4000 ng/mL. The dolutegravir inter-run precision values were 4.1% for 20 ng/mL, 2% for 400 ng/mL, and 2.1% for 4000 ng/mL. The lower limit of quantification for tenofovir was 1 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for tenofovir based on the bioanalytical report. For the ING111604 trial, precision and accuracy were evaluated using plasma tenofovir QC samples at three concentration levels: 3 ng/mL, 75 ng/mL, and 400 ng/mL. The corresponding tenofovir inter-run accuracy values were 9.3% for 3 ng/mL, 3.5% for 75 ng/mL, and 2.2% for 400 ng/mL. The tenofovir inter-run precision values were 5.4% for 3 ng/mL, 2.7% for 75 ng/mL, and 1.2% for 400 ng/mL.

For the ING111604 trial, based on the information submitted by the applicant, dolutegravir plasma samples were stored for less than 2 months at -20°C or -70°C at the trial site and stored between -20°C and -70°C and analyzed within one month of receipt at the GSK bioanalytical laboratory and tenofovir plasma samples were stored for less than 1 month at -30°C or lower at the trial site and stored at -30°C and analyzed within one month of receipt at the GSK bioanalytical laboratory. Based on additional information that was provided by the applicant, tenofovir was stored at -70°C for up to ten days at the trial site and -30°C for up to 14 days at the bioanalytical laboratory. The submitted dolutegravir long term stability data of 480 days (16 months) at -30°C and 265 days at -20°C that was generated by GSK and 373 days at -20°C and 93 days at -70°C in EDTA anticoagulated plasma that was generated (b) (4) appears to cover the duration of dolutegravir long term stability data necessary for the ING111604 trial. The applicant only submitted tenofovir long term stability data of 38 days at -30°C that was generated by GSK that was acceptable; however the lack of -70°C long term stability data for ten days is not anticipated to significantly alter the results of the trial.

Results

Study population results

A total of 16 subjects enrolled in the study. Of these 16 subjects, 15 subjects (94%) completed all three treatment periods as planned. Following Subject 41009 was prematurely discontinued from the study after dosing on Day 6 of Period 2 because of a missed study visit (Day 5). The subject received no further doses of study medication in Period 2 and did not participate in Period 3.

The median age for subjects in the safety population was 39 years. Most subjects were male (15/16, 94%) and non-Hispanic (15/16, 94%). 50% subjects were (8/16) White/Caucasian/European Heritage.

Table 4. Summary of demographic characteristics

Demographics	**All Subjects (N=16)**
Age in Years, Median (Range)	39.0 (20, 58)
Sex, n (%) Female: Male:	 1 (6): 15 (94)
BMI, Median (Range)	26.18 (19.8, 29.5)

Height, Median (Range)	174.0 (160.0, 194.0)
Weight, Median (Range)	82.6 (53.3, 111.1)
Ethnicity, n (%) Hispanic or Latino: Not Hispanic or Latino:	 1 (6) 15 (94)
Race, n (%) African American/African Heritage Asian – South East Asian Heritage White – White/Caucasian/European Heritage	 7 (44) 1 (6) 8 (50)

Concomitant medication

Two subjects used aceaminophen during the study to treat one or more AE. No dosing with a concomitant medication was ongoing at the end of the study.

Treatment compliance

Two subjects reported not fasting prior to one dose of study medication in Period 2. Subject 41002 reported not fasting prior to dosing on Day 4 and subject 41007 reported not fasting prior to dosing on day 7.

Reviewer comments:
Administration of TDF following a high fat meal increases AUC by 40% and C_{max} by 14% according to the VIREAD prescribing information. Information on the type of the meal or timing of intake is not available. For subject 41002, co-administration of TDF with food 3 days prior to the PK sampling is not expected to have significant effects on tenofovir PK. For subject 41007, there was no significant difference between tenofovir exposures in Period 2 (TDF only, given with food) compared to tenofovir exposures in Period 3 (TDF and DTG under fasted condition). Excluding data from subject 41007 did not change the study results.

Pharmacokinetic results

Plasma Pharmacokinetics of DTG

Plasma GSK1349572 concentration-time profiles with and without TDF are shown in Fig 1. Plasma GSK1349572 PK parameters following repeat dose administration with and without TDF are presented in Table 5. The effect of TDF on GSK1349572 PK was primarily evaluated by examining the ratio of GLS means of steady-state plasma GSK1349572 PK. The results of statistical analyses are presented in Table 6.

The results of the comparison showed that co-administration of TDF 300mg q24h with GSK1349572 50mg q24h had no effect on GSK1349572 plasma pharmacokinetics. The GLS mean ratios and 90% confidence intervals for AUC and C_{max} all fell within 0.8-1.25.

Fig.1 Mean steady-state plasma GSK1349572 concentration-time plots with and without TDF.

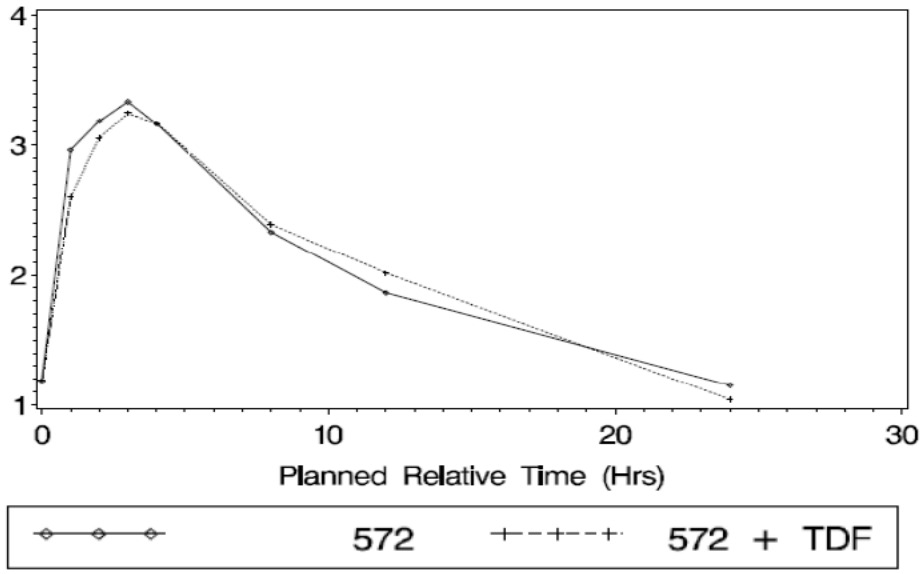


Table 5. Summary of plasma GSK1349572 PK parameters at steady state

Treatment Regimen	N	Cmax (μg /mL)	tmax[b] (h)	AUC(0-τ) (μg.h/mL)	Cτ (μg/mL)
GSK1349572 50mg	15	3.45 (30)	3.00 (1.00-4.00)	46.6 (32)	1.08 (39)
GSK1349572 50mg + TDF 300mg	15	3.34 (26)	3.00 (1.00-4.03)	46.9 (28)	0.99 (32)

The results are expressed as geometric mean (CV%) except Tmax [median, (range)].

Table 6. Summary of treatment comparison

Plasma GSK1349572 PK Parameter	GLS Mean Ratio [90% CI] (n=15)
	GSK1349572 50mg + TDF 300mg vs GSK1349572 50mg
AUC(0-τ)	1.01 [0.908, 1.11]
Cmax	0.969 [0.867, 1.08]
Cτ	0.920 [0.816, 1.04]

Plasma Pharmacokinetics of tenofovir

Plasma tenofovir time-concentration profiles with and without GSK1349572 are shown in Fig 2. Plasma tenofovir PK parameters following repeat dose administration with and without GSK1349572 are presented in Table 7. The effect of GSK1349572 on tenofovir PK was primarily evaluated by examining the ratio of GLS means of steady-state plasma GSK1349572 PK. The results of statistical analyses are presented in Table 8.

The results showed that co-administration of GSK1349572 50mg q24h and TDF 300mg q24h resulted in similar tenofovir $AUC_{(0-\tau)}$ and C_{max} and a slight increase in tenofovir C_τ as compared with TDF administration alone. The slight increase in C_τ is not considered clinically significant.

Fig 2. Mean steady-state plasma tenofovir concentration-time plots with or without GSK1349572

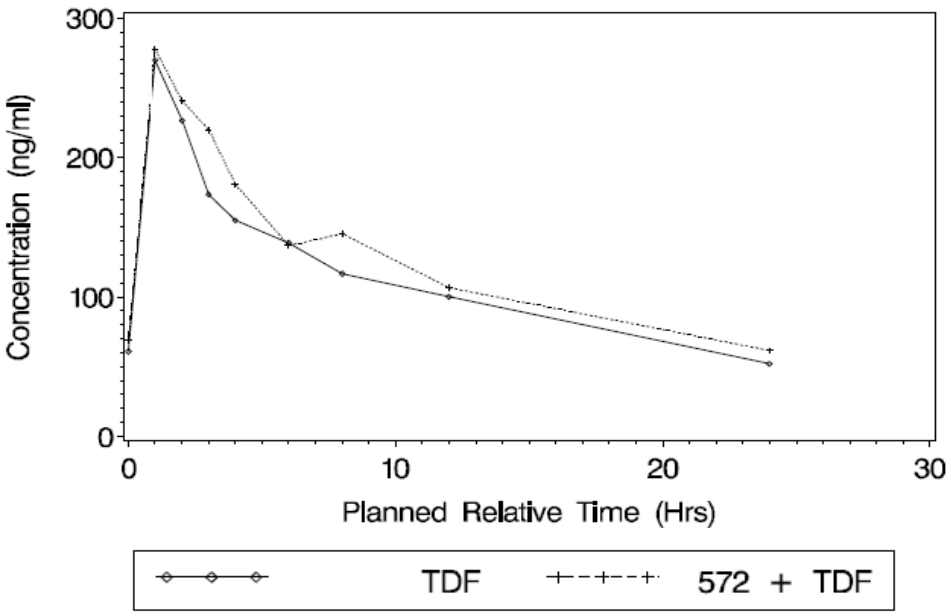


Table 7. Summary of plasma tenofovir PK parameters at steady state

Treatment Regimen	N	Cmax (ng/mL)	Tmax[b] (h)	AUC(0-τ) (ng.h/mL)	Cτ (ng/mL)
TDF 300mg	15	274 (34)	1.00 (1.00-2.00)	2446 (41)	47.2 (49)
GSK1349572 50mg + TDF 300mg	15	300 (34)	1.00 (1.00-4.03)	2738 (39)	56.0 (46)

The results are expressed as geometric mean (CV%) except Tmax [median, (range)].

Table 8. Summary of treatment comparison

Plasma Tenofovir PK Parameter	GLS Mean Ratio [90% CI] (n=50)
	GSK1349572 50mg + Tenofovir 300mg vs Tenofovir 300mg
AUC(0-τ)	1.12 [1.01, 1.24]
Cmax	1.09 [0.974, 1.23]
Cτ	1.19 [1.04, 1.35]

Safety results

GSK1349572 and TDF administered either alone or in combination for 5 to 7 days, were generally well tolerated in healthy adult subjects in this study. No deaths, non-fatal SAEs, pregnancies or drug-related AEs were reported. No subject withdrew from the study due to an AE. Few AEs were reported in Period 2 (TDF 300mg q24h) and all were mild (Grade 1). The most commonly reported AE was headache 3/16, 19%) followed by fatigue (2/16, 13%) and diarrhea (1/16, 6%). No AEs were reported to be related to GSK1349572 (Period 1 and 3).

No clinically significant trends in post-dose laboratory abnormalities, vital signs or ECG values were evident. No Grade 4 laboratory abnormalities were reported, while two subjects each had an isolated, on- or post-treatment Grade 3 laboratory abnormality (decreased hemoglobin [8.2 g/dL] on Day 5 of Period 3 and an increase in creatine kinase [1783 U/L] at the Follow-up visit). The decreased hemoglobin was likely due to a dilutional error, and the increase in creatine kinase was likely related to increase physical exertion (lifting weights) prior to the Follow-up visit.

Conclusion

Plasma PK parameters for GSK1349572 and tenofovir during combination therapy were similar to those when either drug was given alone, indicating the lack of a drug interaction. Therefore, GSK1349572 and TDF can be taken together without a dose adjustment.

Individual study review ING111854

1. Title

Phase I, open-label, randomized, drug-drug interaction study in healthy subjects to investigate the effects of co-administered atazanavir/ritonavir (300mg/100mg) or atazanavir 400mg administered once daily on the steady-state plasma pharmacokinetics of GSK1349572 30mg administered once daily

2. Information Regarding the Duration of the Trial

The trial was conducted from April 7, 2009 (initiation date) to June 9, 2009 (completion date).

3. Objectives

The primary objective of the trial was to evaluate the pharmacokinetics of dolutegravir administered as 30 mg every 24 hours in the presence and absence of atazanavir/ritonavir 300 mg/100 mg every twenty four hours or atazanavir 400 mg every twenty four hours.

4. Trial Design

GS-US-216-110 was an open label, two period, clinical trial that enrolled healthy male and female subjects 18 to 65 years old. Information on the trial design is displayed in Table 1.

Table 1-ING111854 trial design

Cohort	Sequence	Sample Size	Period 1; Days 1-5	Period 2; Days 1-14
1	1	12	Treatment A[1]	Treatment B[2]
	2	12	Treatment A[1]	Treatment C[3]

1. Treatment A = GSK1349572 30mg q24h x 5 days
2. Treatment B = GSK1349572 30mg + ATV/RTV 300/100mg q24h x 14 days
3. Treatment C = GSK1349572 30mg + ATV 400mg q24h x 14 days

5. Excluded Medications, Restrictions or Exceptions

With the exception of acetaminophen (2 grams or less per day) or medications that were permitted on a case by case basis, prescription and nonprescription medications, including herbal products, antacids, vitamins and iron supplements, were not permitted within 7 days (14 days if the medication was a potential inducer) or five half lives (whichever was longer) of first dosing for the trial or during the trial.

6. Dosage and Administration

The medications that were administered to the subjects in the trial are displayed in Table 1. For both Period 1 and Period 2, medication was administered after a moderate fat meal The trial report states that doses were administered within 30 minutes after the start of the moderate fat.

7. Rationale for Doses Used in the Trial

The dosage regimens of atazanavir 400 mg once daily and atazanavir 300 mg coadminstered with ritonavir 100 mg is consistent with the recommended dosage regimens in the atazanavir U.S. prescribing information. The dolutegravir dosage regimen of 30 mg once daily is different from the proposed dosage regimen in the dolutegravir regimen of 50 mg once daily or 50 mg twice daily, depending on the treatment population. The results of the trial are applicable because based on the dolutegravir population pharmacokinetic model, linearity is observed for 10 mg once daily to 50 mg once daily and for 50 mg once daily compared to 50 mg twice daily.

8. Drugs Used in the Trial

Information regarding the medications that were administered in the trial is displayed in Table 2.

Table 2-Information on the medications administered in the ING111854 trial

	Investigational Product		
Product name:	GSK1349572	ATV	RTV
Formulation description:	GSK1349572, D-mannitol, microcrystalline cellulose, povidone, (b) (4) sodium stearyl fumarate, (b) (4) Talc	Atazanavir sulfate, crospovidone, lactose monohydrate, magnesium stearate, gelatin, FD&C Blue #2, titanium dioxide, black iron oxide, red iron oxide, yellow iron oxide	Ritonavir (b) (4) ethanol, (b) (4) polyoxyl 35 castor oil, and titanium dioxide.
Dosage form:	Tablet	Capsule	Soft Gelatin Capsule
Physical description:	6mm white round tablets	300mg: red cap and blue body capsules 200mg: blue cap and blue body capsules	White, soft gelatin capsules
Manufacturer/ source of procurement:	Shionogi Japan	Bristol-Myers-Squibb	Abbott Laboratories
Method for individualizing dosage:	30mg= three 10mg tablets	300mg = one 300mg capsule 400mg = two 200mg capsules	100mg = one 100mg soft gelatin capsule
Batch number	091201613	9A3085A, 9A3102A	706712E21

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical

Analysis

Sample Collection

Dolutegravir (GSK1349572) blood samples were obtained on days 5 (Period 1) and 14 (Period 2) at predose and up to 24 hours postdose. Atazanavir blood samples were obtained on day 14 (Period 2) at predose and up to 24 hours postdose. Trough dolutegravir blood samples were also obtained in Period 2 on days 2, 5, 9, 12 and 13.

Bioanalysis

The method and bioanalysis of dolutegravir and atazanavir are acceptable. Specific information regarding whether current dolutegravir or atazanavir reference standards were used for either the method validation experiments or the bioanalysis of samples from the ING111854 trial was not provided by the applicant. Dolutegravir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by GlaxoSmithKline (GSK). Atazanavir plasma samples were analyzed using a validated LC/MS/MS or UPLC method in EDTA anticoagulated plasma by GlaxoSmithKline. Based on the information provided by the applicant, the blood samples for analysis of dolutegravir and atazanavir appears to have been collected in tubes containing EDTA as an anticoagulant.

For the ING111854 plasma samples that were analyzed for dolutegravir, the lower limit of quantification for dolutegravir was 5 ng/mL and the upper limit of quantification was 5000 ng/mL. There were no precision or accuracy issues identified for dolutegravir based on the bioanalytical report. For the ING111854 trial, precision and accuracy were evaluated using plasma dolutegravir QC samples at three concentration levels: 20 ng/mL, 400 ng/mL, and 4000 ng/mL. The corresponding dolutegravir inter-run accuracy values were -3.5% for 20 ng/mL, -7.4% for 400 ng/mL, and -8.2% for 4000 ng/mL. The dolutegravir inter-run precision values were 7.1% for 20 ng/mL, 3.1% for 400 ng/mL, and 3.5% for 4000 ng/mL. The lower limit of quantification for atazanavir was 10 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for atazanavir based on the bioanalytical report. For the ING111854 trial, precision and accuracy were evaluated using plasma atazanavir QC samples at three concentration levels: 40 ng/mL, 400 ng/mL, and 8000 ng/mL. The corresponding atazanavir inter-run accuracy values were 3.7% for 40 ng/mL, 3.9% for 400 ng/mL, and 0.5% for 8000 ng/mL. The atazanavir inter-run precision values were 2.2% for 40 ng/mL, 1.2% for 400 ng/mL, and 1.7% for 8000 ng/mL.

While incurred sample reanalysis was conducted for both dolutegravir and atazanavir, the comparative results for individual plasma samples were not provided and the acceptance criteria used was different than within 20% using the percentage values of the repeat and original concentrations. Therefore, the incurred sample reanalysis results will not be discussed in detail.

For the ING111854 trial, based on the information submitted by the applicant, dolutegravir plasma samples were stored for less than 2 months at -20°C or -70°C at the trial site and stored between -20°C

and -70°C and analyzed within one month of receipt at the GSK bioanalytical laboratory and atazanavir plasma samples were stored for less than 1 month at -25°C at the trial site and stored at -30°C and analyzed within one month of receipt at the GSK bioanalytical laboratory. The submitted dolutegravir long term stability data of 480 days (16 months) at -30°C and 265 days at -20°C that was generated by GSK and 373 days at -20°C and 93 days at -70°C in EDTA anticoagulated plasma that was generated (b) (4) and the submitted atazanavir long term stability data of 53 days at -30°C that was generated by GSK appears to cover the duration of long term stability data necessary for the ING111854 trial.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for dolutegravir and atazanavir. For the noncompartmental analysis, dolutegravir and atazanavir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0\text{-}24h)}$.

Statistical Analysis

ANOVA was used for the statistical analyses. The trial report did not include specific "no effect" boundaries for the 90% confidence intervals for selected dolutegravir pharmacokinetic parameters.

10. Results

10.1 Subject Demographics and Disposition

Table 3-ING111854 subject demographics

Demographics	GSK134957 2[1] (N=24)	ATV/RTV + GSK134957 2[2] (N=12)	ATV + GSK134957 2[3] (N=12)	Overall (N=24)
Age in Years, Mean (SD)	37.2 (11.2)	39.8 (12.1)	34.6 (10.1)	37.2 (11.2)
Sex, n (%)				
Female:	3 (13%)	1 (8%)	2 (17%)	3 (13%)
Male:	21 (88%)	11 (92%)	10 (83%)	21 (88%)
BMI (kg/m^2), Mean (SD)	25.9 (2.94)	26.3 (2.81)	25.6 (3.15)	25.9 (2.94)
Height (cm), Mean (SD)	172.4 (8.51)	174.4 (7.26)	170.4 (9.48)	172.42 (8.51)
Weight (kg), Mean (SD)	77.4 (12.0)	80.2 (12.2)	74.5 (11.7)	77.4 (12.0)
Ethnicity, n (%)				
Hispanic or Latino:	8 (33%)	3 (25%)	5 (42%)	8 (33%)
Not Hispanic or Latino:	16 (67%)	9 (75%)	7 (58%)	16 (67%)
Race, n (%)				
African American/African Heritage	4 (17%)	1 (8%)	3 (25%)	4 (17%)
American Indian or Alaskan Native	1 (4%)	1 (8%)	0	1 (4%)
White – White/Caucasian/ European Heritage	19 (79%)	10 (83%)	9 (75%)	19 (79%)

Table 4-ING111854 subject disposition

Number of Subjects	GSK1349572 [1]	ATV/RTV + GSK1349572 [2]	ATV + GSK1349572 [3]	Overall
Number of subjects planned, N:	24	12	12	24
Number of subjects randomized, N:	24	12	12	24
Number of subjects included in Safety Population, n (%):	24 (100%)	12 (100%)	12 (100%)	24 (100%)
Number of subjects included in GSK1349572 PK populations, n (%):	24 (100%)	12 (100%)	12 (100%)	24 (100%)
Number of subjects completed as planned, n (%):	24 (100%)	12 (100%)	12 (100%)	24 (100%)
Number of subjects withdrawn (any reason), n (%):	0	0	0	0

1. Treatment A = GSK1349572 30mg q24h x 5 days
2. Treatment B = GSK1349572 30mg + ATV/RTV 300mg/100mg q24h x 14 days
3. Treatment C = GSK1349572 30mg + ATV 400mg q24h x 14 days

10.2 Concomitant Medications

Only one subject (subject 541009) received concomitant medications (cetirizine and hydrocortisone 1% cream).The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

10.3 Pharmacokinetic and Statistical Analysis

Note: the trial report indicates that no subjects experienced emesis with dose administration

Dolutegravir

Table 5-Dolutegravir pharmacokinetic parameters derived using noncompartmental analysis with dolutegravir 30 mg once daily with or without atazanavir 300 mg combined with ritonavir 100 mg once daily (sequence 1) or with or without atazanavir 400 mg once daily (sequence 2)

Treatment Regimen	N	Cmax (µg/mL)	tmax[2] (h)	AUC(0-τ) (µg.h/mL)	Cτ (µg/mL)	C0 (µg/mL)	Cmin (µg/mL)	CL/F (L/hr)	t1/2 (h)
Sequence 1									
GSK1349572 q24h	12	3.21 (19)	3.00 (1.00-4.00)	45.3 (21)	1.00 (30)	0.85 (30)	0.85 (30)	0.66 (21)	13.3 (19)
GSK1349572 q24h + ATV/RTV	12	4.29 (19)	4.00 (2.00-4.00)	73.3 (16)	2.21 (16)	1.79 (23)	1.77 (22)	0.41 (16)	24.1 (11)
q24h									

1. geometric mean (CV%)
2. median (range)

Table 6-Statistical analyses for dolutegravir

Plasma GSK1349572 PK Parameter	GLS Mean Ratio [90% CI]	
	ATV/RTV + GSK1349572 vs GSK1349572 (n=12)	ATV + GSK1349572 vs GSK1349572 (n=12)
AUC(0-τ)	1.62 [1.50, 1.74]	1.91 [1.80, 2.03]
Cmax	1.34 [1.25, 1.42]	1.50 [1.40, 1.59]
Cτ	2.21 [1.97, 2.47]	2.80 [2.52, 3.11]
Cmin	2.10 [1.89, 2.33]	2.72 [2.44, 3.02]
C0	2.31 [2.09, 2.55]	2.89 [2.64, 3.15]
CL/F	0.618 [0.574, 0.667]	0.523 [0.494, 0.555]
t1/2	1.81 [1.64, 1.99]	1.90 [1.68, 2.14]

Atazanavir

Table 7-Atazanavir pharmacokinetic parameters derived using noncompartmental analysis (atazanavir 300 mg combined with ritonavir 100 mg once daily [sequence 1] or without atazanavir 400 mg once daily [sequence 2]) with dolutegravir 30 mg once daily

Treatment Regimen	N	Cmax (μg/mL)	Cτ (μg/mL)	AUC(0-τ) (μg.h/mL)	Cmin (μg/mL)
GSK1349572 q24h + ATV/RTV q24h	12	5.39 (26)	1.08 (42)	53.1 (31)	0.81 (51)
GSK1349572 q24h + ATV q24h	12	4.85 (42)	0.19 (84)	27.5 (45)	0.14 (89)

10.4 Safety Analysis

The most commonly reported adverse events reported in the trial are displayed in Table 8. All adverse events were considered mild except for two subjects that reported maculopapular rash that was considered moderate.

Table 8-Commonly reported adverse events reported in the ING111854 trial

	GSK1349572[1] (N=24)	ATV/RTV + GSK1349572[2] (N=12)	ATV + GSK1349572[3] (N=12)
Any AE, n (%)	4 (17%)	9 (75%)	5 (42%)
Ocular icterus	0	8 (67%)	3 (25%)
Nausea	3 (13%)	1 (8%)	1 (8%)
Diarrhea	1 (4%)	1 (8%)	1 (8%)
Myalgia	1 (4%)	1 (8%)	1 (8%)
Constipation	1 (4%)	1 (8%)	0
Headache	1 (4%)	0	1 (8%)
Pruritus	0	2 (17%)	0
Rash maculopapular	0	2 (17%)	0

11. Discussion and Conclusions

Dolutegravir is metabolized by different pathways including UGT1A1 and CYP3A. Atazanavir is an inhibitor of CYP3A and UGT1A1 according to the atazanavir U.S prescribing information. Ritonavir inhibits CYP 3A and may also induce UGT though the specific UGT isoform is not specified in the ritonavir U.S prescribing information. Based on the results from the ING111854 trial, the following conclusions can be made:

- With 30 mg once dally dosing, the dolutegravir C_{τ}, C_{max} and $AUC_{(0\text{-}24h)}$ were increased by 180%, 50%, and 91% when coadministered with atazanavir 400 mg once daily.
- With 30 mg once daily dosing, the dolutegravir C_{τ}, C_{max} and $AUC_{(0\text{-}24h)}$. were increased by 121%, 34%, and 62% when coadministered with atazanavir 300 mg combined with ritonavir 100 mg once daily

The magnitude of increase was lower for dolutegravir when coadministered with atazanavir 300 mg combined with ritonavir 100 mg once daily when compared to atazanavir 400 mg once daily. Based on the current safety profile for dolutegravir, the increases in dolutegravir exposure when coadminstered with atazanavir 400 mg once daily or atazanavir 300 mg combined with ritonavir 100 mg once daily do not require a dose adjustment in the proposed dolutegravir 50 mg once daily dosage regimen but the clinical relevance of the increase in dolutegravir exposure with proposed dolutegravir 50 mg twice daily dosage regimen is unknown.

Individual study review ING111855

Study title A Double-Blind Study to Evaluate the Pharmacokinetics of an Oral Contraceptive Containing Norgestimate and Ethinyl Estradiol when Co-administered with Dolutegravir in Healthy Adult Female Subjects (ING111855)

Site of investigation Elite Research Institute, Miami, FL, U.S.A

Study initiation date 13-Dec-2011

Study completion date 28-Mar-2012

Objective

Primary

- The primary objective of the study was to demonstrate the lack of an effect of dolutegravir (DTG) on the exposure of norelgestromin (NGMN) and ethinyl estradiol (EE) in healthy female subjects.

Secondary

- To evaluate the safety and tolerability of DTG 50 mg every 12 hours (q12h) when given in combination with Ortho-Cyclen.
- To investigate the effect of DTG on other pharmacokinetic (PK) parameters of NGMN and EE.
- To investigate the pharmacodynamic (PD) effects of DTG administration on luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone levels when given in combination with Ortho-Cyclen compared with these parameters when Ortho-Cyclen was administered alone.
- To evaluate the PK of DTG when co-administered with norgestimate and EE.

Study Rationale

Ortho-Cyclen is a commonly prescribed combination oral contraceptive (OC) that contains a fixed dose of norgestimate 0.25 mg and ethinyl estradiol 0.035 mg throughout the 21 day dosing cycle with an additional 7 placebo tablets. As DTG will likely be co-administered to HIV-infected women receiving OCs, it is important to assess the potential of DTG to alter the pharmacokinetics and pharmacodynamics of either component of the combination OC. Ortho-Cyclen was selected as a the OC for this drug interaction study due to its widespread use, combination estrogen/progesterone content, standardized dose throughout the cycle, and long term safety profile.

Norgestimate (NGM) undergoes both oxidative and reductive metabolism, as does ethinyl estradiol (EE). CYP3A4 and UGT1A1 are known to mediate the oxidative metabolism of ethinyl estradiol. Potential interactions typically involve induction of oxidative and conjugative metabolic clearance. Although the drug interaction potential between DTG and OCs is low, this study was designed to confirm that DTG has no impact on the PK and PD of the OC in a controlled clinical pharmacology study.

Impairment of OC efficacy resulting from a drug interaction is most likely to occur in the early part of the pill cycle when it is critical to maintain adequate circulating exogenous hormone concentrations. To avoid

any menstrual cycle interruption and inter-cycle variability of EE and norgestimate, this study was designed as a two-period crossover design within one menstrual cycle. Completion of the study within one menstrual cycle also minimizes drop-outs.

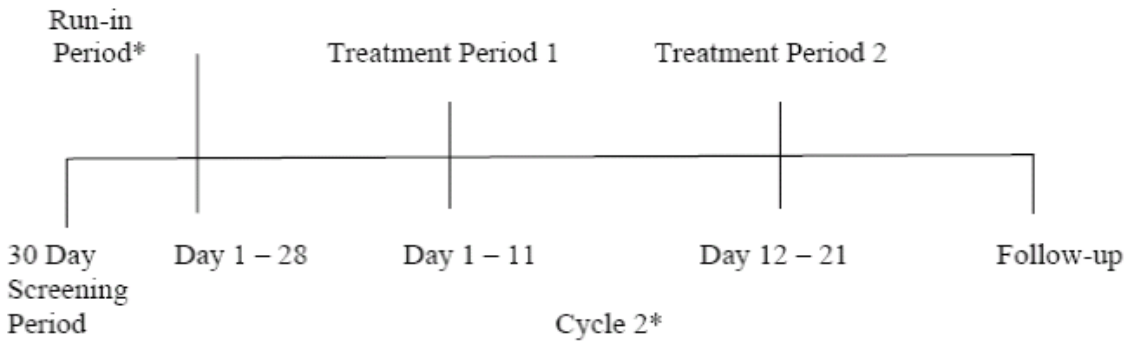
The DTG 50 mg q12h dose (dosing recommendation for integrase inhibitor experienced patients) was used in this study as it would demonstrate the worst case scenario for a possible interaction with OCs. In addition, the protocol has been amended to add dosing under fed conditions to maximize the potential for a drug-drug interaction.

Study Design
This was a randomized, single center, two-period, double-blind, placebo-controlled, cross-over design study. The study consisted of run-in period, treatment Periods 1 and 2.

Run-in period
Subjects who were not already on a stable regimen of Ortho-Cyclen switched to Ortho-Cyclen for a cycle of 21 days to evaluate tolerability, followed by a washout period of 7 days, before continuing to treatment Periods 1 and 2. First day of administration (Day 1 of Run-in Period) of a new package of oral contraceptives for naïve subjects or subjects switching to Ortho-Cyclen generally coincided with the first day of a menstrual cycle but could be adjusted by up to 5 days in order to accommodate weekends and scheduling preferences. Subjects who were already stable on Ortho-Cyclen were permitted to skip the Run-in Period and proceed to treatment period.

Treatment Period 1 and 2
Subjects were instructed to take their study drugs (DTG or placebo) at the same designated time each day (approximately 8 am and 8 pm) with a moderate fat meal. On Day 10, subjects underwent 24-hour serial PK collection for NGMN, EE and 12-hour serial PK collection for DTG following the morning dose on day 21. Following completion of Day 11 predose PK sample, another supply of Period 2 investigational products were dispensed to each subject (DTG or placebo, cross-over). Subjects were instructed to continue to take their study drugs at the same designated time each day with a moderate fat meal. On Day 21 (morning), predose PK blood samples for NGMN, EE, and DTG were collected and subjects were dosed with study drugs followed by 24-hour serial PK blood collection for NGMN and EE as well as 12-hour serial PK blood collection for DTG.

<Treatment design>



<Treatment Schematic>

Treatment Period 1	**Treatment Period 2**
OC + DTG	OC + DTG
OC + Placebo	OC + Placebo

Reviewer comments:
There was no washout period between treatment period 1 and treatment period 2 despite cross-over study design.

Drugs used in this study

	Study Treatment		
Product name:	**Dolutegravir**	**Placebo**	**Ortho-Cyclen**
Dosage form:	Tablet	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	50 mg = 1 tablet Dose = 50 mg	N/A	Strength = norgestimate 0.25 mg and ethinyl estradiol 0.035 mg
Frequency/Duration	q12h/10 days	q12h/10 days	q24h for up to two menstrual cycles
Route/ Administration	Oral	Oral	Oral
Batch Number	111287797	101253402	33801843A

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Female, between 18 and 40 years of age inclusive, at the time of signing the informed consent

- Women of childbearing potential were required to use OC Ortho-Cyclen in combination with one of the following appropriate contraceptive methods; a barrier method plus a spermicide, complete abstinence, or sterilization of male partner
- The subject's body mass index (BMI) was 19 to 30 kg/m^2 and body weight ≥50 kg (110 lbs) and <114 kg (<250 lbs).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.
- Pregnant or lactating females.
- History of any condition that contraindicated OC administration (including hypertension, stroke, ischemic heart disease, venous thromboembolism, etc.).
- Females with conditions or concurrent medications that could adversely affect hormone levels e.g. oopherectomies and females receiving drug eluting intrauterine device (IUDs) (e.g. Mirena).

Permitted Medications

Acetaminophen, at doses of ≤2grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study.

Pharmacokinetic assessments

Bioanalysis assessments

Bioanalysis of ethinylestradiol and NGMN

Bioanalysis of the plasma samples for NGMN and ethinylestradiol was performed (b) (4) with validated analytical methods. The NGMN method was based on liquid-liquid extraction followed by HPLC-MS/MS analysis. The ethinyl estradiol method was based on extraction with an organic solvent, followed by derivatization with dansyl chloride then HPLC-MS/MS analysis.

Bioanalysis of DTG

Bioanalysis of the plasma samples for DTG was performed (b) (4) with a validated analytical method based on protein precipitation followed by high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) analysis.

Quality control (QC) samples were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria.

The standard curve and QC data indicated that the plasma assay methods for EE, NGMN, and DTG were precise and accurate as shown in table 1.

Table 1. Bioanalysis quality control

Analyte	Linear range (ng/mL) (lower limit of quantitation-upper limit of quantitation)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)
Ethinyl estradiol (EE)	2-500 pg/mL R^2> 0.996	3.5 to 6.6	0.5 to 3.9	5, 10, 30, 100, 400 pg/mL
Norelgestromin (NGMN)	0.02-10 R^2> 0.998	2.4 to 13.1	-5.8 to 4.2	0.05, 0.13, 0.45, 1.5, 7.6
Dolutegravir	20-20000 R^2> 0.995	1.7 to 4.8	-1.2 to 6.0	60, 16000, 16000

Reviewer comments

The plasma samples for norelgestromin and ethinylestradiol contain potassium oxalate and sodium fluoride as anticoagulants. The bioanalytical methods have been developed and validated for plasma samples containing those anticoagulants. Bioanalysis methods for PD parameters (FSH, LH, and progesterone) were not provided in the protocol.

Pharmacokinetic analysis

The pharmacokinetic parameters were calculated by standard non-compartmental analysis according to current working practices and using WinNonlin Professional Edition v5.3. Actual elapsed time from dosing was used in the derivation of all PK parameters.

Results

Study population results

A total of 16 subjects enrolled in the study. All 16 subjects received doses of dolutegravir (GSK1349572), Ortho-Cyclen contraceptive and placebo pill. One subject (550015) withdrew from the study during Period 2 due to a family emergency. The treatment blind was not broken at any point during the study. Demographic characteristics are summarized in table 2.

Table 2. Summary of demographic characteristics

Demographics	**Overall**
Age in Years, Mean (SD)	31.1 (7.51)
Sex, n (%)	
Female:	16 (100)
BMI (kg/m2), Mean (SD)	24.67 (3.025)
Height (cm), Mean (SD)	161.64 (7.096)
Weight (kg), Mean (SD)	64.54 (9.541)
Ethnicity, n (%)	
Hispanic or Latino:	16 (100)
Not Hispanic or Latino:	0
Race, n (%)	
White – White/Caucasian/European Heritage	15 (94)
African American/African Heritage	1 (6)

Protocol deviation

The study site discovered on the evening of Day 7 of Period 1 that they had given the wrong treatment to subject 550007 for the first 7 days of Treatment Period 1. Since it is a crossover study and all subjects will receive both treatments, the site was given permission to continue with the incorrect treatment for the remainder of Period 1 and then switch to the opposite treatment for Period 2. Subject 550007 received treatment sequence XBA (OC+placebo then OC+DTG) instead of XAB (OC+DTG then OC+placebo).

Reviewer comments

Subject 55007 had comparable steady-state DTG PK parameters (AUC: 61.71 µg/mL·h and C_{max} 7.37 µg/mL) compared to the geometric mean of DTG obtained in this study (AUC: 70.78 µg/mL·h and C_{max} 7.98 µg/mL). It appears that the subject achieved a comparable level of DTG despite the protocol deviation and this will unlikely affect the study results and conclusion.

Several subjects [how many?] took their doses of study medication at home before coming into the clinic for the pre-dose PK draws on Days 8 and 9 of Period 1 and/or Days 19 and 20 of Period 2. These subjects were considered non-evaluable for the trough PK analyses on those days that they took the doses at home prior to the PK draw.

Reviewer comments: Those samples were drawn only to check whether steady state was reached and was not used for the 24 hour pharmacokinetic analysis and statistical analysis. The deviation is not expected to affect the study results.

Pharmacokinetic results

Plasma pharmacokinetics of NGMN

Median plasma NGMN and EE concentrations are shown in linear concentration vs. time plots in Fig 1. Plasma NGMN PK parameters and the results of the statistical analysis are summarized in table 3. The exposures of NGMN are comparable after treatment with OC alone or in the presence of DTG. At steady state, geometric mean ratios of C_{min}, C_{max}, and AUC_{τ} for NGMN in the presence of DTG were 0.975, 0.890 and 0.932 respectively, and the 90% CIs of the LS mean ratios all fell within the predefined 0.80 to 1.25 limits.

Fig 1. Median plasma NGMN and EE concentration-time plots

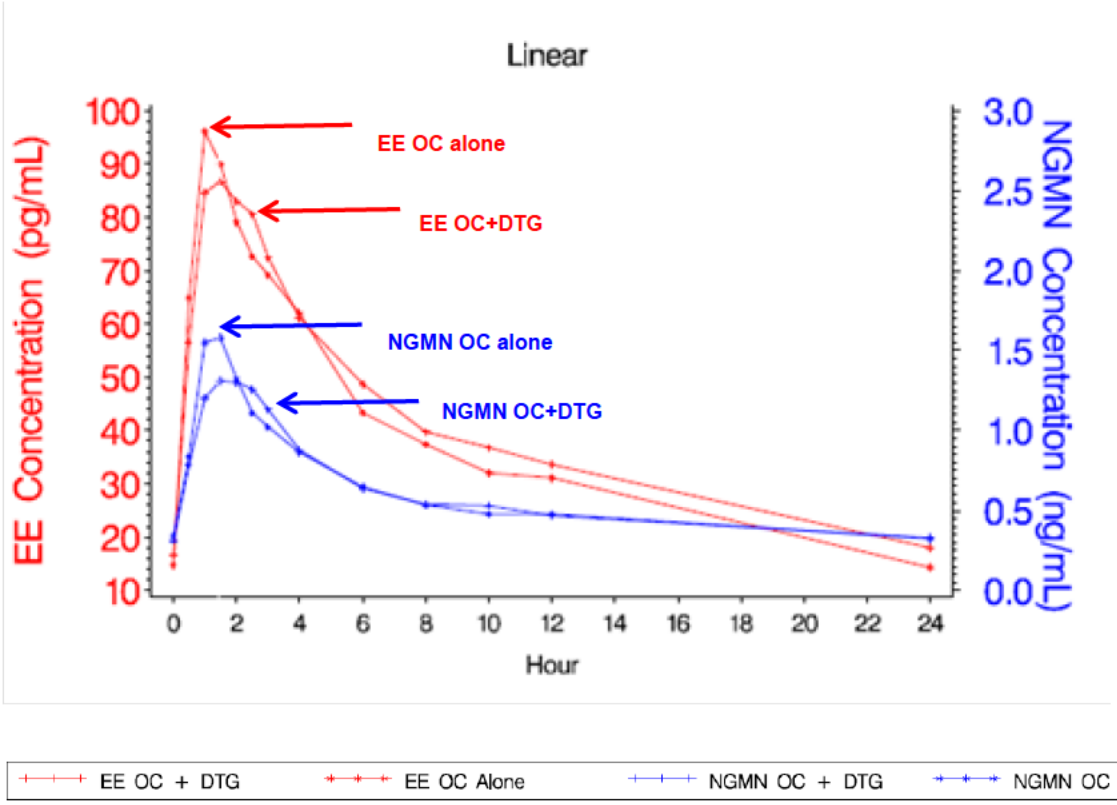


Table 3. Summary of plasma NGMN pharmacokinetic parameters and statistical analysis

Treatment	OC + DTG	OC alone	Ratio of Geometric Mean Ratio (90% CI) OC+DTG vs. OC alone
$AUC_{(0-\tau)}$ (ng h/mL) geometric mean (CV%)	13.8 (16)	14.1 (25)	0.975 [0.910, 1.04]
C_{max} (ng/mL) geometric mean (CV%)	1.42 (18)	1.59 (30)	0.890 [0.815, 0.973]
C_{min} (ng/mL) geometric mean (CV%)	0.30 (26)	0.33 (30)	0.932 [0.846, 1.03]
$t_{1/2}$ (hr) median (range)	22.0 (19)	22.3 (32)	No difference
T_{max} (hr) median (range)	1.50 (1.0-2.5)	1.00 (1.0-3.0)	No difference

Plasma pharmacokinetics of EE

Plasma EE PK parameters and the results of the statistical analysis are summarized in table 4. Overall, the exposures of EE are comparable after treatment with OC alone or in the presence of DTG. At steady state, geometric mean ratio of C_{min}, C_{max}, and AUC_{τ} for EE were 0.975, 0.890, and 0.932, respectively and the 90% CIs of the LS mean ratios all fell within the predefined 0.80 to 1.25 limits.

Table 4. Summary of plasma EE pharmacokinetic parameters and statistical analysis

Treatment	OC + DTG	OC alone	Ratio of Geometric Mean Ratio (90% CI) OC+DTG vs. OC alone
$AUC_{(0-\tau)}$ (pg h/mL) geometric mean (CV%)	952 (19)	916 (27)	1.03 [0.964, 1.11]
C_{max} (pg/mL) geometric mean (CV%)	100 (22)	101 (25)	0.988 [0.907, 1.08]
C_{min} (pg/mL) geometric mean (CV%)	16.6 (19)	16.4 (33)	1.02 [0.934, 1.11]
$t_{1/2}$ (hr) median (range)	14.4 (19)	13.6 (24)	Not obtained
T_{max} (hr) median (range)	1.00 (0.5-2.5)	1.00 (0.5-2.0)	Not obtained

Reviewer comments:

The applicant assessed period effect to evaluate if those subjects who received DTG in the first part of the cycle had a different effect on the OC than those who received DTG in the second part of the cycle. This analysis demonstrated no effect of the order of DTG or placebo treatment on the study results.

Plasma DTG pharmacokinetics

Plasma DTG pharmacokinetic parameters are summarized in table 5. No statistical analysis was performed as this was a one-way study to evaluate effects of DTG on EE and NGMN.

Table 5. Summary of Plasma DTG Pharmacokinetic Parameters

Treatment	**OC + DTG**
$AUC_{(0-t)}$(µg.h/mL)	68.5 (27)
$AUC_{(0-\tau)}$ (µg.h/mL)	68.6 (27)
C_{max} (µg/mL)	7.77 (23)
C_0 (µg/mL)	4.40 (37)
C_τ (µg/mL)	4.00 (36)
C_{min} (µg/mL)	3.79 (35)
CL/F (L/hr)	0.73 (27)
t_{max} (hr)	1.00 (1.0-6.0)

All data are presented as geometric mean (CV%) except Tmax [median (range)]

Reviewer comments: The applicant stated that the PK parameters for the 50 mg BID dose reported in this trial are comparable to those from a previous study (ING115696) using the same dose and given with food. However, 50 mg QD dosing was used in ING115696 (drug interaction study with prednisone). Instead, DTG 50 mg b.i.d was administered to healthy volunteers under fasted conditions in ING114819. The AUC and C_{max} of DTG are 32% and 40% higher in this study compared to those in ING114819 (see table below). The difference can be explained by co-administration of food in this study which can increase the exposure of DTG up to 67%.

Table 10 Summary of Selected Plasma GSK1349572 Pharmacokinetic Parameters Following Repeat Dose Administration in ING114819[1]

Treatment	N	AUC(0-τ) (µg.h/mL)	AUC(0-24) (µg.h/mL)	Cmax (µg/mL)	C0 (µg/mL)	Cτ (µg/mL)
GSK1349572 50mg q24h	11	39.1 (38)	39.1 (38)	2.83 (27)	0.91 (142)	0.84 (61)
GSK1349572 50mg q12h	11	51.6 (36)	103 (36)	5.50 (34)	4.18 (44)	3.02 (40)

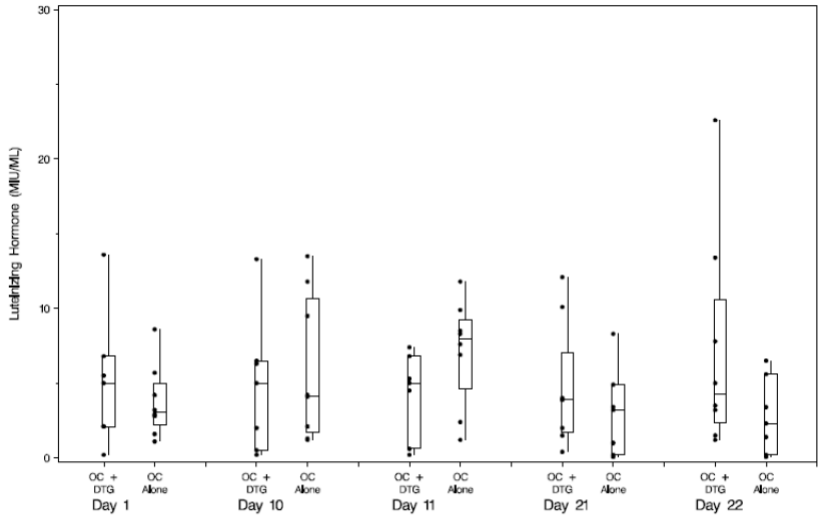
Source Data: Table 11.4

1. Geometric mean (CV%)

Pharmacodynamic results

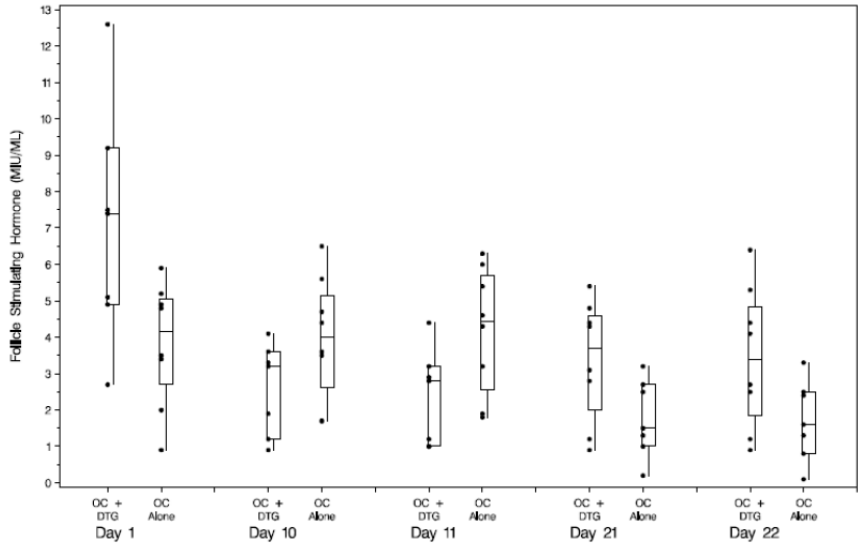
Box plots of LH, FSH, and progesterone concentration (at pre-dose) by treatment and day were provided in Fig. 2, 3, and 4, respectively. There was no systematic trend or significant effect on the concentration of PD markers, including LH, FSH, and progesterone, consistent with PK findings. No statistical analysis was performed with PD results.

Fig 2. Box plot of pre-dose plasma luteinizing hormone (LH) concentrations by day and treatment



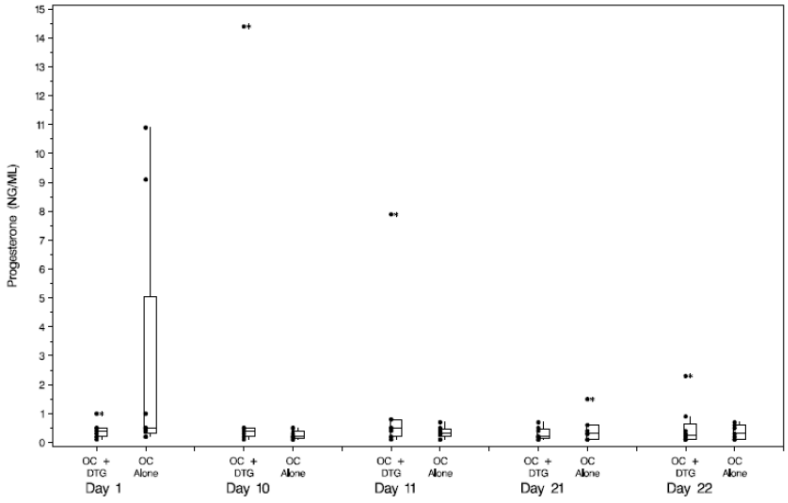
Source Data: Figure 4.4.
Treatment: OC + DTG = Ortho-Cyclen q24h + DTG 50mg q12h; OC Alone = Ortho-Cyclen q24h + placebo q12h.
Note: The bottom and top edges of the box are located at the 25th and 75th percentiles. The center horizontal line is 50th percentile (median). The vertical lines are drawn from the box to the most extreme point less than or equal to 1.5 interquartile ranges Individual raw data overlay on the side of boxplot .

Fig 3. Box plot of pre-dose plasma FSH concentrations by day and treatment



Source Data: Figure 4.5.
Treatment: OC + DTG = Ortho-Cyclen q24h + DTG 50mg q12h; OC Alone = Ortho-Cyclen q24h + placebo q12h.
Note: The bottom and top edges of the box are located at the 25th and 75th percentiles. The center horizontal line is 50th percentile (median). The vertical lines are drawn from the box to the most extreme point less than or equal to 1.5 interquartile ranges Individual raw data overlay on the side of boxplot .

Fig 4. Box plot of pre-dose plasma progesterone concentrations by day and treatment



Source Data: Figure 4.6.
Treatment: OC + DTG = Ortho-Cyclen q24h + DTG 50mg q12h; OC Alone = Ortho-Cyclen q24h + placebo q12h.
Note: The bottom and top edges of the box are located at the 25th and 75th percentiles. The center horizontal line is 50th percentile (median). The vertical lines are drawn from the box to the most extreme point less than or equal to 1.5 interquartile ranges Individual raw data overlay on the side of boxplot .

Reviewer comments: The utility of the PD markers for DDI studies with OC are unclear at this point due to several limitations, including lack of consensus on the optimal study design, significant inter-individual variability, etc. The results should be for descriptive and not inferential purposes.

Safety results

GSK1349572 50mg b.i.d administered alone or in combination with an oral hormonal contraceptive containing EE and NGMN was well tolerated during this study in healthy adult females. No deaths, SAEs, or withdrawals due to AEs were reported. A total of 8 of 16 subjects (50%) reported at least one AE during the study. The most frequently reported AEs were headache (3 subjects; 19%) and dizziness (1 subject; 6%). All AEs were mild (Grade 1) in intensity except one headache AE was recorded as grade 2 intensity. No clinically significant trends in clinical laboratory values, vital signs, or ECGs were observed.

Conclusion

The exposures of two OC components, EE and NGMN, in this study were comparable in the presence of DTG or without DTG. The study confirmed the lack of an interaction and provided in vivo data to support co-administration of EE/NGMN based OCs and DTG. However, this may not be extrapolated to other OC products containing different types of progestins as the metabolism of OC components is complex and involves oxidative, reductive, and conjugative pathways via CYP, UGT, and other unknown pathways (e.g., drospirenone).

Individual study review ING112934

Study title A Phase I, open-label, randomized, three-period, one-way, two- cohort, adaptive crossover study to evaluate the effect of darunavir/ritonavir plus etravirine and lopinavir/ritonavir plus etravirine on GSK 1349572 pharmacokinetics in healthy adult subjects

Site of investigation Buffalo Clinical Research Center, Buffalo, NY

Study initiation date 02 April 2009

Study completion date 20 May 2009

Objective

Primary

- To compare steady-state plasma GSK1349572 pharmacokinetics (PK) following dministration of GSK1349572 50mg every 24 hours (q24h) alone and GSK1349572 50mg q24h in combination with etravirine (ETV)/lopinavir (LPV)/ritonavir (RTV) 200/400/100mg q12h or ETV/darunavir (DRV)/RTV 200/600/100mg every 12 hours (q12h), each for 14 days.

- To compare steady-state plasma GSK1349572 PK following administration of GSK1349572 50mg q24h alone and GSK1349572 50mg q12h in combination with ETV/LPV/RTV 200/400/100mg q12h or ETV/DRV/RTV 200/600/100mg q12h, each for 14 days, if required based on the results from Period 2.

Secondary

- To assess the safety and tolerability of repeat dose co-administration of GSK1349572 and ETV/LPV/RTV or ETV/DRV/RTV, each for 14 days.
- To assess plasma ETV PK following co-administration of GSK1349572 50mg q24h (and 50mg q12h if appropriate) and ETV/LPV/RTV 200/400/100mg q12h or ETV/DRV/RTV 200/600/100mg q12h, each for 14 days

Study Rationale

When ETV was coadministered with GSK1349572, mean GSK1349572 AUC and Cτ decreased by 70-90% in study ING111603. This decrease could be clinically significant, especially in raltegravir (RAL)-resistant subjects, and strategies to use ETV in combination with GSK1349572 were explored. This study was conducted to evaluate if the addition of a RTV-boosted protease inhibitor could attenuate the ETV interaction and allow for concomitant use. Since the interaction with ETV was large, it was anticipated that GSK1349572 exposure may still be substantially reduced when co-administered with ETV+LPV/RTV or ETV+DRV/RTV. Therefore, this study allowed dose adjustment of GSK1349572 from 50mg q24h to 50mg q12h if a significant reduction in GSK1349572 trough concentration was observed when combined with ETV and DRV/RTV or LPV/RTV. The decision to dose adjust in Period 3 was based on interim analysis of PK data obtained in Periods 1 and 2.

It was unlikely that GSK1349572 would affect ETV, LPV, DRV or RTV PK given that these drugs are predominantly metabolized by CYP3A and a previous study demonstrated no effect of GSK1349572 on the PK of the CYP3A substrate midazolam. Therefore, the study was designed to evaluate the one-way interaction between ETV/LPV/RTV and ETV/DRV/RTV on GSK1349572 PK . The PK of LPV, RTV and DRV were not evaluated. A previous study (Study ING111603) demonstrated ETV exposure that was higher than historical data. Therefore, ETV PK was collected in this study.

Study Design

This was a single-center, randomized, open-label, three-period, one-way, two-cohort, adaptive crossover study in healthy adult subjects. A total of approximately 18 subjects were planned to be enrolled (9 per cohort), in order to obtain 12 evaluable subjects (6 per cohort). Periods 1 and 2 evaluated the effect of ETV/LPV/RTV (Cohort 1) and ETV/DRV/RTV (Cohort 2) on GSK1349572 PK following a 50mg q24h dose. After completion of Period 2, PK data were analyzed and a decision was made whether to conduct Period 3. If a significant drug interaction was observed in Period 2, the GSK1349572 regimen in Period 3 would be adjusted to 50mg q12h. If a significant drug interaction was not observed, Period 3 would not be conducted. All doses in period 1 and 2 were administered with 240 mL of water within 30 minutes after the start of a moderate fat meal.

Table 1. Study design

Cohort	Sample Size	Period 1; Days 1-5	Period 2; Days 1-14	Washout 21-28 days	Period 3; Days 1-14
1:ETV/LPV/RTV	9	Treatment A[1]	Treatment B[2]		Treatment D[4]
2:ETV/DRV/RTV	9	Treatment A[1]	Treatment C[3]		Treatment E[5]

1. Treatment A = GSK1349572 50mg q24h x 5 days
2. Treatment B = GSK1349572 50mg q24h + ETV/LPV/RTV 200/400/100mg q12h x 14 days
3. Treatment C = GSK1349572 50mg q24h + ETV/DRV/RTV 200/600/100mg q12h x 14 days
4. Treatment D = GSK1349572 50mg q12h + ETV/LPV/RTV 200/400/100mg q12h x 14 days
5. Treatment E = GSK1349572 50mg q12h + ETV/DRV/RTV 200/600/100mg q12h x 14 days

Reviewer comments

Based on the period 1 and 2 study results, period 3 was not conducted.

Drugs used in this study

Table 2. Identity of investigational products

	Investigational Product				
Product	GSK1349572	ETV	DRV	RTV	LPV/RTV
Dosage form:	Tablet	Tablet	Tablet	Soft Gelatin Capsule	Tablet

Unit dose strength(s)/ Dosage level(s):	Tablet strengths = 10mg Dose level = 50mg	Tablet strength = 100mg Dose level = 200mg	Tablet strengths = 600mg Dose level = 600mg	Soft gelatin capsule strengths = 100mg Dose level = 100mg	Table strengths = 200mg Lopinavir/ 50mg ritonavir Dose level = 400mg Lopinavir/ 100mg ritonavir
Lot Numbers	091201613	8KL5E00	98G497	706692E21	69314AA40

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant)
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

Permitted Medications

Acetaminophen, at doses of ≤2grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor.

Prohibited Medications
Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Pharmacokinetic assessments
The pharmacokinetic parameters of DTG and ETV were determined from the plasma concentration-time data. The pharmacokinetic parameters were calculated by standard non-compartmental analysis according to current working practice and using WinNonlin Professional Edition V5.3. Actual elapsed time from dosing was used in the devidation of all PK parameters.

Bioanalysis assessments
DTG was extracted by protein precipitation using acetonitrile containing [$^{2}H_{7}$,^{15}N]-DTG as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method. Extracts were analyzed by a validated HPLC/MS/MS analysis method. Human plasma samples were analyzed for ETV using a validated analytical method based on protein precipitation, followed by ultra performance liquid chromatography with tandem mass spectroscopy (UPLC/MS/MS) analysis. Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria. The standard curve and QC data indicated that the plasma assay methods of DTG in this study were precise and accurate as shown in the table 3.

Table 1. Summary of bioanalysis quality control

Analyte	**Linear range** (Upper Limit of Qantitation-Lower Limit of Quantitation)	**Between Run Precision (%CV)**	**Between Run Bias (% Deviation)**	**QC samples (ng/mL)**
Etravirine	5-4500 ng/mL R^2> 0.998	1.6% to 3.4%	-8.2% to 5.7%	20, 500, 3600
DTG	5-5000 ng/mL R^2> 0.996	1.6% to 5.5%	2.8% to 5.4%	20, 400, 4000

Reviewer comments
The method was validated and performed with a linear range of 5-5000 ng/mL in plasma. Some subjects in this study had C_{max} values higher than 5000 ng/mL. According to the method validation report, the ability to dilute samples containing DTG at concentrations above the upper limit of quantitation was demonstrated by performing 6 replicate 10-fold dilutions of human plasma samples at 10000 ng/mL.

However, a detailed method of dilution (e.g., dilution ratio) or the list of samples reanalyzed due to being above the upper limit of quantitation is not available in the bioanalysis study report.

Results

Study population results

A total of 17 subjects were enrolled in the study and all subjects completed the study as planned. All subjects were male and approximately half of subjects were White (53%) and half were African American (47%). The mean age was 37.6 years with an age range of 20 to 61 years. The treatment groups were similar with regard to demographic characteristics (Table 4).

Table 4. Summary of demographic characteristics

Demographics	GSK1349572 50mg (N=17)	GSK1349572 50mg + ETV/LPV/RTV (N=8)	GSK1349572 50mg + ETV/DRV/RTV3 (N=9)	Total (N=17)
Age in Years, Mean (SD)	37.6 (12.19)	33.5 (10.45)	41.2 (13.04)	37.6 (12.19)
Sex, n (%)				
Male:	17 (100%)	8 (100%)	9 (100%)	17 (100%)
BMI, Mean (SD)	27.2 (2.16)	26.3 (2.44)	28.1 (1.56)	27.2 (2.16)
Height, Mean (SD)	177.1 (6.68)	180.9 (4.58)	173.7 (6.58)	177.1 (6.68)
Weight, Mean (SD)	85.37 (8.34)	85.94 (7.80)	84.87 (9.24)	85.37 (8.34)
Ethnicity, n (%)				
Hispanic or Latino:	1 (6%)	0	1 (11%)	1 (6%)
Not Hispanic or Latino:	16 (94%)	8 (100%)	8 (89%)	16 (94%)
Race, n (%)				
African American/African Heritage	8 (47%)	5 (63%)	3 (33%)	8 (47%)
White – White/Caucasian/ European Heritage	9 (53%)	3 (38%)	6 (67%)	9 (53%)

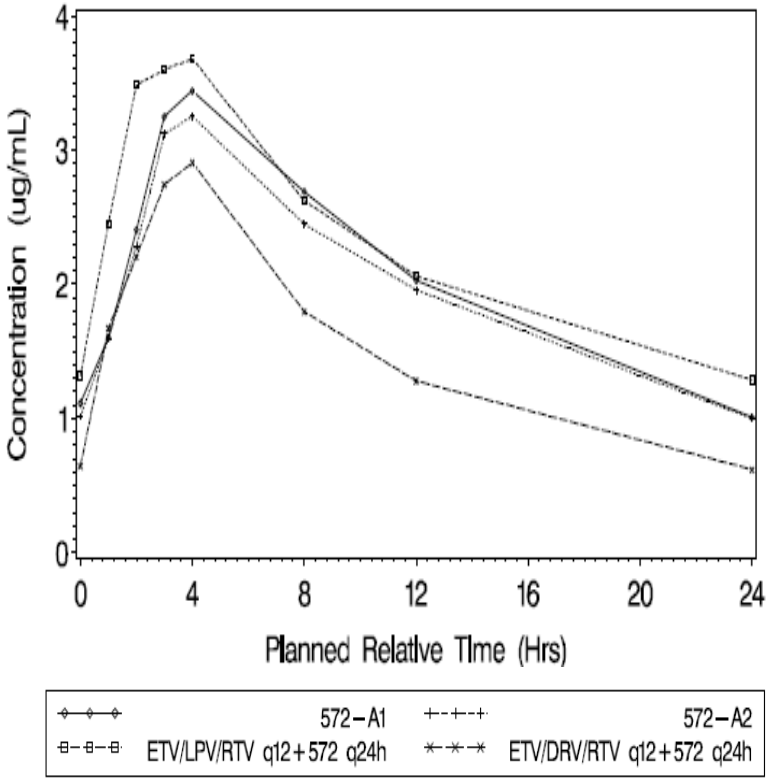
Concomitant medication

Subject 341011 received acetaminophen for treatment of a headache. Subject 341016 received hydrocortisone 1% lotion and diphenhydramine for treatment of contact dermatitis.

Pharmacokinetic results

Plasma DTG pharmacokinetics

Plasma DTG concentration-time profiles in each cohort are shown in Fig 1. Plasma DTG PK parameters following repeat dose administration in each cohort are presented in Table 5. The effect of ETV/DRV/RTV or LPV/DRV/RTV on GSK1349572 PK was primarily evaluated by examining the ratio of GLS means of steady-state plasma GSK1349572 PK. The results of the treatment comparison are presented in Table 6.



Co-administration with ETV/LPV/RTV had no effect on GSK1349572 $AUC_{(0-\tau)}$ and C_{max} while $C\tau$ was increased by 28% and $t_{½}$ increased by 36%. Co-administration with ETV/DRV/RTV resulted in decreased plasma GSK1349572 exposures. Mean plasma GSK1349572 $AUC_{(0-\tau)}$, C_{max}, and C_{τ} were 25%, 12%, and 37% lower when GSK1349572 was co-administered with ETV/DRV/RTV compared to GSK1349572 given alone. DRV/RTV showed a similar decrease in DTG exposure, but DTG efficacy was not compromised in the presence of DRV/RTV in the phase 3 trials. Therefore, the decrease in DTG exposure in the presence of ETV/DRV/RTV is not considered to be clinically significant.

Reviewer comments
Since a previously observed interaction with ETV was large, it was anticipated that GSK1349572 exposure may still be substantially reduced in the presence of a ritonavir-boosted PI. However, the results from Period 2 demonstrated that the addition of LPV/RTV and DRV/RTV counteracted the large decrease in GSK1349572 exposures previously observed with ETV alone and Period 3 was not conducted. Although the exact mechanism is unclear, similar effects (counter-acting of ETV's CYP3A inductive effects by a ritonavir-boosted PI) were observed in drug interaction studies between maraviroc and etravirine.

Fig 1. Mean steady-state plasma GSK1349572 concentration-time plots by cohort

Table 5. Summary of plasma GSK1349572 pharmacokinetic parameters following repeat dose administration

Treatment Regimen	N	Cmax (µg/mL)	tmax[2] (h)	AUC(0-τ (µg.h/mL)	Cτ (µg/mL)	Cmin (µg/mL)	CL/F (L/hr)	t½ (hr)
GSK1349572 (Cohort 1)	8	3.52 (12)	3.50 (2.00-4.00)	47.8 (19)	0.97 (33)	0.94 (36)	1.05 (19)	11.3 (18)
GSK1349572 (Cohort 2)	9	3.38 (26)	3.02 (1.00-12.00)	45.2 (22)	0.94 (40)	0.89 (35)	1.11 (22)	10.4 (17)
GSK1349572 q24h + ETV/LPV/RTV q12h	8	3.78 (12)	3.50 (1.00-4.00)	52.8 (18)	1.23 (32)	1.18 (32)	0.95 (18)	15.4 (25)
GSK1349572 q24h + ETV/DRV/RTV q12h	9	2.98 (18)	4.00 (1.00-4.00)	33.9 (22)	0.59 (33)	0.57 (34)	1.47 (22)	10.2 (16)

Source Data: Table 11.5
1. geometric mean (CV%)
2. median (range)

Table 6. Summary of GSK1349572 treatment comparison

Plasma GSK1349572 PK Parameter	GLS Mean Ratio [90% CI]	
	ETV/LPV/RTV q12h + GSK1349572 vs GSK1349572 q24h in Cohort 1	ETV/DRV/RTV q12h + GSK1349572 vs GSK1349572 q24h in Cohort 2
AUC(0-τ)	1.11 [1.02, 1.20]	0.750 [0.691, 0.814]
Cmax	1.07 [1.02, 1.13]	0.882 [0.781, 0.997]
Cτ	1.28 [1.13, 1.45]	0.629 [0.523, 0.758]
Cmin	1.26 [1.13, 1.40]	0.637 [0.552, 0.735]
CL/F	0.905 [0.832, 0.984]	1.33 [1.23, 1.45]
t½	1.36 [1.20, 1.54]]	0.993 [0.891, 1.11]

Source Data: Table 11.6

Plasma etravirine pharmacokinetics

Plasma ETVPK parameters following repeat dose administration in each cohort are presented in Table 7. Because GSK1349572 is not an inhibitor or inducer of CYP enzymes which governs the primary route of elimination of ETV, GSK1349572 was not expected to impact plasma ETV exposure.

Table 7. Summary of plasma etravirine PK parameters at steady state in ING112934 and ING111603

Treatment Regimen	N	Cmax* (ng/mL)	AUC(0-τ)* (ng.h/mL)	Cτ* (ng/mL)
GSK1349572 q24h+ ETV q12h (ING111603)	15	1125 (28)	10294 (24)	639 (24)
GSK1349572 q24h + ETV/LPV/RTV q12h (ING112934)	8	974 (73)	8834 (79)	585 (93)

GSK1349572 q24h + ETV/DRV/RTV q12h (ING112934)	9	886 (32)	7691 (34)	495 (42)

* Geometric mean (CV%)

Reviewer comments
Please refer to the review of study ING111603 for etravirine historical PK data. Overall, the exposure of ETV observed in both studies (ING111603 and ING112934) is comparable with the historical data. Of note, when ETV was co-administered with LPV/RTV, ETV AUC decreased by 35%. When ETV was co-administered with DRV/RTV, ETV AUC was decreased by 37%. When the exposure of ETV in this study is compared to that in study ING111603, ETV AUC is 15% lower in the presence of LPV/RTV and 25% lower in the presence of DRV/RTV (Table 7), comparable with data in Intelence® PI.

Safety analysis
The combination of GSK1349572 with either ETV and LPV/RTV or ETV and DRV/RTV was generally well-tolerated in healthy adult subjects. No deaths, non-fatal SAEs, pregnancies in female partners of male subjects or withdrawals due to AEs were reported. No severe AEs were reported. Few AEs were reported. The most frequently reported AEs were constipation (2 subjects) and headache (2 subjects). All other AEs were reported by only one subject each. Similar numbers of AEs were reported in each treatment group. All AEs were mild (Grade 1) in intensity. Almost all AEs (with the exception of one report of headache) were considered to be drug-related. The most frequently reported AEs have been observed previously during administration of GSK1349572, ETV, DRV/RTV, or LPV/RTV. No clinically significant trends in clinical laboratory, vital sign, or ECG abnormalities were observed.

Reviewer comments
Increases in triglyceride values from baseline (104.6 mg/dL, respectively) were noted during co-administration of GSK1349572 with DRV/RTV (172.1 and 173.1mg/dL on day 7 and day 14 of period 2, respectively) or LPV/RTV (141.4 and 160.6 mg/dL on day 7 and day 14 of period 2, respectively). Lipid elevations have been described with LPV/RTV and DRV/RTV.

Conclusion
Co-administration of either LPV/RTV or DRV/RTV with ETV and GSK1349572 attenuated the effect of ETV on GSK1349572 exposure. Co-administration with ETV/LPV/RTV had no effect on GSK1349572 steady state plasma $AUC_{(0-\tau)}$ and C_{max}, while Cτ increased by 28%. Thus, GSK1349572 can be co-administered with ETV/LPV/RTV without dose adjustment.

Co-administration with ETV/DRV/RTV decreased plasma GSK1349572 AUC(0-τ), Cmax, and Cτ by 25%, 12%, and 37%, respectively. The effect of ETV/DRV/RTV on GSK1349572 exposure is not considered clinically relevant based on the exposure-response relationship for GSK1349572. Thus, GSK1349572 may be co-administered with ETV without a dosage adjustment if the patient is receiving concomitant LPV/RTV or DRV/RTV.

Individual study review ING112941

Study title A randomized, open-label study to evaluate the effects of omeprazole 40 mg daily and a high fat meal on the pharmacokinetics of GSK1349572 50 mg in healthy adult subjects (ING112941)

Reviewer comments: The study report consists of two parts: a food effect study and a drug interaction study with omeprazole. The first part (the food effect study) is not reviewed here.

Site of investigation Parexel Baltimore early phase clinical unit, Baltimore, MD

Study initiation date 23 Jul 2009

Study completion date 28 Sep 2009

Objective
To compare the plasma GSK1349572 PK following administration of a single dose GSK1349572 50 mg under fasting conditions with and without omeprazole 40 mg q24h.

Study Rationale
Omeprazole is a commonly used proton pump inhibitor indicated for several gastrointestinal disorders. It has a drug interaction potential to impact the absorption of co-administered drugs by increasing gastric pH. Omeprazole is also an inhibitor of CYP2C19 and a weak inducer of CYP1A2. GSK1349572 is not a substrate of either enzyme. Therefore, the interaction observed in this study would be primarily due to changes in pH, thus affecting absorption.

Omeprazole inhibits gastric acid secretion by 50% of maximum at 24 hours with a duration of action of up to 72 hours. This inhibitory effect reaches a plateau after 4 days thus necessitating a repeat dose study.

Study Design
The study was an open-label trial to evaluate the effects of omeprazole on the exposure of GSK1349572. All subjects received GSK1349572 50 mg x 1 dose administered under fasted conditions on Day 1. Forty-eight hour serial PK samples were collected after dosing on Day 1. The first dose of omeprazole was administered immediately after the completion of 48-hr PK collection. Subjects received omeprazole 40 mg q24h for 5 days under fasted conditions. On Day 5, subjects also received GSK1349572 50 mg x 1 dose administered 2 hours after omeprazole (under fasted conditions) and serial PK samples for GSK1349572 were collected.

Drugs used in this study
GSK1349572 50 mg single dose as 25 mg X 2 tablets (batch/lot number: A9105)
Omeprazole (Prilosec®, AstraZeneca): 40 mg X 1 capsule (batch/lot number: D008889)

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) or of childbearing potential and greed to use the acceptable contraception methods
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

Permitted Medications

Acetaminophen, at doses of ≤ 2 grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor.

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Bioanalysis

GSK1349572 was extracted by protein precipitation using acetonitrile containing [$^{2}H_{7}$,^{15}N]- GSK1349572 as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method. Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria. The standard curve and QC data indicated that the plasma assay methods of GSK1349572 in this study were precise and accurate as shown in the table 1.

Table 1. Bioanalysis quality control

Analyte	**Linear range (ng/mL)**	**Between Run Precision (%CV)**	**Between Run Bias (% Deviation)**	**QC samples (ng/mL)**
Dolutegravir	5-5000 ng/mL R^2> 0.996	2.6% to 4.0%	-4.7% to 1.0%	20, 400, 4000 ng/mL

Results

Study population results

A total of 14 subjects were enrolled. Two subjects withdrew early: one subject due to a serious adverse event (manic episode) considered unrelated to study drug and another subject due to failure to present for the second dosing period.

Table 2. Summary of subject disposition and demographic characteristics

Number of Subjects	**N=14**
Demographics	
Age in Years, Mean (SD)	40.6 (10.2)
Sex, n (%)	
Female:	2 (14)
Male:	12 (86)
BMI (kg/m2), Mean (SD)	27.5 (3.1)
Height (cm), Mean (SD)	175.3 (10.8)
Weight (kg), Mean (SD)	84.7 (13.4)
Ethnicity, n (%)	
Hispanic or Latino:	1 (7)
Not Hispanic or Latino:	13 (93)
Race, n (%)	
African American/African Heritage	7 (50)
American Indian or Alaskan Native	1 (7)
Mixed Race	6 (43)

Pharmacokinetic results

Plasma GSK1349572 PK parameters following single dose administration (50 mg) with or without omeprazole are presented in Table 3. The results of the statistical analysis for the effects of omeprazole on the exposure of GSK1349572 are presented in Table 4. Co-administration of omeprazole had no effect on plasma GSK1349572.

Table 3. Summary of Plasma GSK1349572 pharmacokinetic parameters following single dose (50 mg) administration with or without omeprazole

Treatment Regimen	**N**	**C_{max} (µg/mL)**	**T_{max} (h)**	**$AUC_{(0-\infty)}$ (µg.h/mL)**	**C_{24} (µg/mL)**	**$AUC_{(0-t)}$ (µg.h/mL)**	**CL/F (L/hr)**	**Vdz (L)**	**$t_{½}$ (hr)**
572 50 mg fasted	12	1.84 (44)	4.00 (1.00-5.00)	34.7 (57)	0.56 (63)	31.0 (53)	1.44 (57)	29.9 (42)	14.4 (21)
572 50 mg fasted +	12	1.69 (19)	3.00 (1.00-5.03)	34.8 (26)	0.53 (27)	30.0 (22)	1.44 (26)	33.7 (18)	16.3 (20)

Table 4. Summary of statistical analysis of GSK1349572 exposures with or without omeprazole

Plasma GSK1349572 PK Parameter	**GLS Mean Ratio [90% CI]**
	572 50 mg + omeprazole vs 572 50 mg (N=12)
$AUC_{(0-t)}$	0.971 [0.783, 1.203]
$AUC_{(0-\infty)}$	1.00 [0.808, 1.25]
C_{max}	0.915 [0.754, 1.11]
C_{24}	0.954 [0.752, 1.21]

Reviewer comments

No clinically significant changes in GSK1349572 exposure were observed in the presence of omeprazole. This suggests that GSK1349572 exposure is not significantly dependent on gastric pH. The results also support the applicant's explanation that the decreased GSK1349572 exposure caused by cation-containing antacid (Maalox) is not due to changes in pH, but due to chelation.

Conclusion

Omeprazole had no effect on GSK1349572 plasma PK. GSK1349572 can be co-administered with omeprazole without dose adjustment.

Individual study review ING113096

Study title An Open-Label, Single Sequence, Three-Period Drug Interaction Study of GSK1349572 and Tipranavir/Ritonavir in Healthy Adult Subjects (ING113096)

Site of investigation PPD development, Austin, TX

Study initiation date 15 FEB 2010

Study completion date 05 APR 2010

Objective

Primary

- To compare steady-state plasma GSK1349572 pharmacokinetics (PK) following administration of GSK1349572 50 mg once daily alone and with tipranavir (TPV)/ ritonavir (RTV) 500/200 mg twice daily (BID).

Secondary

- To assess the safety and tolerability of repeat dose co-administration of GSK1349572 50 mg once daily alone, TPV/RTV 500/200 mg BID alone, and GSK1349572 50 mg once daily in combination with TPV/RTV 500/200 mg BID.

Study Rationale

TPV is a protease inhibitor and primarily eliminated through metabolism mediated by CYP3A. TPV must be co-administered with ritonavir (RTV) to achieve therapeutic concentrations. The construction of a new antiretroviral regimen with GSK1349572 in raltegravir- resistant subjects will likely require less commonly used agents such as TPV/RTV. In vivo, after a single dose, TPV/RTV moderately inhibits CYP3A and intestinal P-gp. After repeated dosing, TPV/RTV induces CYP3A, UGT and P-gp. RTV is primarily metabolized by CYP3A. When TPV and RTV are combined, there is an approximate 40% decrease in plasma RTV exposure, and thus the RTV dose is higher with TPV (200 mg) than with other protease inhibitors (100 mg).

Due to its induction of drug metabolizing enzymes and P-gp, concomitant use of TPV/RTV can lead to decreased exposure of GSK1349572. GSK1349572 is primarily metabolized by UGT1A1 with CYP3A as a minor route. GSK1349572 does not affect (induce or inhibit) the enzyme activity of cytochrome (CYP)P450 3A as evidenced by unchanged midazolam PK with co-administration with GSK1349572; therefore GSK1349572 should not affect the exposure of TPV and RTV. Thus, this study will evaluate the effect of TPV/RTV on GSK1349572 pharmacokinetics (PK) in healthy subjects, and not vice versa.

Study Design

This was a single-center, open-label, three-period, single sequence study in adult male and female healthy subjects.

Period 1
All subjects received GSK1349572 50 mg once daily (Treatment A) from Day 1 to Day 5. Serial PK samples were collected on Day 5.

Period 2
Day 1 of Period 2 was the day after Day 5 of Period 1. Subjects received TPV/RTV 500/200 mg BID (Treatment B) from Day 1 to Day 7. The first dose of Treatment B was given after the Period 1 Day 5 24 hour PK sample was collected.

Period 3
Day 1 of Period 3 was the day after Day 7 of Period 2. Subjects received GSK1349572 50 mg once daily and TPV/RTV 500/200 mg BID (Treatment C) from Day 1 to Day 5. All doses were administered following a moderate fat meal. Subjects were housed in the unit for the entire duration of the period. Serial PK samples were collected on Day 5 for plasma GSK1349572 concentration. Subjects were discharged after the 24 hour PK sample on the morning of Day 6.

Table 1. Study design

Cohort	Sample Size	Period 1 Days 1-5	Period 2 Days 1-7	Period 3 Days 1-5
1	18	Treatment A	Treatment B	Treatment C

Treatment A: GSK1349572 50 mg once daily x 5 days
Treatment B: TPV/RTV 500/200 mg BID x 7 days
Treatment C: GSK1349572 50 mg once daily and TPV/RTV 500/200 mg BID x 5 days

Drugs used in this study
Table 2. Identity of investigational products

	Investigational Product		
Product name:	GSK1349572	Tipranavir	Ritonavir
Dosage form:	Tablet	Soft gelatin capsule	Soft Gelatin Capsule
Unit dose strength(s)/Dosage level(s):	Tablet strengths = 25 mg Dose level = 50 mg	Soft gelatin capsule strengths = 250 mg Dose level = 500 mg	Soft gelatin capsule strengths = 100 mg Dose level = 200 mg
Route/ Administration/ Duration:	Administered 50 mg orally once daily for 5 days in Period 1 and 3	Administered orally, BID for 7 days in Period 2 and for 5 days in	Administered orally, BID for 7 days in Period 2 and for 5 days in Period 3
Batch/Lot Number:	091213013	91316988	819582E21

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) or child-bearing potential and agreed to use one of the contraception methods
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Use of NSAIDs or aspirin compounds within 21 days of the first dose of study medication.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of regular use of tobacco- or nicotine-containing products within 3 months prior to screening.
- History of sensitivity to any of the study medication.

Permitted Medications

Concomitant medications were considered on a case by case basis by the GSK Medical Monitor. Administration of influenza vaccines (for both seasonal and novel H1N1 influenza) was permitted during the study period at least 4 days prior to and at least 48 hours after a study dose.

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron

supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Pharmacokinetic assessments

PK analyses of plasma GSK1349572 concentration-time data were conducted using noncompartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 5.3 (Pharsight Corporation, Mountain View, CA) according to the standard operating procedures described in Standard Methods for the Non- Compartmental Analysis of Pharmacokinetic Data (GUI-CPK-3001 v02, 17-Dec-08). Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable subjects

Bioanalysis assessments

DTG was extracted by protein precipitation using acetonitrile containing [$^{2}H_{7}$,^{15}N]-DTG as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method. Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria. The standard curve and QC data indicated that the plasma assay methods of DTG in this study were precise and accurate as shown in Table 3.

Table 3. Summary of bioanalysis quality control

Analyte	**Linear range (ng/mL) Upper limit of quantitation- Lower limit of quantitation**	**Between Run Precision (%CV)**	**Between Run Bias (% Deviation)**	**QC samples (ng/mL)**
Dolutegravir	20-20000 ng/mL R2> 0.997	3.1% to 4.7%	4.4% to 7.2%	60, 1600, 16000

Results

Study population results

A total of 18 subjects were enrolled into the study. Five subjects withdrew early: four subjects due to an adverse event and another subject was lost to follow-up. Most subjects were males; the mean age (range) was 29.3 years (19 to 45 years). Most subjects were either of White/Caucasian/European Heritage (44%) or African American/African heritage (39%).

Table 4. Summary of subject disposition and demographic characteristics

Number of Subjects	GSK1349572 50 mg QD	TPV/RTV 500/200 mg BID	GSK1349572 50 mg QD+ TPV/RTV 500/200 mg BID	Overall
Number of subjects planned, N:	18	18	16	18
Number of subjects entered, N:	18	18	16	18
Number of subjects completed as planned, n (%):	18 (100)	16 (89)	13 (81)	13 (72)
Number of subjects withdrawn (any reason), n (%):	0	2 (11)	3 (19)	5 (28)
Number of subjects withdrawn for AE, n (%):	0	2 (11)	2 (13)	4 (22)
Number of subjects lost to follow-up, n (%):	0	0	1 (6)	1 (6)
Demographics				
Age in Years, Mean (SD)	29.3 (8.4)	29.3 (8.4)	28.8 (8.3)	29.3 (8.4)
Sex, n (%)				
Female:	4 (22)	4 (22)	4 (25)	4 (22)
Male:	14 (78)	14 (78)	12 (75)	14 (78)
BMI (kg/m²), Mean (SD)	27.3 (2.9)	27.3 (2.9)	27.7 (2.8)	27.3 (2.9)
Height (cm), Mean (SD)	173.8 (7.3)	173.8 (7.3)	173.8 (7.6)	173.8 (7.3)
Weight (kg), Mean (SD)	82.8 (13.3)	82.8 (13.3)	84.1 (13.2)	82.8 (13.3)
Ethnicity, n (%)				
Hispanic or Latino:	4 (22)	4 (22)	3 (19)	4 (22)
Not Hispanic or Latino:	14 (78)	14 (78)	13 (81)	14 (78)
Race, n (%)				
African American/African Heritage	7 (39)	7 (39)	6 (50)	7 (39)
South East Asian Heritage	2 (11)	2 (11)	2 (13)	2 (11)
Arabic/North African Heritage	1 (6)	1 (6)	0	1 (6)
White/Caucasian/European Heritage	8 (44)	8 (44)	8 (50)	8 (44)

Source Data: Table 9.1, Table 9.2, Table 9.5, and Table 9.6
Treatment:
GSK1349572 50 mg QD= GSK1349572 50 mg once daily x 5 days,
TPV/RTV 500/200 mg BID=TPV/RTV 500/200 mg BID x 7 days,
GSK1349572 50 mg QD+ TPV/RTV 500/200 mg BID=GSK1349572 50 mg once daily + TPV/RTV 500/200 mg BID x 5 days.

Concomitant medication

Subject 961007 received paracetamol (acetaminophen) in Period 1 (GSK1349572 50 mg) for treatment of a headache.

Pharmacokinetic results

Plasma GSK1349572 time-concentration profiles with and without TPV/RTV are shown in Fig 1. Plasma GSK1349572 PK parameters following repeat dose administration with and without TPV/RTV are presented in Table 5. The effect of TPV/RTV on GSK1349572 PK was primarily evaluated by examining the ratio of GLS means of steady-state plasma GSK1349572 PK. The results of statistical analyses are presented in Table 6.

Co-administration with TPV/RTV resulted in 59%, 46%, and 76% decrease in GSK1349572 $AUC_{(0-\tau)}$, C_{max}, and C_{τ}, respectively. This is likely due to the net inductive effect of TPV/RTV on UGT and CYP enzymes, as well as on intestinal P-gp. TPV/RTV is known to decrease concentrations of drugs which are metabolized by CYP3A4 and/or UGT1A1 (e.g., raltegravir, saquinavir, lopinavir, and amprenavir).

Reviewer comments

In the study report, the applicant stated that the decrease in DTG exposure in the presence of TPV/RTV is not likely to be clinically significant because GSK1349572 Cτ from co-administration with TPV/RTV in this study showed a geometric mean of 0.35 µg/mL, which is ~5.5 fold higher than the protein-adjusted-EC90 (0.064 µg/mL). However, The PopPK analysis using Study ING111762 data (SAILING: 50 mg q.d. DTG in subjects with optimized background regimen) indicated that subjects receiving DTG 50 mg once daily in combination with efavirenz (EFV) or TPV/RTV had significantly lower C_0 and lower virologic

response. Therefore, a DTG dose adjustment from 50 mg q.d. to 50 mg b.i.d in treatment-naïve or INI naïve subjects receiving TPV/RTV is recommended. There are insufficient data to make a dosing recommendation when DTG is co-administered with TPV/RTV in INI-experienced patients whose dosing regimen is already 50 mg b.i.d. Caution is warranted and clinical monitoring is recommended when DTG is co-administered with TPV/RTV in INI-experienced patients.

The applicant did not determine the plasma concentrations of TPV/RTV in this study. Therefore, it is unknown whether the exposure of TPV/RTV in this study was clinically relevant or not. Two implications need to be addressed to interpret the study results in the absence of TPV/RTV exposure data.

i) Is potential for DTG metabolic induction by TPV/RTV demonstrated in this study reliable and clinically relevant?
Co-administration of TPV/RTV and DTG in a phase III trial (SAILING: ING111762) resulted in a significant decrease in DTG C_0 (↓70-80%) comparable with the results in this study. Therefore, the study results appear to be reliable and clinically relevant despite the lack of information on TPV/RTV concentrations.
ii) Does DTG alter the pharmacokinetics of TPV/RTV?
The effect is currently unknown. However, it is reasonable to conclude that DTG has a very low potential for significant drug interactions with TPV/RTV as a perpetrator based on in vitro studies as well as previous in vivo drug interaction studies.

Fig 1. Mean plasma GSK1349572 concentration-time plots with and without TPV/RTV

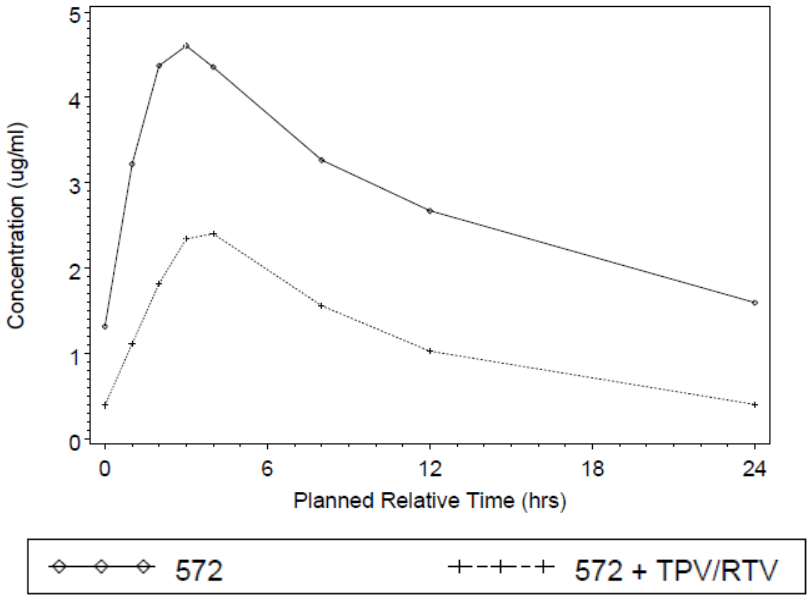


Table 5. Summary of Plasma GSK1349572 pharmacokinetic parameters following repeat dose administration

Treatment	N	Cmax (µg/mL)	Tmax[b] (h)	AUC(0-τ) (µg.h/mL)	Cτ (µg/mL)	C0 (µg/mL)	Cmin (µg/mL)	CL/F (L/hr)	t½ (hr)
GSK1349572 50 mg once daily	14	4.53 (23)	3.00 (2.00-3.00)	64.5 (28)	1.48 (40)	1.19 (49)	1.19 (49)	0.78 (28)	14.8 (22)
GSK1349572 50 mg once daily + TPV/RTV 500/200 mg BID	14	2.42 (23)	4.00 (1.00-4.00)	26.4 (30)	0.35 (54)	0.35 (52)	0.34 (50)	1.89 (30)	7.88 (20)

Source Data: Table 11.4
a. geometric mean (CV%)
b. median (range)

Table 6. Summary of GSK1349572 treatment comparison with and without TPV/RTV

Plasma GSK1349572 PK Parameter	GLS Mean Ratio [90% CI]
	GSK1349572 50 mg once daily + TPV/RTV 500/200 mg BID vs GSK1349572 50 mg once daily N=14
AUC(0-τ)	0.409 [0.379, 0.443]
Cmax	0.535 [0.500, 0.572]
C0	0.298 [0.260, 0.342]
Cτ	0.239 [0.212, 0.270]
Cmin	0.282 [0.247, 0.323]
Cl/F	2.44 [2.26, 2.64]
t½	0.533 [0.500, 0.570]

Source Data: Table 11.6

Safety results

GSK1349572 50 mg co-administered with TPV/RTV 500/200 mg, was well-tolerated during this study in healthy subjects. Hepatotoxicity due to TPV treatment has been well described (b) (4) For this reason, healthy subjects were frequently monitored during the study for changes in liver chemistry tests. Conservative stopping criteria were also employed such that any subject reaching a Grade 2 increase in ALT or AST were discontinued from the trial. Four subjects experienced a Grade 2 ALT (n=4) increase, deemed related to study medication (TPV/RTV). Study medication was discontinued and these subjects were withdrawn from the study. As increases in ALT were expected with TPV/RTV, the study was over-enrolled so that 18 subjects were enrolled to achieve 10 evaluable. In this study, no deaths or SAEs were reported.

Two of 18 subjects (11%) reported at least one AE during GSK134972 dosing and headache was most frequently reported (2 subjects [11%]). A total of 6 of 18 subjects (33%) reported at least one AE during TPV/RTV dosing and the most frequently reported AEs during the TPV/RTV dosing were nausea (4 subjects [22%]), vomiting (2 subjects [11%]), ALT (2 subjects [11%]) and AST (2 subjects [11%]). The most frequently reported AEs during GSK1349572+TPV/RTV and GSK1349572 periods were ALT increased (2 subjects [13%]) and headache (2 subject [11%]), respectively. Grade 2 AEs included ALT increased (n=4), AST increased (n=3), nausea (n=1), and vomiting (n=3), which were considered by the investigator to be related to TPV. No clinically significant trends in vital signs, or ECGs were observed.

Conclusion

Co-administration with TPV/RTV resulted in a 59%, 46%, and 76% decrease in plasma GSK1349572 AUC(0-τ), C_{max}, and Cτ, respectively. A DTG dose adjustment from 50 mg q.d. to 50 mg b.i.d in treatment-naïve or INI naïve subjects receiving TPV/RTV is recommended. Caution is warranted and clinical monitoring is recommended in INI-experienced subjects when DTG is co-administered with TPV/RTV.

Individual study review ING113099

Study title Phase 1, open label, two arm, fixed sequence study to evaluate the effect of rifampin and rifabutin on GSK1349572 pharmacokinetics in healthy male and female volunteers

Site of investigation Johns Hopkins School of Medicine, Baltimore, MD

Study initiation date 13 May 2011

Study completion date 28 November 2011

Objective

Primary

- To compare the steady state pharmacokinetic (PK) of dolutegravir (DTG) 50 mg twice daily when co-administered with rifampin (RIF) 600 mg once daily to those of DTG 50 mg once daily and DTG 50 mg twice daily administered alone.
- To compare the steady state PK of DTG 50 mg once daily when co-administered with rifabutin (RBT) 300mg once daily to those of DTG 50 mg once daily administered alone.

Secondary

- To assess the safety and tolerability of DTG administered alone and in combination with RIF 600 mg once daily.
- To assess the safety and tolerability of DTG administered alone and in combination with RBT 300 mg once daily.
- To describe steady state PK of DTG 50 mg twice daily administered alone.

Study Rationale

The current study was designed to evaluate the PK of DTG when it was given together with RIF (Arm 1) or RBT (Arm 2) with the goal of finding doses of DTG that could be given safely with RIF or RBT and can result in therapeutic DTG concentrations. Because DTG does not induce or inhibit the enzymes that metabolize RIF and RBT, an evaluation of DTG's effects on RIF and RBT pharmacokinetics was unwarranted and was not evaluated in this study.

Because co-administration of RIF was expected to markedly reduce plasma DTG exposure, RIF 600 mg once daily was co-administered with DTG 50 mg twice daily and compared to DTG administered alone as 50 mg once daily and 50 mg twice daily. Because co-administration of RBT was not expected to significantly reduce plasma DTG exposure, RBT was co-administered with DTG 50 mg once daily and compared to DTG 50 mg once daily administered alone.

Demonstrating that co-administration of multiple doses of RIF and DTG is safe and well-tolerated will support the co-treatment of human immunodeficiency virus (HIV) and drug-sensitive tuberculosis (TB) with DTG and a rifampin- or rifabutin-based TB regimen

Study Design

This study was a Phase I, open-label, two-arm, 2- or 3-period, fixed-sequence crossover study to evaluate the effect of the 2 most commonly-used rifamycin antibiotics, RIF and RBT, on the steady-state PK of DTG and the safety and tolerability of DTG. All doses were administered with 240 mL of water in the fasted state.

Arm 1, Period 1

All subjects received DTG 50 mg QD (Treatment A) from Day 1 to Day 7. Serial PK samples were collected over 24 hours on Day 7. Subjects received the first dose in Period 2 after the last PK sample from Period 1 was collected.

Arm 1, Period 2

Day 1 of Period 2 was the day after Day 7 of Period 1. All subjects received DTG 50 mg BID (Treatment B) from Day 1 to Day 7. Serial PK samples were collected over 12 hours on Day 7. Subjects were discharged from the clinical unit after the last PK sample was collected on the evening of Day 7.

Arm 1, Period 3

Day 1 of Period 3 was the day after Day 7 of Period 2. Subjects received DTG 50 mg BID and RIF 600 mg QD (Treatment C) from Day 1 to Day 14. No evening dose of DTG was given on Day 14. Serial PK samples were collected over 12 hours on Day 14.

Arm 2, Period 1

All subjects received DTG 50 mg QD (Treatment A) from Day 1 to Day 7. Serial PK samples were collected over 24 hours on Day 7. Subjects received the first dose in Period 2 after the last PK sample from Period 1 was collected.

Arm 2, Period 2

Day 1 of Period 2 was the day after Day 7 of Period 1. Subjects received DTG 50 mg QD and RBT 300 mg QD (Treatment D) from Day 1 to Day 14. Serial PK samples were collected over 24 hours on Day 14.

Table 1. Study Design: Arm 1 and Arm 2

Arm	Sample Size	Period 1; Days 1 to 7[1]	Period 2; Days 1 to 7[a] (Total Days 8 to 14)	Period 3; Days 1 to 14 (Total Days 15 to 28)
1	12	Treatment A[2]	Treatment B[3]	Treatment C[4]

1. There were no washouts between periods
2. Treatment A = DTG 50 mg QD x 7 days
3. Treatment B = DTG 50 mg BID x 7 days
4. Treatment C = DTG 50 mg BID + RIF 600 mg QD x 14 days. There was no evening dose of DTG on Day 14 of Period 3.

Arm	Sample Size	Period 1; Days 1 to 7[1]	Period 2; Days 1 to 14[1] (Total Days 8 to 21)
2	12	Treatment A[2]	Treatment D[3]

1. There was no washout between periods.
2. Treatment A = DTG 50 mg QD x 7 days
3. Treatment D = DTG 50 mg QD + RBT 300 mg QD x 14 days

Drugs used in this study

Table 2. Identity of investigational products

	Study Treatment		
Product name:	**DTG**	**Rifampin**	**Rifabutin**
Dosage form:	Tablet	Capsule	Capsule
Unit dose strength(s)/ Dosage level(s):	Tablet strengths = 50 mg Dose level = 50 mg	Capsule strength = 300 mg Dose level = 600 mg	Capsule strength = 150 mg Dose level = 300 mg
Route/ Administration/ Duration:	Administered orally for 28 days in Arm 1 or 21 days in Arm 2.	Administered orally for 14 days in Arm 1 only	Administered orally for 14 days in Arm 2 only
Batch Number	101258083	ME100746	N363A

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) or of childbearing potential had agreed to be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%
- Body weight in the range 53 to 100 kg (inclusive).
- Within 28 or fewer days prior to enrollment, a complete blood count (CBC) with differential, comprehensive serum chemistry profile, HIV antibody test, and Hepatitis C antibody test was performed, with the following laboratory values:
    - Alanine aminotransferase (ALT), alkaline phosphatase and bilirubin ≤upper limit of normal (ULN)
    - Hemoglobin ≥12.0 for men, ≥11.0 for women
    - Serum creatinine ≤1.5 mg/dL
    - Platelet count ≥125,000 /cu mm
    - Absolute neutrophil count ≥1250 /cu mm

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.

- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.
- Site investigator suspicion of active TB.

Permitted Medications
Acetaminophen, (≤2 g/day), ibuprofen (≤1200 mg/day), and diphenhydramine (≤25 mg/day) was permitted. Other concomitant medication was considered on a case by case basis by the GSK Medical Monitor.

Prohibited Medications
Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Pharmacokinetic Endpoints and analysis
The pharmacokinetic parameters of DTG were determined from the plasma concentration-time data. The pharmacokinetic parameters were calculated by standard non-compartmental analysis according to current working practice and using WinNonlin Professional Edition V5.2. Actual elapsed time from dosing was used in the derivation of all PK parameters. The following pharmacokinetic parameters were determined from the plasma concentration-time data: C_{τ}, C_{max}, $AUC_{(0-\tau)}$, $AUC_{(0-24)}$, C_{min}, t_{min}, C_0, t_{max}, CL/F, and $t_{1/2}$.

Bioanalysis
Concentrations of DTG were determined in plasma samples using a validated analytical methodology. Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria. The standard curve and

QC data indicated that the plasma assay methods of DTG in this study were precise and accurate as shown in the table 3.

Table 3. Summary of bioanalysis quality control

Analyte	**Linear range (ng/mL) (Lower limit of quantitation- Upper limit of quantitation)**	**Between Run Precision (%CV)**	**Between Run Bias (% Deviation)**	**QC samples (ng/mL)**
Dolutegravir	20-20000 ng/mL $R^2 > 0.989$	6.1% to 7.9%	1.3% to 6.1%	60, 1600, 16000

Results

Study population results

A total of 27 subjects were enrolled in the study. Twenty subjects (74%) completed the study as planned. Two subjects (7%) were withdrawn due to AEs, one subject was withdrawn due to a dosing deviation, 3 subjects withdrew consent, and one subject was withdrawn prior to dosing. The overall mean age was 44.7 years (Table 4). The majority of subjects enrolled were male (19/27, 73%) and African American (18/27, 69%).

Table 4. Summary of demographic characteristics

Demographics	**Arm 1 (N=12)**	**Arm 2 (N=14)**	**Total (N=26)**
Age in Years, Mean (SD)	47.9 (8.62)	41.9 (8.57)	44.7 (8.96)
Sex, n (%)			
Female:	2 (17)	5 (36)	7 (27)
Male:	10 (83)	9 (64)	19 (73)
BMI, kg/m2, Mean (SD)	26.3 (4.01)	28.5 (3.74)	27.5 (3.95)
Height, cm, Mean (SD)	174. (12.0)	172 (9.6)	173 (10.6)
Weight, kg, Mean (SD)	79.6 (12.98)	84.2 (8.81)	82.1 (11.0)
Ethnicity, n (%)			
Hispanic or Latino:	0	2 (14)	2 (8)
Not Hispanic or Latino:	12 (100)	12 (86)	24 (92)
Race, n (%)			
African American/African Heritage	8 (67)	10 (71)	18 (69)
White – White/ Caucasian/ European Heritage	4 (33)	4 (29)	8 (31)

Subject 992010 withdrew prior to Day 1 based on investigator discretion, and no treatment was taken

Protocol deviation and treatment compliance

All subjects were compliant with DTG treatment as planned in the protocol, with the exception of Subject 992102 who took 3 DTG tablets on the morning of Day 11 instead of 1 DTG tablet and 2 RBT tablets. This subject was discontinued from the study since the dosing error was so close to the serial PK day that he would not be evaluable. The reason for discontinuation was recorded as a protocol violation.

Subject 991002 took an extra dose of RIF on the evening of Period 3, Day 9 or 10 by mistake. Since this occurred 4-5 days prior to the serial PK day, the investigator and GSK agreed that this would not affect the PK analysis and the subject was permitted to remain in the study. The extra dose of RIF was reported to the IRB.

Subject 992009 only took 1 tablet of RBT 150 mg instead of 2 tablets (300 mg) on Days 3 and 4 of Period 2 by mistake. Since the serial PK day was on Day 14 of Period 2 the subject was allowed to continue in the study and was deemed evaluable.

Reviewer comments:
Exclusion of subject 992102 and inclusion of subjects 991002 and 992009 are acceptable based on the description of the events. The DTG PK values obtained from 991002 and 992009 are not significantly different from the data of the remaining subjects.

Concomitant medication
Four subjects received a concomitant medication during the study. Subject 991003 used ibuprofen for headache while receiving DTG 50 mg BID + RIF. Subject 991009 used acetaminophen for headache while receiving DTG 50 mg QD. Subject 991005 (Arm 2) used plantago ovata for constipation while receiving DTG 50 mg QD + RBT. The same subject (991005) also used an unspecified analgesic for headache while receiving DTG 50 mg QD and multiple ingredient cold medication (acetaminophen, dextromethorphan, and doxylamine succinate) for help falling asleep while receiving DTG 50 mg QD + RBT**.**

Reviewer comments
The drug interaction potential of plantago ovata (psyllum) and the unspecified analgesic is unknown. The PK results obtained from subject 991005 are comparable with results from other subjects in this study.

Pharmacokinetic results
Plasma DTG PK parameters following repeat dose administration in each arm are presented in Table 5. The effect of RIF or RBT on DTG PK was primarily evaluated by examining the ratio of GLS means of steady-state plasma DTG PK. The results of statistical analysis are presented in Table 6.

Co-administration of DTG 50 mg twice daily with RIF 600 mg once daily significantly reduced plasma DTG concentrations relative to DTG 50 mg twice daily alone. The AUC, C_{max}, and C_0 of DTG were decreased by 55%, 43% and 72%, respectively in the presence of RIF. The exposure of DTG 50 mg twice daily in the presence of RIF was comparable with the exposure of DTG 50 mg once daily without RIF. 50

mg DTG BID in the presence of RIF was resulted in 18 % higher C_{max}, 33% higher in $AUC_{(0-24)}$, and 22% higher in C_τ than DTG 50 mg once daily alone (Table 13).

Co-administration of DTG 50 mg once daily with RBT 300 mg once daily resulted in a 16% increase in DTG C_{max}, no change in $AUC_{(0-\tau)}$, and 30% reduction in C_τ compared to those following administration of DTG 50 mg once daily (Table 6).

Reviewer comments
The PK DTG at 50 mg twice daily given together with standard-dose RIF resulted in concentrations similar to those of DTG 50 mg given once-daily alone. These data suggest that twice-daily DTG 50 mg with RIF is an appropriate regimen for patients who require concomitant treatment of HIV and TB. This DTG 50 mg BID strategy could be used in subjects who are naive to INIs or those currently receiving raltegravir and are virologically suppressed and wish to switch to DTG. Since subjects who are resistant to raltegravir would already be receiving 50 mg BID DTG, caution should be used in adding rifampin to a twice daily DTG regimen in this population.

DTG 50 mg with RBT 300 mg once daily resulted in overall plasma DTG AUC similar to DTG 50 mg once daily alone. It is agreed that 30% reduction in C_τ would not require a dose adjustment.

Table 5. Summary of plasma DTG PK

Treatment	DTG 50 mg QD Arm 1	DTG 50 mg BID	DTG 50 mg BID +RIF	DTG 50 mg QD Arm 2	DTG 50 mg QD + RBT
AUC(0-τ) (μg.h/mL)	32.1 (44)	46.3 (55)	21.3 (31)	39.1 (38)	37.0 (32)
AUC(0-24) (μg.h/mL)	32.1 (44)	92.7 (55)	42.6 (31)	39.1 (38)	37.0 (32)
Cmax (μg/mL)	2.65 (32)	5.55 (49)	3.13 (25)	2.95 (38)	3.41 (23)
C0 (μg/mL)	0.79 (44)	2.70 (245)	0.76 (60)	0.98 (34)	0.69 (50)
Cmin (μg/mL)	0.52 (87)	1.95 (214)	0.60 (53)	0.75 (42)	0.47 (54)
Cτ (μg /mL)	0.55 (91)	2.41 (77)	0.67 (55)	0.76 (43)	0.53 (56)
t1/2 (h)	10.7 (40)	9.54 (48)	4.24 (23)	11.9 (11)	8.64 (22)
CL/F (L/hr)	1.56 (44)	1.08 (55)	2.35 (31)	1.28 (38)	1.35 (32)
Tmax[2] (h)	1.08 (1.0-5.0)	1.02 (1.0-4.0)	2.00 (1.0-5.0)	3.00 (1.0-5.1)	3.00 (1.0-4.0)
Tmin[2] (h)	24.02 (0.0-24.1)	11.98 (0.0-12.1)	12.00 (0.0-12.0)	24.00 (0.0-24.1)	24.00 (0.0-24.1)

Source Data: Table 11.2
1. Geometric mean (CV%)
2. Median (range)

Table 6. Statistical comparison of plasma DTG PK parameters

Comparison	Ratio of GLS Means (90% CI)		
	DTG 50 mg BID + RIF vs DTG 50 mg BID (Arm 1)	DTG 50 mg BID + RIF vs DTG 50 mg QD (Arm 1)	DTG 50 mg QD + RBT vs DTG 50 mg QD (Arm 2)
AUC(0-τ)	0.46 (0.38, 0.55)	ND[1]	0.95 (0.82, 1.10)
AUC(0-24)	ND	1.33 (1.15, 1.53)	0.95 (0.82, 1.10)
Cmax	0.57 (0.49, 0.65)	1.18 (1.03, 1.37)	1.16 (0.98, 1.37)
C0	0.28 (0.16, 0.48)	0.97(0.57, 1.67)	0.70 (0.53, 0.93)
Cmin	0.31 (0.20, 0.46)	1.15 (0.76, 1.72)	0.63 (0.54, 0.74)
Cτ	0.28 (0.23, 0.34)	1.22 (1.01, 1.48)	0.70 (0.57, 0.87)
CL/F	2.2 (1.87, 2.53)	1.51 (1.30, 1.75)	1.06 (0.91, 1.22)
t1/2	0.45 (0.38, 0.46)	0.40 (0.34, 0.46)	0.72 (0.64, 0.82)

Source Data: Tables 11.5 (Arm 1) and 11.6 (Arm 2)
1. ND: not determined

Safety results

No deaths occurred during this study. The combination of RIF and DTG was well tolerated. There were no discontinuations for adverse events (AEs) and no Grade 3 or higher AEs. One subject experienced grade 2 lymphopenia at the end of Period 3 and a self-limited rash after completing study drugs.

More AEs were observed during the combination of DTG and RBT. One subject experienced a serious adverse event (SAE) (drug hypersensitivity reaction) and was withdrawn from the study. The SAE was considered to be a case of suspected RHS. RHS is a well-described syndrome associated with rifamycin antibiotics including RIF and RBT and is more common when these drugs are dosed intermittently or are given at a high dose. However, this case had some unique features: the symptoms occurred after only 1 dose of RBT, the subject was given standard, not high-dose, RBT, and the subject had prominent complaints of confusion and agitation which are atypical for RHS. However, since the subject was fully tolerating DTG alone without any reported symptoms or AEs for 7 days and had a normal physical examination and no complaints on the morning of the day of the first dose of RBT (prior to the dose being given) and the SAE occurred within hours of the first dose of RBT, the time course suggests a temporal relationship with RBT as the suspected cause. Whether the co-administration of DTG with RBT potentiated the hypersensitivity reaction is unknown.

One other subject was withdrawn from the study due to an AE (decreased lymphocyte count). Cytopenias, including neutropenia and lymphopenia, are a known potential toxicity of rifamycin antibiotics, including RIF and RBT. The timing of the AE (Day 10 of combination therapy) further suggests that it was likely attributable to RBT. Thus, the AEs documented in this study are consistent with known adverse reactions to RBT.

The most commonly reported AEs during the study were increased blood glucose, increased lipase, headache, and decreased neutrophil count. Headache was reported in 5 subjects and decreased neutrophil count was reported in 3 subjects. All other AEs occurred in 2 or fewer subjects each. Headache, reported in 5 subjects, has been observed in other studies of DTG in healthy volunteers. Seven subjects experienced Grade 2/3 lipase elevations during treatment with DTG alone and DTG in combination with RBT or RIF. Of the 2 Grade 3 events, one occurred at predose/Day -1, and the other occurred in a subject with Grade 2 elevated lipase values at predose/Day -1. No events of elevated lipase were accompanied by

signs or symptoms of pancreatitis. Increased lipase has been observed previously in DTG phase 1 studies. The incidence of this finding in the DTG alone periods is higher than expected.

No Grade 4 AEs were reported during the study. There were no Grade 4 laboratory abnormalities. The most commonly reported Grade 2 to 4 clinical laboratory values were increased lipase and increased blood glucose. Two subjects had Grade 3 clinical laboratory abnormalities: increased lipase (DTG 50 mg BID) and decreased lymphocyte count (DTG 50 mg QD + RBT). No significant changes in vital signs or electrocardiograms (ECGs) were observed during the study.

Reviewer comments
Please refer to the clinical reviewers' safety analysis for a detailed evaluation on DTG-mediated hypersensitivity or lipase increase.

Conclusion
Co-administration of DTG 50 mg twice daily with RIF 600 mg once daily resulted in decreased DTG plasma exposures: $AUC_{(0-\tau)}$, C_{max}, and C_{τ} decreased by 54%, 43%, and 72% , respectively. DTG 50 mg twice daily with RIF achieved similar DTG exposure as DTG 50 mg once daily given alone. DTG may be given at 50mg twice daily with RIF in HIV-1 infected subjects who are not INI-experienced. This combination should be used with caution in INI-experienced HIV-1 infected subjects. Co-administration of RBT 300 mg once daily resulted in no change in DTG $AUC_{(0-\tau)}$, 16% increase in C_{max}, and 30% reduction in C_{τ}, respectively; no dose adjustment is needed when DTG is co-administered with RBT in any patient population.

One subject experienced a SAE (drug hypersensitivity reaction) on the first day of DTG and RBT co-administration and was withdrawn from the study. One other subject was withdrawn from the study due to an AE (decreased lymphocyte count) which occurred on Day 10 of DTG and RBT co-administration. Both events were assessed by the investigator as likely attributable to RBT.

Individual study review ING114005

Study title A Phase 1, Open Label, Single Sequence, Three Period Study to Evaluate the Single Dose pharmacokinetics of GSK1349572 100 mg versus 50 mg and the Effect of Efavirenz 600 mg Once Daily on the Pharmacokinetics, Safety and Tolerability of GSK1349572 50 mg Once Daily in Healthy Adult Subjects (ING114005)

Reviewer comments: The study report consists of two parts (50 mg DTG PK vs 100 mg DTG PK and a drug interaction study with efavirenz. The first part (50 mg DTG PK vs. 100 mg DTG PK) is not reviewed here.

Site of investigation Buffalo clinical research center, Buffalo, NY

Study initiation date 16 Mar 2010

Study completion date December 2010

Objective

Primary

- To compare steady-state plasma GSK1349572 PK following administration of GSK1349572 50 mg q24h with and without EFV 600 mg q24h.

Secondary

- To assess the safety and tolerability of repeat dose co-administration of GSK1349572 50 mg q24h with and without EFV 600 mg q24h.

- To evaluate the steady-state plasma EFV PK following co-administration of GSK1349572 50 mg q24h with EFV 600 mg q24h.

Study Rationale

Sustiva (efavirenz, EFV) is a non-nucleoside HIV reverse transcriptase inhibitor (NNRTI) that is a frequent component of highly active antiretroviral therapy (HAART). EFV may be used as a component of a background regimen in treatment-experienced subjects in combination with GSK1349572 (DTG). GSK1349572 is primarily metabolized via UGT1A1 and CYP3A4. EFV is an inducer of CYP3A4 and possibly UGTs, thus it is likely that EFV will reduce GSK1349572 exposure when co-administered. In vitro assays have shown that EFV is also an inhibitor of CYP3A4, CYP2C9, CYP2B6, and CYP2C19 with Ki values that are in the same range as therapeutic plasma concentrations.

In vitro studies have shown that EFV is highly plasma protein bound (99%) and primarily metabolized by CYP2B6 with minor contribution by CYP3A4 and CYP1A2 [Ward, 2003; Sustiva Package Insert, 2009]. Renal elimination of unchanged EFV is negligible. GSK1349572 is not an inhibitor (CYP1A2, 2C9, 2C19, 2D6 and 3A4) or inducer (CYP1A2, 2B6, and 3A4) of CYP isozymes, and was not expected to

have impact on the pharmacokinetics (PK) of EFV. However, EFV concentrations were collected during co- administration with GSK1349572 and compared to historical data since GSK1349572 has not been studied *in vitro* for effects on CYP2B6.

Study Design

This is an open-label, single-sequence, three-period, study in healthy adult subjects. A total of approximately 12 subjects were enrolled, in order to obtain approximately 10 evaluable subjects. In the first treatment period, all subjects received a single dose of GSK1349572 100 mg (Treatment A) followed by a washout of ≥6 days. In Period 2 subjects received GSK1349572 50 mg q24h in the morning for 5 days (Treatment B). In Period 3, subjects received GSK1349572 50 mg q24h in the morning plus EFV 600 mg q24h (Treatment C) in the evening for 14 days. There was no washout between Treatment Periods 2 and 3. Day 1 of Period 3 was the day after Day 5 of Period 2.

EFV 600 mg was dosed once daily at bedtime on an empty stomach to minimize the adverse events associated with Cmax. GSK1349572 was dosed once daily in the morning. GSK1349572 may be given with or without food, however, in this trial it was administered in the fasting state.

Table 1 Study Design

Cohort	Sample Size	Period 1; Day 1	Washout; ≥6 days	Period 2; Days 1-5	Period 3; Days 1-14
1	12	Treatment A		Treatment B	Treatment C

a. Treatment A = GSK1349572 100 mg single dose
b. Treatment B = GSK1349572 50 mg q24h in the morning for 5 days
c. Treatment C = GSK1349572 50 mg q24h in the morning plus efavirenz 600 mg q24h in the evening for 14 days

Drugs used in this study

Table 2. Identity of investigational products

	Investigational Product	
Product name:	**GSK1349572**	**Efavirenz**
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	Tablet strengths = 25 mg Dose level = 50 mg	Tablet strength = 600 mg Dose level = 600 mg

Route/ Administration/ Duration:	Administered orally q24h in the morning for 5 days in Period 2 and 14 days in Period 3	Administered orally, q24h in the evening for 14 days in Period 3. The evening dose was not required to be 12 hours after the morning dose of GSK1349572.
Batch numbers:	091213013	9F55511A

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant)
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

Permitted Medications

Concomitant medications were considered on a case by case basis by the GSK Medical Monitor. Administration of influenza vaccines (for both seasonal and novel H1N1 influenza) was permitted during the study period at least 4 days prior to and at least 48 hours after a study dose.

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within

7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up.

Pharmacokinetic analysis

PK analyses of plasma GSK1349572 and efavirenz concentration-time data were conducted using noncompartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 5.3 (Pharsight Corporation, Mountain View, CA). Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable subjects.

Bioanalysis assessments

DTG was extracted by protein precipitation using acetonitrile containing [$^{2}H_{7}$,^{15}N]-DTG as an internal standard. Extracts were analyzed by a validated HPLC/MS/MS analysis method. Human plasma samples were analyzed for efavirenz using a validated analytical method based on protein precipitation, followed by HPLC/MS/MS analysis.

Quality control (QC) samples, prepared at three different analyte concentrations and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria. The standard curve and QC data indicated that the plasma assay methods of DTG and efavirenz in this study were precise and accurate as shown in the table 1.

Table 3. Summary of bioanalysis quality control

Analyte	Linear range (ng/mL) (Lower limit of quantitation-Upper limit of quantitation)	Between Run Precision (%CV)	Between Run Bias (% Deviation)	QC samples (ng/mL)
DTG	20-20000 ng/mL R^2> 0.996	3.0% to 5.3%	4.7% to 6.6%	60, 1600, 16000
Efavirenz	100-20000 ng/mL R^2> 0.995	2.4% to 5.8%	1.5% to 12.4%	300, 4000, 16000

Pharmacogenetic analysis

The pharmacogenetic (PGx) population included nine subjects from ING114005 who gave consent for PGx evaluation, provided a PGx sample and had genotyping results for at least one of the genetic markers tested. Based on higher-than-expected EFV exposures in four patients, a pharmacogenetic evaluation of CYP2B6 poor metabolizer alleles was conducted to assist in the interpretation of the data.

Results

Study population results

A total of 12 subjects were enrolled into the study and all 12 subjects completed. All subjects were males; the mean age (range) was 38.7 years (20 to 65). Most subjects were of White/Caucasian/European Heritage (92%).

Table 4. Summary of subject disposition and demographic characteristics

Number of Subjects	**Overall**
Number of subjects planned, N:	12
Number of subjects entered, N:	12
Number of subjects completed as planned, n (%):	12 (100)
Number of subjects withdrawn (any reason), n	0
Demographics	
Age in Years, Mean (SD)	38.7 (15.2)
Sex, Male n (%)	12 (100)
BMI (kg/m2), Mean (SD)	26.6 (3.2)
Height (cm), Mean (SD)	176.8 (8.1)
Weight (kg), Mean (SD)	83.3 (12.6)
Race, n (%)	
African American/African Heritage	1 (8)
White/Caucasian/European Heritage	11 (92)

Concomitant medication

There was no concomitant medication use reported.

Pharmacokinetic results

Plasma DTG pharmacokinetics

Plasma GSK1349572 time-concentration profiles in each cohort are shown in Fig 1. Plasma GSK1349572 PK parameters following repeat dose administration in each cohort are presented in Table 5. The effect of EFV on GSK1349572 PK was primarily evaluated by examining the ratio of GLS means of steady-state plasma GSK1349572 PK. The results of the treatment comparison are presented in Table 6. A significant decrease in GSK1349572 exposure was observed in the presence of EFV. Co-administration with EFV resulted in a 57%, 39%, and 75% decrease in plasma GSK1349572 $AUC_{(0-\tau)}$, C_{max}, and C_{τ}, respectively.

Reviewer comments

EFV significantly reduced the plasma concentrations of DTG likely due to CYP3A4 and UGT1A1 induction. The PopPK analysis using Study ING111762 data (SAILING: 50 mg q.d. DTG in subjects with optimized background regimen) also indicated that subjects receiving DTG 50 mg once daily in combination with EFV had significantly lower C_0 and lower virologic response. Therefore, a DTG dose adjustment from 50 mg q.d. to 50 mg b.i.d in treatment-naïve or INI naïve subjects receiving EFV is recommended. There are insufficient data to make a dosing recommendation when DTG is co-administered with EFV in INI-experienced patients whose dosing regimen is already 50 mg b.i.d. Caution is warranted and clinical monitoring is recommended.

Fig 1. Mean plasma GSK1349572 concentration-time plots

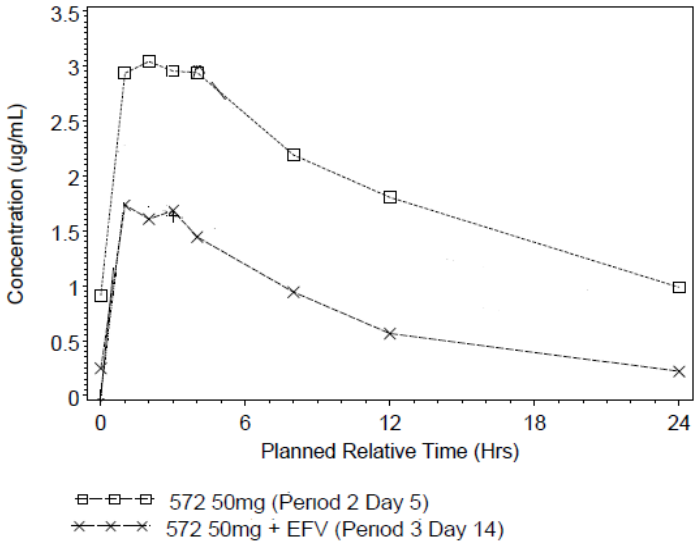


Table 5. Summary of plasma GSK1349572 PK parameters with or without efavirenz and statistical analysis

Plasma GSK1349572 PK Parameter	**GSK1349572 50mg q24h (n=12)**	**GSK1349572 50mg + EFV q24h (n=12)**	**GLS Mean Ratio [90% CI]** GSK1349572 50 mg + EFV vs GSK1349572 50 mg
$AUC_{(0-\tau)}$	42.3 (39)	18.2 (50)	0.431 [0.346, 0.536]
C_{max}	3.08 (30)	1.87 (42)	0.608 [0.506, 0.730]
C_0	0.83 (53)	0.24 (67)	0.287 [0.226, 0.364]
C_τ	0.91 (53)	0.22 (76)	0.245 [0.179, 0.336]
C_{min}	0.82 (52)	0.21 (70)	0.254 [0.196, 0.329]
Cl/F	1.18 (39)	2.75 (50)	2.32 [1.86, 2.89]
$t_{½}$	13.9 (23)	7.82 (21)	0.562 [0.508, 0.622]
T_{max} (hr)	2.00 (1.0-4.0)	1.00 (1.0-4.0)	Not determined

Results are expressed as geometric mean (CV%) except T_{max} [median (Range)]

Plasma efavirenz pharmacokinetics

Plasma efavirenz (EFV) PK parameters by CYP2B6 allele following repeat dose administration of EFV are presented in table 6. Subjects who are CYP2B6 *1/*1 or *1/*6 had similar EFV exposures to those values presented in the Sustiva product label. In the label, the mean $AUC_{(0-\tau)}$ is 184 µM·h (58.1 µg·h/mL), mean C_{max} is 12.9 µM (4.07 µg/mL), and mean Cmin is 5.6 µM (1.77 µg/mL) (Sustiva Package Insert, 2010). Subjects who are CYP2B6*6 homozygous have 2-4 fold higher EFV exposure than CYP2B6 *1/*1 or *1/*6, consistent with other reports. CYP2B6*6 genotype has been well described to result in a

"poor metabolizer" status and is associated with high EFV concentrations. (Tozzi et al, 2010). Thus, it can be assumed that the unexpectedly high EFV concentrations in these 3 subjects observed in Period 3 (when GSK1349572 was co-administered with EFV) of this study was due to subjects who carry the *CYP2B6*6* allele and not an effect of GSK1349572 on EFV pharmacokinetics.

Table 6. Summary of plasma efavirenz PK parameters following repeated dose administration

CYP2B6 Genotype	N	Cmax (µg/mL)	Tmax (h)	AUC(0-τ) (µg.h/mL)	Cτ (µg/mL)	C0 (µg/mL)	Cmin (µg/mL)	CL/F (L/hr)	t½ (hr)
All	12*	6.02 (40)	2.50 (2.0-5.0)	84.2 (62)	2.41 (80)	2.30 (83)	2.21 (86)	7.13 (62)	22.2 (54)
CYP2B6*6 homozygous	3	9.50 (27)	2.00 (2.0-3.0)	174 (26)	5.85 (25)	5.86 (28)	5.76 (27)	3.45 (26)	39.1 (34)
CYP2B6*1/*1 or *1/*6	6	4.52 (17)	2.5 (2.0-5.0)	55.7 (28)	1.45 (40)	1.45 (48)	1.36 (47)	10.8 (28)	15.6 (24)

Results are expressed as geometric mean (CV%) except T_{max} [median (Range)]
* 3 Subjects did not consent to participate in genetic research.

Safety results

GSK1349572 50 mg once daily alone and co- administered with EFV 600 mg, was well-tolerated during this study in healthy subjects. Treatment with EFV is associated with a variety of gastrointestinal, CNS, rash, and psychiatric symptoms. For this reason, healthy subjects were inpatients for this study and frequently monitored for AEs. Two of 12 subjects (17%) reported at least one AE during GSK134972 50 mg once daily dosing. The AEs were not considered to be related to DTG (hematoma, hyperhidrosis). A total of 11 of 12 subjects (92%) reported at least one AE during GSK1349572 + EFV dosing and the most frequently reported AEs were dizziness (11 subjects [92%]) and abnormal dreams (5 subjects [42%]), which were considered by the investigator to be related to EFV. No clinically significant trends in vital signs, or ECGs were observed. AEs were mild (Grade 1) to moderate (Grade 2, n=1) in intensity. No deaths or SAEs were reported.

Conclusion

Co-administration with EFV resulted in a 57%, 39%, and 75% decrease in plasma GSK1349572 $AUC_{(0-\tau)}$, Cmax, and Cτ, respectively. A GSK1349572 dose adjustment from 50 mg q.d. to 50 mg b.i.d in treatment-naïve or INI naïve subjects receiving EFV is recommended. Co-administration with GSK1349572 appears to increase EFV exposure slightly when it is compared to historical data. EFV exposure is dependent on CYP2B6*6 genotype (having CYP2B6*6 homozygous genotype is associated with 2-4 fold higher EFV exposure than CYP2B6 *1/*1 or *1/*6).

Individual study review ING115696

1. Title

An Adaptive, Two part, Two period, Single Sequence, Drug Interaction Study between Dolutegravir 50 mg and Prednisone in Adult Healthy Volunteers

2. Information Regarding the Duration of the Trial

The trial was conducted from September 1, 2011 (initiation date) to October 17, 2011 (completion date).

3. Objectives

The primary objectives of the trial were to evaluate the pharmacokinetics of dolutegravir administered as 50 mg every 24 hours in the presence and absence of prednisone 60 mg or 20 mg (if conducted) every twenty four hours for 5 days (with a 5 day taper).

4. Trial Design

ING115696 was an open label, two period, clinical trial that enrolled healthy male and female subjects 18 to 65 years old. Information on the trial design is displayed in Table 1.

Table 1-ING115696 trial design

Part	Number of subjects	Period 1 (5 days)[1]	Period 2 (10 days)
1	12	DTG 50 mg q24h for 5 days (Treatment A)	DTG 50 mg q24h Days 1-10 + prednisone q24h doses as follows: 60 mg Days 1-5, 50 mg Day 6, 40 mg Day 7, 30 mg Day 8, 20 mg Day 9 and 10 mg Day 10 (Treatment B)
2[2]	12	DTG 50 mg q24h for 5 days (Treatment A)	DTG 50 mg q24h Days 1-10 + prednisone q24h doses as follows: 20 mg Days 1-5, 10 mg Days 6 and 7, 5 mg Days 8-10 (Treatment C)

1. There was no washout between Periods 1 and 2.
2. Subject to the results from Part 1 an additional Part 2 of the study was to be conducted with a lower prednisone dose. Based upon the data obtained from Part 1 of the study, Part 2 of this study was not conducted.

5. Excluded Medications, Restrictions or Exceptions

With the exception of acetaminophen (2 grams or less per day), ibuprofen 1200 mg pr less per day, diphenydramine (25 mg or less per day) or medications that were permitted on a case by case basis,

prescription and nonprescription medications, including herbal products, antacids, vitamins and iron supplements, were not permitted within 7 days (14 days if the medication was a potential inducer) or five half lives (whichever was longer) of first dosing for the trial or during the trial.

6. Dosage and Administration

The medications that were administered to the subjects in the trial are displayed in Table 1. For both dolutegravir and prednisone, medication was administered after a moderate fat meal. The trial report states that doses were administered within 30 minutes after the start of the moderate fat meal.

7. Rationale for Doses Used in the Trial

The dosage regimens of prednisone up to 60 mg once daily are within the recommended initial dosing range of prednisone in the U.S prescribing information. The proposed dolutegravir dosage regimens are 50 mg once daily or 50 mg twice daily, depending on the treatment population. The results of the trial are applicable to both dosage regimens because based on the dolutegravir population pharmacokinetic model, linearity is observed for 10 mg once daily to 50 mg once daily and for 50 mg once daily compared to 50 mg twice daily.

8. Drugs Used in the Trial

Information regarding the medications that were administered in the trial is displayed in Table 2.

Table 2-Information on the medications administered in the ING115696 trial

	Study Treatment	
Product name:	**Dolutegravir Tablets**	**Prednisone Tablets**
Formulation description:	dolutegravir, D-mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate (b) (4) (b) (4)	Prednisone plus excipients as per manufacturer's product information
Dosage form:	Tablet	Tablet
Unit dose strength(s)/ Dosage level(s):	50 mg = 1 tablet Dose = 50 mg	5 mg and 20 mg
Route/ Administration/ Duration:	Administered orally q24h for 5 days in Period 1 and 10 days in Period 2.	Administered orally in Period 2.
Dosing instructions:	Administered with 240 mL of tap water within 30 min after a moderate fat breakfast	Administered with 240 mL of tap water within 30 min after a moderate fat breakfast
Physical description:	9 mm white, film-coated, round tablets	Tablet
Manufacturer/ source of procurement:	GSK	Prednisone 5 mg: (b) (4) Prednisone 20 mg: (b) (4)
Method for individualizing dosage:	50 mg = one tablet	Investigator judgment was allowed regarding combination of strength/number of tablets for prednisone dosing. 5 mg and 20 mg tablets were used
Batch number	101258084	Prednisone 5 mg: Lot No. C0350611A Prednisone 20 mg: Lot No. 69196B

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Dolutegravir (GSK1349572) blood samples were obtained on day 5 (Period 1) and day 5 and 10 (Period 2) at predose and up to 24 hours postdose. Trough dolutegravir blood samples were obtained on days 8 and 9 (Period 2).

Bioanalysis

The method and bioanalysis of dolutegravir is acceptable. Dolutegravir plasma samples were analyzed using a validated LC/MS/MS method in K_3EDTA anticoagulated plasma (b) (4) Based on the information provided by the applicant, the blood samples for analysis of dolutegravir appears to have been collected in tubes containing K_3EDTA as an anticoagulant.

For the ING115696 plasma samples that were analyzed for dolutegravir, the lower limit of quantification for dolutegravir was 20 ng/mL and the upper limit of quantification was 20000 ng/mL. There were no precision or accuracy issues identified for dolutegravir based on the bioanalytical report. For the ING115696 trial, precision and accuracy were evaluated using plasma dolutegravir QC samples at four concentration levels: 60 ng/mL, 1600 ng/mL, 16000 ng/mL, and 20000 ng/mL (20000 ng/mL was the upper limit of quantification). The corresponding dolutegravir inter-run accuracy values were -0.3% for 60 ng/mL, -0.5% for 1600 ng/mL, -1.8% for 16000 ng/mL, and -8.7% for 20000 ng/mL. The

dolutegravir inter-run precision values were 6% for 60 ng/mL, 3.5% for 1600 ng/mL, 1.9% for 16000 ng/mL, and 13.9% for 20000 ng/mL.

For the ING115696 trial, based on the information submitted by the applicant, dolutegravir plasma samples were stored for less than 2 months at -20°C or -70°C at the trial site and stored between -20°C and -70°C and analyzed within one month of receipt at the (b) (4) bioanalytical laboratory. The submitted dolutegravir long term stability data of 480 days (16 months) at -30°C and 265 days at -20°C that was generated by GSK and 373 days at -20°C and 93 days at -70°C in K_3EDTA anticoagulated plasma that was generated (b) (4) appears to cover the duration of dolutegravir long term stability data necessary for the ING115696 trial.

Of the 36 samples selected for incurred sample reanalysis for cobicistat, all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of samples that were reanalyzed represents 5% to 10% of the total number of samples that were initially analyzed.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for dolutegravir. For the noncompartmental analysis, dolutegravir plasma pharmacokinetic parameters were calculated, including C_{max} and $AUC_{(0\text{-}24h)}$.

Statistical Analysis

ANOVA was used for the statistical analyses. The trial report did not include specific "no effect" boundaries for the 90% confidence intervals for selected dolutegravir pharmacokinetic parameters.

10. Results

10.1 Subject Demographics and Disposition

Table 3-ING115696 subject demographics

Age in Years, Mean (SD)	28.5 (4.81)
Sex, n (%)	
Female:	7 (58)
Male:	5 (42)
BMI, kg/m^2, Mean (SD)	24.43 (2.616)
Height, cm, Mean (SD)	173.38 (8.133)
Weight, kg, Mean (SD)	73.74 (11.478)
Ethnicity, n (%)	
Hispanic or Latino:	2 (17)
Not Hispanic or Latino:	10 (83)
Race, n (%)	
African American/African Heritage	5 (42)
American Indian or Alaskan Native	1 (8)
Asian – East Asian Heritage	1 (8)
White – White/Caucasian/European Heritage	5 (42)

Table 4-ING115696 subject disposition

Number of Subjects	All Subjects
Number of subjects planned, N:	12
Number of subjects dosed, N:	12
Number of subjects included in Safety Population, n (%):	12 (100)
Number of subjects included in PK Concentration Population, n (%):	12 (100)
Number of subjects included in PK Summary Population, n (%):	12 (100)
Number of subjects completed as planned, n (%):	12 (100)
Number of subjects withdrawn (any reason), n (%):	0

10.2 Concomitant Medications

One subject (subject 661001) received ibuprofen and two subjects (subjects 661008 and 661009) received acetaminophen during the trial. Subject 661008 also received hydrocodone and penicillin during the trial. The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

10.3 Pharmacokinetic and Statistical Analysis

Dolutegravir

Table 5-Dolutegravir pharmacokinetic parameters derived using noncompartmental analysis with dolutegravir 50 mg once daily with or without prednisone 60 mg once daily

Treatment	Treatment A (Day 5)	Treatment B (Day 5)	Treatment B (Day 10)
AUC(0-τ) (μg.h/mL)	58.6 (32)	65.9 (37)	65.0 (37)
Cmax (μg/mL)	4.27 (25)	4.47 (31)	4.54 (29)
Cmin (μg/mL)	1.33 (40)	1.43 (43)	1.42 (46)
C0 (μg/mL)	1.61 (43)	1.55 (47)	1.57 (53)
Cτ (μg/mL)	1.32 (40)	1.59 (47)	1.53 (50)
t1/2 (h)	13.8 (21)	15.2 (17)	14.6 (24)
CL/F (L/hr)	0.85 (32)	0.76 (38)	0.77 (37)
tmax (hr)	4.0 (1.0-4.0)	3.5 (1.0-4.0)	3.5 (1.0-4.0)

1. Geometric mean (CV%), except for tmax where median (range) is reported.
Treatment A = DTG 50 mg q24h for 5 days
Treatment B = DTG 50 mg q24h Days 1-10 + prednisone q24h doses as follows: 60 mg Days 1-5, 50 mg Day 6, 40 mg Day 7, 30 mg Day 8, 20 mg Day 9 and 10 mg Day 10

Table 6-Statistical analyses for dolutegravir

Statistical Comparison of Plasma DTG Pharmacokinetic Parameters		
Comparison	Ratio of GLS Means (90% CI)	
	Treatment B (Day 5) vs Treatment A	Treatment B (Day 10) vs Treatment A
AUC(0-τ)	1.13 (1.04, 1.21)	1.11 (1.03, 1.20)
Cmax	1.05 (0.977, 1.12)	1.06 (0.991, 1.14)
Cmin	1.08 (0.992, 1.17)	1.07 (0.984, 1.16)
C0	0.966 (0.859, 1.09)	1.02 (0.928, 1.13)
Cτ	1.21 (1.10, 1.32)	1.17 (1.06, 1.28)
CL/F	0.888 (0.824, 0.957)	0.900 (0.835, 0.970)
t1/2	1.11 (1.00, 1.22)	1.07 (0.966, 1.18)

GLS = Geometric least squares
Treatment A = DTG 50 mg q24h for 5 days
Treatment B = DTG 50 mg q24h Days 1-10 + prednisone q24h doses as follows: 60 mg Days 1-5, 50 mg Day 6, 40 mg Day 7, 30 mg Day 8, 20 mg Day 9 and 10 mg Day 10

10.4 Safety Analysis

The adverse events reported in the trial are displayed in Table 7. All adverse events were considered mild.

Table 7-Adverse events reported in the ING115696 trial

Preferred Term	DTG 50 mg q24h N=12	DTG 50 mg q24h + Prednisone 60 mg N=12
Subjects with Any AE, n (%)	5 (42)	2 (17)
Headache	2 (17)	1 (8)
Migraine	1 (8)	0
Musculoskeletal chest pain	0	1 (8)
Abnormal dreams	1 (8)	0
Dysmenorrhea	1 (8)	0

11. Discussion and Conclusions

Dolutegravir is metabolized by UGT1A1 and CYP3A. According to the FDA's February 2012 draft drug interaction guidance document, prednisone is a weak CY3A inducer. Based on the results from the ING115696 trial, the following conclusions can be made:

- With 50 mg once daily dosing, on Day 5, the dolutegravir $AUC_{(0\text{-}24h)}$, C_{max}, and C_{τ} were increased by 13%, 5%, and 21%, respectively, when coadministered with prednisone 60 mg once daily for 5 days (with a 5 day taper).
- With 50 mg once daily dosing, on Day 10, the dolutegravir $AUC_{(0\text{-}24h)}$, C_{max}, and C_{τ} were increased by 11%, 6%, and 17%, respectively, when coadministered with prednisone 60 mg once daily for 5 days (with a 5 day taper).

With concomitant use of dolutegravir and prednisone (60 mg once daily) for 5 days followed by 5 days of prednisone tapering, the magnitude of change in dolutegravir exposure ($AUC_{(0\text{-}24h)}$, C_{max}, and C_{τ}) is not anticipated to result in any clinically relevant safety issues. However, the drug interaction data for dolutegravir from the ING115696 trial does not provide information regarding the effects of prednisone on dolutegravir exposure when prednisone is administered for longer durations at clinically relevant doses.

Individual study review ING115697

Study title A Phase I, open label, randomized, two cohort, two period, one- way study to evaluate the effect of Boceprevir and Telaprevir on Dolutegravir pharmacokinetics in healthy adult subjects (ING115697).

Site of investigation PPD development, Austin, TX

Study initiation and completion date Not available

Objective

Primary

- To compare plasma dolutegravir (DTG) pharmacokinetics (PK) following administration of DTG 50 mg with and without boceprevir (BCV) 800 mg every 8 hours (q8h) or telaprevir (TVR) 750 mg q8h.

Secondary

- To compare plasma TVR and BCV PK to historical data following administration of DTG 50 mg with BCV 800 mg q8h or TVR 750 mg q8h for 10 days.
- To assess the safety and tolerability of DTG 50 mg with and without BCV 800 mg q8h or TVR 750 mg q8h

Study Rationale

Dolutegravir is primarily metabolized via UGT1A1 with a minor component of CYP3A4. DTG is a substrate for P-glycoprotein (P-gp) but because of its high permeability, significant alterations in absorption due to P-gp inhibition/induction would not be expected. BCV and TVR have been shown to be strong CYP3A4/5 inhibitors and as such, may inhibit DTG metabolism. However, a significant increase in plasma DTG exposure is not expected with either of these hepatitis C virus (HCV) protease inhibitors. *In vitro* studies suggest that TVR has a low potential to induce CYPs; however, co-administration of TVR decreased the concentrations of a variety of CYP substrates, including escitalopram, ethinyl estradiol/norethindrone, methadone, zolpidem, darunavir/ritonavir, and fosamprenavir/ritonavir, suggesting that telaprevir may induce drug metabolizing enzymes and/or significantly affect intestinal or hepatic transporters.

Following oral dosing, BCV and TVR are primarily cleared via hepatic metabolism. BCV is primarily metabolized by aldoketoreductase (AKR1 and AKR3), with minor CYP3A4 contribution. TVR is primarily metabolized via CYP3A4. Both BCV and TVR are P-gp substrates. DTG is not expected to alter plasma TVR exposure because DTG does not induce or inhibit CYP3A or P-gp. DTG's inhibition potential for AKR is not known, but a significant drug interaction is unlikely because co-administration of potent AKR inhibitors (diflunisal and ibuprofen) did not alter plasma BCV exposure to a clinically significant extent. Given the low potential for DTG to alter plasma BCV and TVR exposures, a complete two-way evaluation of DTG's effects on TVR and BCV PKs was not warranted.

Study Design

This was a single-center, randomized, open-label, two-cohort, two-period, one way study in healthy adult subjects. A total of approximately 32 subjects were planned to be enrolled, in order to obtain 24 evaluable subjects (12 per cohort). In the first treatment period, all subjects received DTG 50 mg q24h for 5 days (Treatment A). In Period 2, subjects received DTG 50 mg q24h with either BCV 800 mg q8h (Treatment B) for 10 days or TVR 750 mg q8h (Treatment C) for 10 days. There was no washout between treatment periods. Day 1 of Period 2 was the day after Day 5 of Period 1. All doses were administered with a moderate fat meal or snack.

Table 1. Study design

Cohort	Sample Size	Period 1; Days 1-5	Period 2; Days 1-10
1	16	Treatment A[1]	Treatment B[2]
2	16	Treatment A[1]	Treatment C[3]

1. Treatment A = DTG 50 mg q24h x 5 days
2. Treatment B = BCV 800 mg q8h + DTG 50 mg q24h x 10 days
3. Treatment C = TVR 750 mg q8h + DTG 50 mg q24h x 10 days

Drugs used in this study

Table 2. Identity of investigational products

	Study Treatment		
Product name:	DTG	BCV	TVR
Dosage form:	Tablet	Capsule	Tablet
Unit dose strength(s)/Dosage level(s):	50 mg = 1 tablet Dose = 50 mg	200 mg = 1 capsule Dose = 800 mg	375 mg = 1 tablet Dose = 750 mg
Route/ Administration/ Duration:	Administered by mouth q24h for 5 days in Period 1 and 10 days in Period 2.	Administered by mouth q8h for 10 days in Period 2 (Cohort 1).	Administered by mouth q8h for 10 days in Period 2 (Cohort 2).
Batch numbers:	101258084	1HCEO21	243568

Key Inclusion Criteria

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) or child-bearing potential and had agreed to be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1%
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).
- Single QTcB ≤ 450 msec. A single repeat was allowed for eligibility determination.

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive Hep B surface antigen, positive HepC antibody, or positive HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- History of sensitivity to any of the study medication.

Permitted Medications

Acetaminophen, at doses of ≤2grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor.

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study.

Pharmacokinetic assessments

The pharmacokinetic parameters of DTG and TVR were determined from the plasma concentration-time data. The pharmacokinetic parameters were calculated by standard non-compartmental analysis using WinNonlin Professional Edition V5.3. Actual elapsed time from dosing was used.

Bioanalysis assessments

Bioanalysis of the plasma samples for DTG was performed (b) (4) with a validated analytical method based on protein precipitation followed by high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) analysis. Bioanalysis of the plasma samples for (S)-TVR, the active enantiomer of TVR, was performed (b) (4) with validated analytical methods based on liquid extraction followed by HPLC-MS/MS analysis.

Quality control (QC) samples were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and

no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria. The standard curve and QC data indicated that the plasma assay methods of DTG and TVR in this study were precise and accurate as shown in the table 3.

Table 3. Summary of bioanalysis quality control

Analyte	**Linear range**	**Between Run Precision (%CV)**	**Between Run Bias (% Deviation)**	**QC samples**
Dolutegravir	20-20000 ng/mL R^2> 0.998	3.6% to 7.5%	2.3% to 10.1%	60, 1600, 16000 ng/mL
Telaprevir	0.1-20 µg/mL R^2> 0.998	2.3% to 8.6%	-8.8% to -2.2%	0.25, 0.5 1.5 4 16 (µg/mL)

Reviewer Comments
Bioanalytical data for BCV were unavailable at the time of this report due to technical difficulties with the assay and a significant delay in the procurement of analytical standards. The sponsor state that this report will be amended when the BCV data become available.

Results
Study population results
A total of 32 subjects were enrolled in the study. Twenty-eight subjects completed the study as planned, and 4 subjects were withdrawn due to AEs. The overall mean age was 42.5 years (standard deviation [SD]=16.56). The majority of subjects were male (59%) and White (72%).

Table 4. Summary of subject disposition and demographic characteristics

Number of Subjects	DTG (N=32)	DTG + BCV (N=16)	DTG + TVR (N=16)	Overall (N=32)
Number of subjects planned, N:	32	16	16	32
Number of subjects withdrawn for AE, n (%):	0	3 (19)	1 (6)	4 (13)
Age in Years, Mean (SD)	42.5 (16.56)	45.2 (17.71)	39.9 (15.44)	42.5 (16.56)
Sex, n (%)				
Female:	13 (41)	6 (38)	7 (44)	13 (41)
Male:	19 (59)	10 (63)	9 (56)	19 (59)
BMI, kg/m2, Mean (SD)	25.8 (3.31)	25.7 (3.25)	25.8 (3.47)	25.8 (3.31)
Height, cm, Mean (SD)	169 (9.99)	169 (10.3)	169 (9.98)	169 (9.99)
Weight, kg, Mean (SD)	73.8 (13.3)	73.9 (13.4)	73.7 (13.7)	73.8 (13.3)
Ethnicity, n (%)				

Hispanic or Latino:	11 (34)	9 (56)	2 (13)	11 (34)
Not Hispanic or Latino:	21 (66)	7 (44)	14 (88)	21 (66)
Race, n (%)				
African American/African Heritage	4 (13)	1 (6)	3 (19)	4 (13)
American Indian or Alaskan Native	3 (9)	2 (13)	1 (6)	3 (9)
White – Arabic/North African Heritage	1 (3)	1 (6)	0	1 (3)
White – White/Caucasian/European Heritage	23 (72)	12 (75)	11 (69)	23 (72)
Mixed race	1 (3)	0	1 (6)	1 (3)

Concomitant medication

Five subjects received concomitant medications during the study. The most commonly-used concomitant medications were acetaminophen (3 subjects) and hydrocortisone cream (2 subjects).

Pharmacokinetic results

Plasma DTG PK

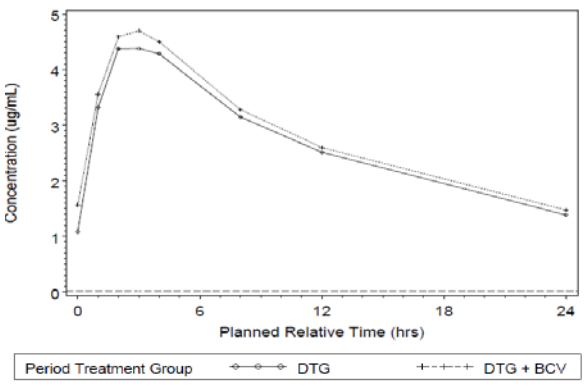
Plasma DTG time-concentration profiles in each cohort are shown in Fig 1. Plasma DTG PK parameters following repeat dose administration in each cohort are presented in Table 5. The effect of BCV or TVR on DTG PK was primarily evaluated by examining the ratio of GLS means of steady-state plasma DTG PK parameters. The results of the treatment comparison are presented in Table 6.

Neither BCV nor TVR had a clinically significant effect on plasma DTG exposure. Co-administration of BCV had no effect on plasma DTG $AUC_{(0-\tau)}$ or C_{max}, and slightly increased DTG $C\tau$ by 8%. Co-administration of TVR increased DTG plasma exposures compared to administration of DTG alone. $AUC_{(0-\tau)}$, C_{max}, and $C\tau$ of DTG are increased by 25%, 19%, and 37%, respectively in the presence of TVR.

Reviewer comments.

The modest increase in DTG exposure in the presence of telaprevir is thought to be due to the inhibition of CYP3A4 and P-gp by TVR. The increased DTG exposure by TVR is not considered clinically significant as adverse events of DTG are generally mild and not exposure-dependent. BCV appears to have no significant effect on DTG PK.

Fig 1. Mean plasma DTG concentration-time plots with/without BCV (left) or TVR (right)



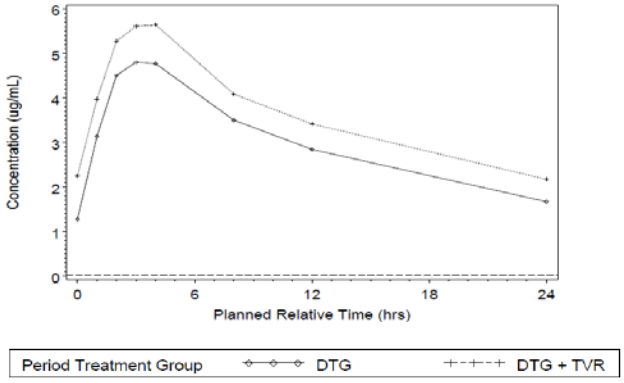


Table 5. Summary of plasma DTG PK parameters

Cohort/ Treatment	**1/DTG (n=16)**	**1/DTG + BCV (n=13)**	**2/DTG (n=16)**	**2/DTG + TVR (n=15)**
$AUC_{(0-\tau)}$ (µg.h/mL)	61.5 (27)	65.3 (22)	68.9 (25)	84.2 (21)
C_{max} (µg/mL)	4.62 (21)	4.82 (17)	4.99 (23)	5.81 (15)
C_{τ} (µg/mL)	1.31 (38)	1.40 (36)	1.59 (35)	2.09 (28)
C_{min} (µg/mL)	1.00 (45)	1.36 (37)	1.18 (41)	2.03 (30)
$t_{1/2}$ (h)	13.2 (18)	13.8 (19)	14.5 (19)	16.7 (18)
t_{max} (h)	2.50 (1.0, 4.0)	3.00 (1.0, 4.0)	3.00 (1.0, 4.0)	4.00 (1.1, 4.0)

Data are expressed as geometric mean (CV%) except Tmax [median, (range)]

Table 6. Statistical comparison of plasma DTG PK parameters

Plasma DTG PK Parameter	**Ratio of GLS Means (90% CI)**	
	DTG + BCV vs DTG	**DTG + TVR vs DTG**
AUC(0-τ)	1.07 (0.948, 1.20)	1.25 (1.20, 1.31)
C_{max}	1.05 (0.960, 1.15)	1.19 (1.11, 1.26)
C_{τ}	1.08 (0.911, 1.28)	1.37 (1.29, 1.45)
C_{min}	1.36 (1.15, 1.62)	1.76 (1.60, 1.92)
$t_{1/2}$	1.05 (0.959, 1.14)	1.18 (1.08, 1.28)

Plasma telaprevir PK

Plasma TVR PK parameters in the presence and historical data from INCIVEK® prescribing information are presented in Table 7. Plasma TVR PK data for the DTG-TVR combination treatment were similar to historical TVR data, indicating no significant effect of DTG on TVR exposure. This is expected because DTG does not inhibit or induce CYP3A4, the primary metabolic pathway for TVR.

Table 7. Summary of plasma TVR PK parameters in the presence of DTG and historical data

Cohort/ Treatment	**DTG + TVR (n=15)**	**TVR**

$AUC_{(0-\tau)}$ (µg.h/mL)	19.5	22.3
C_{max} (µg/mL)	3.25	3.51
C_{min} (µg/mL)	1.76	2.03

1. Data presented as arithmetic mean
2. Source Data: Incivek Product Information, 2012

Safety analysis

No deaths or SAEs were reported during the study. Four subjects were withdrawn from the study due to the following AEs: increased ALT, cellulitis, increased serum creatinine, and dizziness.

- Subject 671007 (DTG + BCV, Period 2) experienced Grade 3 elevated ALT on Period 2, Day 5 which was reported as an AE and the subject was withdrawn from the study. It was considered to be related to study drugs and resolved within 32 days.
- Subject 671011 (DTG + BCV, Period 2) experienced Grade 1 cellulitis on Period 2 Day 6. The AE was not considered by the investigator to be related to the study drug.
- Subject 671013 (DTG + BCV, Period 2) experienced Grade 1 increased serum creatinine (1.68 mg/dL, Grade 1) on Period 2 Day 6. The AE was considered by the investigator to be related to the study drug and was considered to be resolved after 14 days. This subject had normal creatinine values at screening and Day -1 (1.19 mg/dL), and Grade 1 increased serum creatinine on Period 1, Day 5 (1.45 mg/dL) after receiving DTG and at Period 2, Day 5 (1.51 mg/dL) after receiving DTG + BCV. The follow-up serum creatinine value (1.12 mg/dL) for this subject was within the normal range.
- Subject 672010 (DTG, Period 1) experienced mild dizziness on Period 1 Day 4. The AE was not considered by the investigator to be related to the study drug and was considered to be resolved after 5 days.

The most common AEs were headache, anorectal discomfort, dysgeusia, and maculopapular rash. The most frequently reported drug-related AEs were headache, dysgeusia, and maculopapular rash. These AEs are consistent those reported in the TVR and/or BCV label. All AEs were mild in intensity, except for 1 subject with an AE of Grade 3 elevated ALT describe above. One subject became pregnant during the study. The outcome of the pregnancy was unknown at the time of reporting.

No consistent, treatment related or clinically significant changes in mean or median hematology and clinical chemistry were observed in the study. There was a small overall trend toward increased mean serum creatinine values at Period 2, Day 5 for both treatment with DTG + BCV (1.15 mg/dL) and DTG + TVR (1.20 mg/dL) compared to screening (0.812 mg/dL) and follow-up (0.811 mg/dL). Four subjects (672006, 672008, 672009, and 672014) had Grade 1 increased serum creatinine values on Period 2, Day 5 after treatment with DTG + TVR and 1 subject (671013) had a Grade 1 increased serum creatinine value on Period 1, Day 5 after receiving DTG and on Period 2, Day 5 after receiving DTG + BCV. Serum creatinine for all 5 of these subjects was within the normal range at screening and at follow-up.

Table 8. Summary of serum creatinine (mg/dL) values over time

Treatment	Visit	N	Mean (SD)	Median (Range)
	Screening	32	0.812 (0.1657)	0.820 (0.54, 1.19)
DTG	Period 1 Day -1	32	0.870 (0.1563)	0.885 (0.57, 1.18)
	Period 1 Day 5	32	1.014 (0.1809)	1.045 (0.68, 1.45)
DTG + BCV	Period 2 Day 5	16	1.145 (0.1834)	1.115 (0.83, 1.51)
	Period 2 Day 10	14	0.999 (0.1690)	0.955 (0.75, 1.24)
DTG + TVR	Period 2 Day 5	16	1.202 (0.1776)	1.230 (0.99, 1.50)
	Period 2 Day 10	15	1.085 (0.1641)	1.110 (0.79, 1.32)
	Follow-up	32	0.811 (0.1625)	0.830 (0.54, 1.12)

Reviewer comments
The increase in serum creatinine is primarily due to the inhibition of OCT2 by DTG. The magnitude of increase in serum creatinine in this study appears to be slightly higher than historical data from other DTG clinical studies (most increase 10-20 mg/dL from the baseline. Whether it is inter-study variability or a PD based drug interaction (the mechanism is yet to be identified) is unknown.

Conclusion
Co-administration of DTG with TVR resulted in increased DTG plasma concentrations compared to those following administration of DTG alone: $AUC_{(0-\tau)}$, C_{max}, C_{τ}, increased by 25%, 19%, and 37%. These changes are not considered to be clinically significant. Plasma TVR PK data for the DTG-TVR combination treatment were similar to historical TVR data, indicating no effect of DTG on TVR exposure. BCV appears to have no significant effect on DTG PK.

Individual study review ING115698

Study title A Phase 1, Open-Label, 2-Period Drug Interaction Study to Assess Steady State Plasma Methadone Enantiomer Pharmacokinetics Following Co-Administration of Methadone QD with Dolutegravir (GSK1349572) 50 mg twice daily in Opiate-Dependent, HIV Seronegative Adult Subjects.

Site of investigation INC research, Toronto, Ontario, Canada

Study initiation date 02 December 2011

Study completion date 30 December 2011

Objective

Primary

- To compare steady-state plasma total and R-methadone pharmacokinetics (PK) following administration of an individualized methadone dose with and without dolutegravir (DTG) 50 mg twice daily (BID) in subjects on stable methadone therapy.

Secondary

- To assess the safety and tolerability of methadone when given in combination with DTG 50 mg BID.
- To evaluate the steady state plasma DTG PK following administration of DTG 50 mg BID with methadone.
- To compare steady-state plasma S-methadone PK with and without DTG 50 mg BID.
- To compare steady-state unbound plasma concentrations of R- methadone with and without DTG 50 mg q12 h, if significant difference found in total R-methadone.
- To evaluate the changes in subject's treatment effect with methadone alone and when given in combination with DTG 50 mg BID.
- To measure the physiological opioid effects using pupillometry with methadone alone and when given in combination with DTG 50 mg BID.

Study Rationale

Dolutegravir (DTG; GSK1349572) is primarily metabolized via UGT1A1 with a minor component of cytochrome (CYP)3A4. In vitro DTG was not a direct inhibitor of the transporters organic anion-transporting polypeptide (OATP)1B1, OATP1B3, multidrug resistance-associated protein 2 (MRP2), or of the enzymes UGT2B7, CYP1A2, CYP2A6, or CYP2C8, and did not induce CYP1A2, CYP2B6, or CYP3A4. In vitro DTG was a weak inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), UGT1A1, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 but has low potential as a perpetrator of drug interactions.

Medications used to treat human immunodeficiency virus type 1 (HIV-1) are commonly used concurrently with methadone, where methadone is useful for the treatment of opioid dependence. This

study evaluated the drug-drug interaction potential between DTG and methadone. Methadone is primarily metabolized by CYP2B6 and CYP2C19 while CYP3A4 also plays a role. Methadone is administered as a chiral mixture of R and S isomers in which the opioid effect is primarily mediated through R-methadone. Given the low potential for DTG to cause drug interactions by inhibition or induction of these enzymes, it is unlikely that methadone concentrations will be altered by concomitant use with DTG. To investigate potential large pharmacokinetic variability in R-methadone or in unbound R-methadone, pharmacogenetic (PGx) samples and AAG measurements are included.

Since methadone demonstrates no inhibition or induction effects on UGTs or CYPs, this study only directly evaluated the effect of DTG on methadone. This study characterized the pharmacokinetics of methadone with and without DTG, and provided information on the need to alter methadone dosing when co-administered with DTG.

Study Design

Eligible subjects were identified at the methadone clinic(s) and potential subjects were referred to the Contract Research Organization (CRO; INC Research, Canada). In Period 1, (starting Day 1 to Day 3), approximately 12 subjects received their stable individual doses of methadone once daily. In Period 2, (starting Day 1 – one day after Day 3 in Period 1), subjects received DTG 50 mg BID for 5 days while continuing on their stable methadone therapy. There was no washout period between Period 1 and Period 2. The same subjects from Period 1 continued onto Period 2, if all eligibility was met for a period of 5 days. Subjects were discharged on Day 5 after the last PK sampling had been obtained. There were no food restrictions on non-PK days; however, an 8-hour fast was required on serial PK days (i.e., Period 1, Day 3 and Period 2, Day 5). On PK days, meals were allowed after the 4 hours post-dose PK sampling. Water was limited up to 250 mL within 1 hour before and after dosing.

Table 1. Study design

Number of subjects	Period 1 (Days 1-3)	Period 2 (Days 1-5)
12	Treatment A Stable individual once daily methadone dose.	Treatment B Co-administration of DTG 50 mg BID x 5 days + stable individual methadone dose from Period 1.

Drugs used in this study

Methadone: various, individualized

DTG 50 mg as one tablet b.i.d for 5 days in period 2 (batch number: 111287797/R513667)

Key Inclusion Criteria

- Subject was enrolled in a methadone maintenance program for at least 12 weeks prior to Period 1, Day 1, and was expected to continue in the program though the duration of this study. Subject was receiving a methadone QD regimen that had remained unchanged for 14 days prior to Pre-Screening Visit and the dose was ≤200 mg daily.

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. Subjects with positive serology for hepatitis B or C may have been entered at the discretion of the investigator, if there was no evidence of active disease or hepatic impairment and it was not a new diagnosis.
- Male or female between 18 and 65 years of age. A female subject was eligible to participate if she was of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) or of child-bearing potential and agreed to use one of the contraception methods
- Body weight ≥50kg for men and ≥ 45kg for women and body mass index (BMI) within the range 18.5-33.0kg/m^2 (inclusive).
- AST, ALT, alkaline phosphatase and bilirubin ≤1.5 x the upper limit of normal (ULN).

Key Exclusion Criteria

- Subjects with a pre-existing condition interfering with normal gastrointestinal anatomy or motility, hepatic and/or renal function, that could have interfered with the absorption, metabolism, and/or excretion of the study drugs.
- A positive test for HIV antibody.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication would not interfere with the study procedures or compromise subject safety.
- Consumption of red wine, seville oranges, grapefruit, pummelos, exotic citrus fruits or fruit juices containing such products from 7 days prior to the first dose of study medication.
- The subject had participated in a clinical trial and had received an investigational product within 30 days or donated blood in excess of 500 mL within a 56-day period.
- A positive pre-study drug/alcohol screen.
- History of regular alcohol consumption.
- Heavy smokers who were unable to abstain from at least 8 hours as required by the protocol
- History of sensitivity to any of the study medication.

Permitted Medications

Acetaminophen at doses of ≤2 grams/day was permitted. Other concomitant medication may have been considered on a case by case basis by the GSK Medical Monitor. Subjects were permitted to use the following concomitant mediations during the study if necessary and after consultation with the GSK Medical Monitor and was not limited to: amitriptyline, testosterone, citalopram, escitalopram, clonazepam, oxybutynin, venlafaxine, paroxetine, fluoxetine, mirtazapine, quetiapine, trazodone, sertraline, olanzapine, and bupropion.

Prohibited Medications

Subjects must have abstained from taking prescription or non-prescription drugs within

7 days (or 14 days if the drug was a potential enzyme inducer) or 5 half-lives (whichever was longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication would not interfere with the study. Use of antacids, vitamins, and iron supplements were strictly prohibited within 7 days prior to the first dose of study medication and for the duration of the trial, including follow-up. Acetaminophen use was prohibited in patients with acute viral hepatitis.

Pharmacokinetic analysis

The pharmacokinetic parameters of DTG and methadone were determined from the plasma concentration-time data. The pharmacokinetic parameters were calculated by standard non-compartmental analysis according to current working practice and using WinNonlin Professional Edition V5.3. Actual elapsed time from dosing was used in the derivation of all PK parameters. The following pharmacokinetic parameters were determined from the plasma concentration-time data for DTG, R-methadone, S-methadone and total methadone: AUC(0-τ), C_{max}, Cτ, C0, Cmin, and CL/F. The ratio of R/S-methadone AUC (0-τ) was also calculated.

Bioanalysis

Bioanalysis of plasma samples for DTG was performed (b) (4)
Human plasma samples were analyzed for DTG using validated analytical methods based on protein precipitation, followed by high-performance liquid chromatography tandem mass spectrometric (HPLC/MS/MS) analysis.

Plasma methadone enantiomer concentrations were determined (b) (4) Human plasma samples containing K3EDTA and methadone were analyzed for (R)-methadone and (S)-methadone concentrations using a validated method. The analytes and the internal standard, (±)-methadone-d9 , were isolated through supported liquid extraction using an ISOLUTE 200-mg SLE + plate and eluted with dichloromethane. Sample extraction steps were controlled and automated using a Tomtec Quadra 96 Model 320. The eluate was evaporated under a nitrogen stream at approximately 45 °C. The remaining residue was reconstituted with 1000 µL of 12% isopropyl alcohol in 10 mM ammonium acetate. The final extract was analyzed via HPLC with MS/MS detection.

Quality control (QC) samples, prepared and stored with study samples, were analyzed with each batch of samples against separately prepared calibration standards. For the analysis to be acceptable, no more than one-third of the total QC results and no more than one-half of the results from each concentration level were to deviate from the nominal concentration by more than 15%. The applicable analytical runs met all predefined run acceptance criteria. The standard curve and QC data indicated that the plasma assay methods of DTG and methadone in this study were precise and accurate as shown in the table 2.

Table 2. Summary of bioanalysis quality control

Analyte	**Linear range (ng/mL) Lower limit of quantitation-**	**Between Run Precision (%CV)**	**Between Run Bias (%**	**QC samples (ng/mL)**

	Upper limit of quantitation		Deviation)	
DTG	20-20000 ng/mL R2>0.994	1.5% to 3.3%	-2.2% to 3.9%	60, 1600, 16000
R-methadone	5-1000 ng/mL R2>0.998	1.8% to 3.3%	-3.3% to -0.9%	10, 25, 70, 200, 750
S-methadone	5-1000 ng/mL R2> 0.998	2.0% to 4.9%	-4.6% to 1.9%	10, 25, 70, 200, 750

Pharmacodynamic assessments

Both the Opioid Symptom Questionnaire and Pupillometry were used as PD measures in this study. The questionnaire consisted of 32 visual analogue scale (VAS) items made up of the Agonist subscale and Withdrawal subscale. The summations were reported as the overall opiate agonist score and withdrawal score. The odd-numbered items in the questionnaire were the 16 opioid withdrawal items, and the even-numbered items were the 16 agonist symptoms. The questionnaire was administered on the PK days at baseline and 2 hours post-dose time points in both Period 1 and 2. Subjects were asked to respond to the following question: "Indicate how much you feel the following symptom right now." The 16 opiate agonist symptoms checked were, nodding, nervous, dry mouth, good mood, turning of stomach, high, skin itchy, sleepy, relaxed, drunken, coasting, soapbox (talkative), pleasant sick, rush, drive (energy), and friendly. The 16 withdrawal symptoms checked were yawning, sweating, restless, hot or cold feelings, watery eyes, abdominal cramps, runny nose, backache, sick to stomach, skin clammy/damp, irritable, muscle cramps, tense and jittery, painful joints, chills or gooseflesh, and heavy/sluggish feeling. These assessments were administered as a 0-100 VAS anchored by "Not at all" (0) and "Extremely" (100).

Pupillometry is a measure of pupil diameter. Generally, opiates cause constriction of the pupils associated with a decrease in the light reflexes [Pickworth, 1998]. In this study, pupillometry was included at various time points on the PK days, as specified in Attachment 2, Time and Event Table. NeurOptics Pupillometer (Irvine, CA, USA) was used to measure pupil diameter. Data from a series of frames were used in the calculation, and the final display showed the weighted average and standard deviation of the pupil size. Measurements were collected under mesopic lighting conditions. For each subject, every effort was made to use the same eye for all assessments throughout the study.

Results

Study population results

A total of 12 subjects were enrolled and 11 subjects completed the study. One subject was withdrawn from the study due to an AE (moderate hematuria). The overall mean age was 34.5 years (standard deviation [SD]=6.11). A similar number of males and females were enrolled (6 male, 5 female). All 11 subjects were White.

Table 3. Summary of demographic characteristics

Number of Subjects	Methadone (N=11)	DTG 50 mg BID + Methadone (N=11)
Age in Years, Mean (SD)	34.5 (6.11)	34.5 (6.11)

Sex, n (%)		
Female:	5 (45)	5 (45)
Male:	6 (55)	6 (55)
BMI, kg/m2, Mean (SD)	27.74 (4.02)	27.74 (4.02)
Height, cm, Mean (SD)	171.64 (9.45)	171.64 (9.45)
Weight, kg, Mean (SD)	81.55 (13.21)	81.55 (13.21)
Ethnicity, n (%)		
Hispanic or Latino:	0	0
Not Hispanic or Latino:	11 (100)	11 (100)
Race, n (%)		
White – White/Caucasian/European Heritage	11 (100)	11 (100)

Concomitant medication

Four subjects received medication for treatment of AEs. Subjects 981001, 981006, and 981010 received paracetamol for headache. Subject 981011 received lorazepam for panic attack. This subject (981011) was withdrawn from the study due to an AE (moderate hematuria)

Pharmacokinetic results

Plasma (R)-and (S)-methadone pharmacokinetics

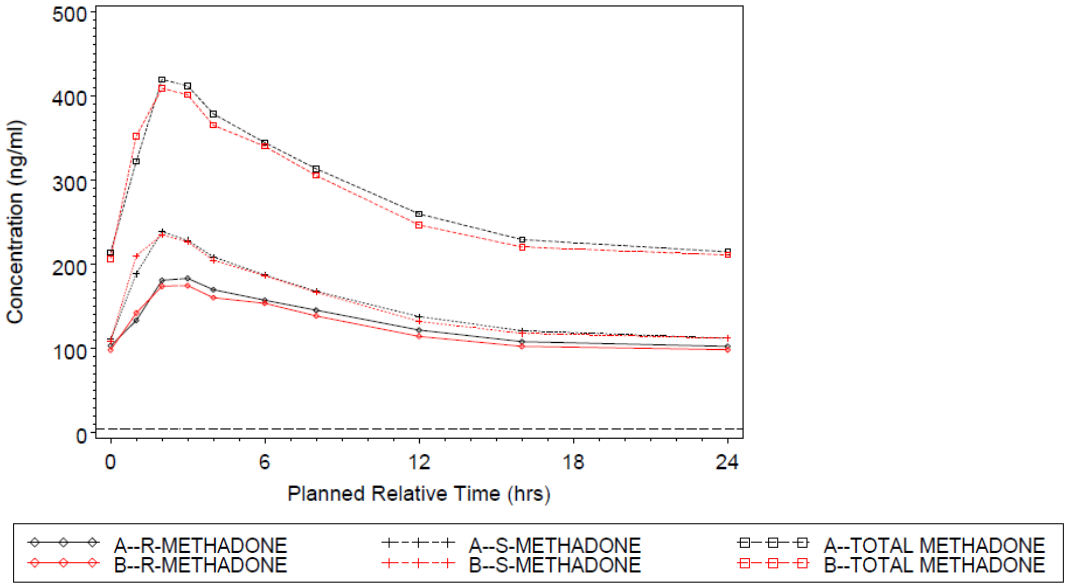
Plasma (R)-and (S)-methadone time-concentration profiles are shown in Fig 1. Plasma (R)-and (S)-methadone PK parameters are presented in Table 4. The effect of DTG on Plasma (R)-and (S)-methadone PK parameters was primarily evaluated by examining the ratio of GLS means of steady-state plasma (R) and (S) methadone PK parameters. The results of the treatment comparison are presented in Table 5.

The results of the statistical comparisons showed that plasma exposures of total, R-, and S-methadone were not affected by co-administration of 50 mg DTG BID. Additionally, the AUC ratios of R- and S-methadone showed no statistically significant differences between the two treatments suggested absence of stereo-specific effect of DTG.

Reviewer comments

These results of this study were expected since in vitro studies have demonstrated that DTG does not affect the metabolic pathways that are responsible for methadone metabolism. According to the applicant, the results from the current study were consistent with previous studies which showed slightly lower R-methadone exposures compared to those with S-methadone following methadone administration. The AUC difference between these two isomers was approximately 10%.

Fig 1. Mean plasma R-, S-, and total methadone concentration (ng/mL)-time plots



Treatment A: Stable individual once daily methadone dose
Treatment B: DTG 50 mg q12h X 5 days + stable individual once daily methadone dose

Table 4. Summary of plasma methadone PK paramters

	Total Methadone		R-Methadone		S-Methadone	
Treatment	A	B	A	B	A	B
AUC(0-τ) (ng.h/mL)	5320 (83.2)	5226 (80.6)	2505 (77.9)	2388 (77.7)	2789 (90.3)	2814 (85.4)
Cmax (ng/mL)	337 (86.5)	337 (80.1)	150 (81.4)	145 (78.5)	188 (91.4)	195 (82.3)
C0 (ng/mL)	168 (83.7)	163 (81.7)	83.6 (77.0)	78.5 (77.5)	83.3 (93.9)	83.0 (89.5)
Cmin (ng/mL)	164 (85.7)	161 (83.1)	80.9 (78.3)	76.8 (79.2)	81.3 (96.3)	82.3 (90.5)
Cτ (ng/mL)	166 (86.9)	164 (84.9)	81.9 (79.9)	77.9 (80.6)	83.0 (97.3)	84.7 (92.7)
CL/F (L/hr)	9.41 (23.3)	9.58 (29.3)	20.0 (20.1)	21.0 (24.3)	17.9 (29.8)	17.8 (36.2)
R/S Methadone AUC Ratio	NA	NA	0.90 (21.1)	0.85 (20.6)	NA	NA

Source Data: Table 11.5
1. Geometric mean (CV%)
Treatment A: Stable individual once daily methadone dose
Treatment B: DTG 50 mg BID x 5 days + stable individual methadone dose

Table 5. Statistical comparison of plasma methadone PK parameters

Plasma Methadone PK Parameter	Ratio of GLS Means (90% CI)		
	Total Methadone B vs A	R-Methadone B vs A	S-Methadone B vs A
AUC(0-τ)	0.98 (0.91, 1.06)	0.95 (0.89, 1.02)	1.01 (0.93, 1.09)
Cmax	1.00 (0.94, 1.06)	0.97 (0.91, 1.03)	1.03 (0.97, 1.10)
C0	0.97 (0.89, 1.05)	0.94 (0.87, 1.01)	1.00 (0.90, 1.10)
Cτ	0.99 (0.91, 1.07)	0.95 (0.89, 1.02)	1.02 (0.93, 1.12)
Cmin	0.98 (0.91, 1.06)	0.95 (0.89, 1.01)	1.01 (0.92, 1.12)
CL/F	1.02 (0.95, 1.09)	1.05 (0.98, 1.12)	0.99 (0.92, 1.07)
R/S Methadone AUC Ratio	NA	0.94 (0.92, 0.97)	NA

Source Data: Table 11.8
Treatment A: Stable individual once daily methadone dose
Treatment B: DTG 50 mg BID x 5 days + stable individual methadone dose

Plasma DTG pharmacokinetics

DTG PK parameters observed in this study are comparable to other Phase I PK studies with multiple dose administration of DTG 50 mg b.i.d . There was no obvious or significant effect of methadone on DTG PK.

Table 6. Summary of plasma DTG PK parameters [Geometric mean (CV%)]

Treatment	DTG 50 mg BID + Methadone
$AUC_{(0-\tau)}$ (µg h/mL)	44.3 (37)
C_{max} (µg/mL)	4.88 (35)
C_0 (µg/mL)	3.45 (28)
C_{min} (µg/mL)	2.63 (41)
C_τ (µg/mL)	2.63 (41)
CL/F (L/hr)	1.13 (37)

Pharmacodynamics

Pharmacodynamic (PD) measurements were incorporated into this study in the event of differences in pharmacokinetics of methadone with and without DTG. Two PD measurements were employed in this study; the Opioid Symptom Questionnaire and pupillometry.

Results of overall opiate agonist score and withdrawal score by treatment and time are summarized in Table 7. In general, no significant difference was noted between subjects receiving methadone only and subjects receiving DTG 50 mg BID + methadone for overall opiate agonist and withdrawal scores. Changes in minimum pupillometry diameter (mm) from baseline and PAOE (pupillometry area over the effect curve) are presented in Table 8 and Table 9, respectively. In general, results were similar between subjects receiving methadone and subjects receiving DTG 50 mg BID + methadone for minimum pupillometry diameter and PAOE.

Overall, co-administration of repeat doses of 50 mg DTG had no effect on the PD changes seen after methadone administration. No statistically significant difference was noted between subjects receiving methadone only and subjects receiving DTG 50 mg BID + methadone for overall opiate agonist and withdrawal scores. The combination of no differences in either PK or PD measurements in opiate dependent subjects receiving methadone demonstrate the lack of interaction between DTG and methadone.

Table 7. Summary of overall opiate agonist and withdrawal scores by treatment and time

Overall VAS Parameter	Treatment	Visit	n	Mean (SD)	Median (Min, Max)
Opiate agonist Absolute Values	Methadone	Period 1 Day 3 Hour 0	11	315.818 (153.5206)	302.000 (41.00, 545.00)
		Period 1 Day 3 Hour 2	11	305.364 (119.4406)	325.000 (128.00, 504.00)
	DTG 50 mg BID + methadone	Period 2 Day 5 Hour 0	11	257.273 (132.6243)	253.000 (0.00, 471.00)
		Period 2 Day 5 Hour 2	11	276.727 (126.1373)	244.000 (24.00, 476.00)
Opiate agonist Change from Baseline	Methadone	Period 1 Day 3 Hour 2	11	-10.455 (119.6214)	26.000 (-347.00, 87.00)
	DTG 50 mg BID + methadone	Period 2 Day 5 Hour 2	11	19.455 (79.1067)	24.000 (-158.00, 149.00)
Withdrawal Absolute Values	Methadone	Period 1 Day 3 Hour 0	11	88.545 (91.9134)	62.000 (0.00, 274.00)
		Period 1 Day 3 Hour 2	11	27.727 (28.8100)	21.000 (1.00, 100.00)
	DTG 50 mg BID + methadone	Period 2 Day 5 Hour 0	11	80.000 (104.5266)	46.000 (0.00, 356.00)
		Period 2 Day 5 Hour 2	11	43.727 (50.3510)	21.000 (0.00, 154.00)
Withdrawal Change from Baseline	Methadone	Period 1 Day 3 Hour 2	11	-60.818 (89.8074)	-31.000 (-255.00, 20.00)
	DTG 50 mg BID + methadone	Period 2 Day 5 Hour 2	11	-36.273 (117.9365)	-1.000 (-352.00, 71.00)

Treatment:
A: Stable individual once-daily methadone dose
B: GSK1349572 50 mg BID x 5 days + stable individual once daily methadone dose

Table 8. Summary of change from baseline in minimum pupillometry diameter by treatment and time

Treatment	Visit	n	Mean (SD)	Median (Min, Max)
Methadone	Period 1 Day 3 Hour 1	11	-0.609 (0.8191)	-0.800 (-1.90, 1.20)
	Hour 3	11	-1.309 (0.9864)	-1.500 (-2.70, 0.90)
	Hour 6	11	-0.964 (0.8869)	-0.900 (-2.00, 0.90)
	Hour 12	11	-0.555 (0.7712)	-0.600 (-2.10, 0.70)
	Hour 24	11	-0.255 (0.5939)	-0.200 (-1.20, 0.70)
DTG 50 mg BID + methadone	Period 2 Day 5 Hour 1	11	-0.791 (0.6156)	-0.400 (-2.00, -0.20)
	Hour 3	11	-1.300 (0.8037)	-1.400 (-2.70, -0.10)
	Hour 6	11	-1.118 (0.6911)	-1.200 (-2.60, 0.10)
	Hour 12	11	-0.727 (0.5293)	-0.900 (-1.30, 0.20)
	Hour 24	11	-0.345 (0.3830)	-0.300 (-1.10, 0.10)

Table 9. Summary of PAOE (pupillometry area over the effect curve) by treatment

Analyte	Treatment	n	Mean (SD)	Median (Min, Max)
PAOE (0-1 h)(mm*hr)	Methadone	11	0.528 (0.7278)	0.693 (-1.08, 1.69)
	DTG 50 mg BID + methadone	11	0.664 (0.4462)	0.370 (0.20, 1.41)
PAOE (0-3 h)(mm*hr)	Methadone	11	2.446 (2.4695)	2.493 (-3.18, 6.29)
	DTG 50 mg BID + methadone	11	2.678 (1.5380)	2.187 (0.84, 5.71)
PAOE (0-6 h)(mm*hr)	Methadone	11	5.855 (5.0875)	6.296 (-5.88, 13.19)
	DTG 50 mg BID + methadone	11	6.308 (3.5078)	6.071 (1.89, 13.66)
PAOE (0-12 h)(mm*hr)	Methadone	11	10.410 (8.9800)	12.666 (-10.68, 20.69)
	DTG 50 mg BID + methadone	11	11.844 (6.3261)	12.813 (2.03, 23.86)
PAOE (0-24 h)(mm*hr)	Methadone	11	15.098 (15.0456)	16.814 (-17.05, 33.30)
	DTG 50 mg BID + methadone	11	18.279 (9.7716)	20.613 (3.23, 35.26)

Safety results

Dolutegravir 50 mg BID + methadone was well tolerated in this study. No deaths or serious AEs occurred. One subject was withdrawn from the study due to an AE of moderate hematuria, which was considered by the investigator to be related to the study drug. Headache was reported in 4 subjects receiving methadone and 3 receiving DTG 50 mg BID + methadone. Constipation was reported in 1 subject receiving methadone and 2 subjects receiving DTG 50 mg BID + methadone. All other AEs were reported in 2 or fewer subjects overall. All AEs were mild or moderate in intensity. No clinically significant changes in clinical laboratory values, vital signs, or ECGs were observed during the study

Conclusion

Co-administration of methadone with repeat dose of 50 mg DTG had no effect on total, R-, and S-methadone pharmacokinetics. Co-administration of methadone with repeat dose of 50 mg DTG had no effect on methadone induced PD markers. No dose adjustment in methadone is required when given in combination with DTG. Dolutegravir 50 mg BID + methadone was well tolerated in this study.

Individual study review LAI116181

1. Title

A Phase 1, Open-Label, Crossover Study to Evaluate the Pharmacokinetics and Safety of GSK1265744 and Rilpivirine and Dolutegravir and Rilpivirine in Healthy Adult Subjects

2. Information Regarding the Duration of the Trial

The trial was conducted from November 7, 2011 (initiation date) to February 20, 2012 (completion date).

3. Objectives

The primary objectives of the trial were to evaluate the pharmacokinetics of dolutegravir administered as 50 mg every 24 hours in the presence and absence of rilpivirine 25 mg every 24 hours, and to evaluate the pharmacokinetics of rilpivirine 25 mg administered every 24 hours in the presence and absence of dolutegravir 50 mg every 24 hours or GSK1265744 30 mg every 24 hours. An additional primary objective was to evaluate the pharmacokinetics of GSK1265744 administered as 30 mg every 24 hours in the presence and absence of rilpivirine 25 mg every 24 hours.

4. Trial Design

LAI116181 was an open label, three period, two cohort clinical trial that enrolled healthy male and female subjects 18 to 55 years old. Information on the trial design is displayed in Table 1.

Table 1-LAI116181 trial design

Cohort	Sample size	Period 1 Days 1-5	Washout ≥7 Days	Period 2 Days 1-11	Period 3 Days 1-5
1	16	Treatment A		Treatment B	Treatment C

Treatment A = DTG 50 mg q24h x 5 days
Treatment B = RPV 25 mg q24h x 11 days
Treatment C = RPV 25 mg q24h + DTG 50 mg q24h x 5 days

Cohort	Sample size	Period 1 Days 1-12	Washout ≥14 Days	Period 2 Days 1-12	Period 3 Days 1 -12
2	12	Treatment D		Treatment B	Treatment E

Treatment D = GSK1265744 30 mg q24h X 12 days
Treatment B = RPV 25 mg q24h X 12 days
Treatment E = RPV 25 mg q24h + GSK1265744 30 mg q24h X 12 days

5. Excluded Medications, Restrictions or Exceptions

With the exception of acetaminophen (2 grams or less per day) or medications that were permitted on a case by case basis, prescription and nonprescription medications, including herbal products, antacids, vitamins and iron supplements, were not permitted within 7 days (14 days if the medication was a potential inducer) or five half lives (whichever was longer) of first dosing for the trial or during the trial.

6. Dosage and Administration

The medications that were administered to the subjects in the trial are displayed in Table 1. For all periods, medication was administered after a moderate fat meal according to the time and events table in the trial report. The trial report states that doses were administered within 30 minutes after the start of the moderate fat meal.

7. Rationale for Doses Used in the Trial

The dosage regimen of rilpivirine 25 mg once daily is consistent with the recommended dosage regimens in the rilpivirine U.S. prescribing information. The proposed dolutegravir dosage regimens are 50 mg once daily or 50 mg twice daily, depending on the treatment population. The results of the trial are applicable to both dosage regimens because based on the dolutegravir population pharmacokinetic model, linearity is observed for 10 mg once daily to 50 mg once daily and for 50 mg once daily compared to 50 mg twice daily. GSK1265744 is an investigational HIV medication and the appropriate dosing regimen is currently being evaluated in trials.

8. Drugs Used in the Trial

Information regarding the medications that were administered in the trial is displayed in Table 2.

Table 2-Information on the medications administered in the LAI116181 trial

Compound	GSK1265744	Dolutegravir	Edurant
Formulation:	(b) (4)	dolutegravir, D-mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, sodium stearyl fumarate, (b) (4) (b) (4)	Rilpivirine hydrochloride, croscarmellose sodium, magnesium stearate, lactose monohydrate, povidone K30, polysorbate 20 and silicified microcrystalline cellulose. The tablet coating contains hypromellose 2910 6 mPa.s, lactose monohydrate, Polyethylene glycol (PEG) 3000, titanium dioxide and triacetin
Dosage form:	Tablet	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	Tablet strength: 5 mg Dose level: 30 mg (six tablets)	Tablet strength: 50 mg Dose level = 50 mg (one tablet)	Tablet strength: 25 mg Dose level = 25 mg (one tablet)
Route of Administration	Administered orally, once daily	Administered orally, once daily	Administered orally, once daily
Batch Number	091215458	111287797	AJL2K01P1

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

In cohort 1, dolutegravir (GSK1349572) blood samples were obtained on day 5 (Period 1 and Period 3) at predose and up to 24 hours postdose and rilpivirine blood samples were obtained on day 11 (Period 2) and day 5 (Period 3) at predose and up to 24 hours postdose. In cohort 2, for Period 1 and Period 3, GSK1265744 blood samples were obtained on day 12 at predose and up to 24 hours postdose with predose samples on days 10 and 11 and rilpivirine blood samples were obtained on day 12 (Period 2 and Period 3) at predose and up to 24 hours postdose.

Bioanalysis

(Reviewer note: The GSK1265744 bioanalytical information was not reviewed and will not be discussed).

The method and bioanalysis of dolutegravir and rilpivirine are acceptable. Dolutegravir plasma samples were analyzed using a validated LC/MS/MS method in K_3EDTA anticoagulated plasma (b) (4) Rilpivirine plasma samples were analyzed using a validated LC/MS/MS method in heparin anticoagulated plasma (b) (4) Based on the information in the trial report, the blood samples for analysis of dolutegravir were collected in tubes containing K_3EDTA as an anticoagulant and blood samples for analysis of rilpivirine were collected in tubes containing lithium heparin as an anticoagulant.

For the LAI116181 plasma samples that were analyzed for dolutegravir, the lower limit of quantification for dolutegravir was 20 ng/mL and the upper limit of quantification was 20000 ng/mL. There were no precision or accuracy issues identified for dolutegravir based on the bioanalytical report. For the LAI116181 trial, precision and accuracy were evaluated using plasma dolutegravir QC samples at four concentration levels: 60 ng/mL, 1600 ng/mL, 16000 ng/mL, and 20000 ng/mL (20000 ng/mL was the upper limit of quantification). The corresponding dolutegravir inter-run accuracy values were 2.5% for 60 ng/mL, 3.6% for 1600 ng/mL, -1.0% for 16000 ng/mL, and -5.7% for 20000 ng/mL. The dolutegravir inter-run precision values were 3.1% for 60 ng/mL, 4.8% for 1600 ng/mL, 3.9% for 16000 ng/mL, and 3.1% for 20000 ng/mL. The lower limit of quantification for rilpivirine was 1 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for rilpivirine based on the bioanalytical report. For the LAI116181 trial, precision and accuracy were evaluated using plasma rilpivirine QC samples at three concentration levels: 2.73 ng/mL, 54.6 ng/mL, and 1560 ng/mL. The corresponding rilpivirine inter-run accuracy values were -5.9% for 2.73 ng/mL, 0.2% for 54.6 ng/mL, and 2.6% for 1560 ng/mL. The rilpivirine inter-run precision values were 5.8% for 2.73 ng/mL, 3.1% for 54.6 ng/mL, and 4.9% for 1560 ng/mL.

For the LAI116181 trial, based on the information submitted by the applicant, dolutegravir plasma samples were stored for less than 2 months at -20°C or -70°C at the trial site and stored between -20°C and -70°C and analyzed within one month of receipt at the (b) (4) bioanalytical laboratory and rilpivirine plasma samples were stored for less than 1 month at -20°C or lower at the trial site and stored at -20°C and analyzed within one month of receipt at the bioanalytical laboratory. Based on additional information that was provided by the applicant, the interval between the first sample collection and the last sample analysis was 101 days with samples stored at-20°C at the trial site and the bioanalytical laboratory. The submitted dolutegravir long term stability data of 480 days (16 months) at -30°C and 265 days at -20°C that was generated by GSK and 373 days at -20°C and 93 days at -70°C in EDTA anticoagulated plasma that was generated (b) (4) appears to cover the duration of dolutegravir long term stability data necessary for the LAI116181 trial. For the LAI116181 trial, the submitted rilpivirine long term stability data of 1528 days at -18°C in heparin anticoagulated plasma that was generated (b) (4) appears sufficient to cover the duration of stability data needed for rilpivirine.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for dolutegravir, rilpivirine and GSK1265744. For the noncompartmental analysis, dolutegravir, rilpivirine and GSK1265744 plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0\text{-}24h)}$.

Statistical Analysis

ANOVA was used for the statistical analyses. In cohort 1, dolutegravir in combination with rilpivirine was the test arm and dolutegravir or rilpvirine were the reference arms. In cohort 2, GSK1265744 in combination with rilpivirine was the test arm and GSK1265744 or rilpvirine were the reference arms. The trial report did not include specific "no effect" boundaries for the 90% confidence intervals for selected dolutegravir, rilpivirine, or GSK1265744 pharmacokinetic parameters.

10. Results

10.1 Subject Demographics and Disposition

Table 3-LAI116181 subject demographics

Demographics	Cohort 1 (N=16)	Cohort 2 (N=12)	Overall (N=28)
Age in Years, Mean (SD)	34.4 (11.33)	27.4 (10.57)	31.4 (11.37)
Sex, n (%)			
Female:	2 (13)	2 (17)	4 (14)
Male:	14 (88)	10 (83)	24 (86)
BMI (kg/m^2), Mean (SD)	26.51 (2.58)	27.03 (3.24)	26.73 (2.83)
Height (cm), Mean (SD)	178.50 (10)	175.75 (12.71)	177.32 (11.11)
Weight (kg), Mean (SD)	84.46 (10.56)	83.74 (15.23)	84.15 (12.51)
Ethnicity, n (%)			
Hispanic or Latino:	4 (25)	1 (8)	5 (18)
Not Hispanic or Latino:	12 (75)	11 (92)	23 (82)
Race, n (%)			
African American/African Heritage	4 (25)	7 (58)	11 (39)
American Indian or Alaska Native	1 (6)	0	1 (4)
Native Hawaiian or Other Pacific Islander	1 (6)	0	1 (4)
White – White/Caucasian/European Heritage	10 (63)	5 (42)	15 (54)

Table 4-LAI116181 subject disposition

Number of Subjects	Period 1 GSK1265744	Period 2 RPV	Period 3 GSK1265744 + RPV
Enrolled, N	12	12	12
Completed, n (%)	12 (100)	12 (100)	11 (92)
Withdrawn, n (%)	0	0	1 (8)
Reason for Withdrawal, n	0	0	1
Investigator discretion, n (%)	0	0	1 (100)

10.2 Concomitant Medications

Three subjects (subjects 811002 in cohort 1, 812004 and 812011 in cohort 2) received acetaminophen during the trial and one subject (subject 812003 in cohort 2) received procain hydrochloride and subsequently benzyl penicillin and hydrocodone. The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

10.3 Pharmacokinetic and Statistical Analysis

(Reviewer note: The GSK1265744 pharmacokinetic data is displayed for informational purposes only and will not be discussed).

Dolutegravir

Table 5-Dolutegravir statistical analysis and pharmacokinetic parameters derived using noncompartmental analysis with dolutegravir 50 mg once daily with or without rilpivirine 25 mg once daily

Plasma DTG PK Parameter	DTG[1] (n=16)	DTG + RPV[1] (n=16)	DTG + RPV vs DTG[2]
AUC(0-τ) (µg.h/mL)	48.8 [40.8, 58.4] (35)	54.7 [46.1, 64.9] (33)	1.12 [1.05, 1.19]
Cmax (µg/mL)	3.46 [2.96, 4.04] (30)	3.90 [3.43, 4.44] (25)	1.13 [1.06, 1.21]
Cτ (µg/mL)	1.07 [0.850, 1.34] (45)	1.31 [1.04, 1.65] (46)	1.22 [1.15, 1.30]
Tmax[3] (h)	3.50 (1.0-4.0)	3.50 (1.0-4.0)	-------

1. Geometric mean [95% CI] (Between subject variability CVb%)
2. GLS Mean Ratio [90% CI]
3. Median (range)

Treatments:
DTG = DTG 50 mg QD x 5 days
DTG + RPV = DTG 50 mg QD + RPV 25 mg QD x 5 days

Rilpivirine

Table 6-Rilpivirine statistical analysis and pharmacokinetic parameters derived using noncompartmental analysis with dolutegravir 50 mg once daily with or without rilpivirine 25 mg once daily

Plasma RPV PK Parameter	Cohort 1: RPV with or without DTG		
	RPV[1] (n=16)	DTG + RPV[1] (n=16)	DTG + RPV vs RPV[2]
AUC(0-τ) (ng.h/mL)	2227 [1872, 2649] (33)	2368 [1985, 2825] (34)	1.06 [0.976, 1.16]
Cmax (ng/mL)	148 [128, 173] (29)	164 [136, 197] (36)	1.10 [0.992, 1.22]
Cτ (ng/mL)	74.5 [60.3, 92.2] (41)	90.5 [70.9, 115] (48)	1.21 [1.07, 1.38]
Tmax[3] (h)	4.00 (4.0-6.0)	4.00 (2.0-5.0)	------

1. Geometric mean [95% CI] (CVb%)
2. GLS Mean Ratio [90% CI]
3. Median (range)

Table 7-Rilpivirine statistical analysis and pharmacokinetic parameters derived using noncompartmental analysis with dolutegravir 50 mg once daily with or without GSK1265744 30 mg once daily

Plasma RPV PK Parameter	Cohort 2: RPV with or without GSK1265744		
	RPV[1] (n=11)	GSK1265744 + RPV[1] (n=11)	GSK1265744 + RPV vs RPV[2]
AUC(0-τ) (ng.h/mL)	2473 [2034, 3008] (30)	2441 [1916, 3110] (37)	0.987 [0.890, 1.09]
Cmax (ng/mL)	171 [137, 213] (34)	165 [120, 226] (50)	0.963 [0.849, 1.09]
Cτ (ng/mL)	87.4 [66.8, 114] (42)	80.3 [58.6, 110] (50)	0.919 [0.789, 1.07]
Tmax[3] (h)	4.00 (3.0-6.0)	4.00 (3.0-5.0)	------

1. Geometric mean [95% CI] (CVb%)
2. GLS Mean Ratio [90% CI]
3. Median (range)

GSK1265744

Table 8-GSK1265744 statistical analysis and pharmacokinetic parameters derived using noncompartmental analysis with GSK1265744 30 mg once daily with or without rilpivirine 25 mg once daily

Plasma GSK1265744 PK Parameter	GSK1265744[1] (n=11)	GSK1265744 + RPV[1] (n=11)	GSK1265744 + RPV vs GSK1265744[2]
AUC(0-τ) (µg.h/mL)	142 [118, 171] (28)	159 [138, 183] (21)	1.12 [1.05, 1.19]
Cmax (µg/mL)	8.22 [6.83, 9.89] (28)	8.65 [7.69, 9.72] (18)	1.05 [0.963, 1.15]
Cτ (µg/mL)	4.65 [3.73, 5.78] (33)	5.29 [4.49, 6.23] (25)	1.14 [1.04, 1.24]
Tmax[3] (h)	4.00 (2.0-4.0)	4.00 (1.0-4.0)	-------

1. Geometric mean [95% CI] (CVb%)
2. GLS Mean Ratio [90% CI]
3. Median (range)

10.4 Safety Analysis

The adverse events reported in the trial are displayed in Table 9. All adverse events were considered Grade 1, with the exception of three adverse events that were Grade 2 (insomnia, catheter site inflammation, and toothache).

Table 9-Adverse events reported in the LAI116181 trial

Preferred Term	Number (%) of Subjects					
	Cohort 1			Cohort 2		
	DTG (N=16)	RPV (N=16)	DTG + RPV (N=16)	GSK1265744 (N=12)	RPV (N=12)	GSK1265744 + RPV (N=12)
Any event	**2 (13)**	**3 (19)**	**8 (50)**	**3 (25)**	**2 (17)**	**5 (42)**
Headache	2 (13)	1 (6)	3 (19)	0	1 (8)	2 (17)
Dizziness	0	0	1 (6)	0	0	1 (8)
Somnolence	0	0	0	0	0	1 (8)
Toothache	0	0	0	0	0	1 (8)
Oral herpes	0	0	0	0	0	1 (8)
Decreased appetite	0	0	0	1 (8)	0	1 (8)
Catheter site related reaction	0	0	2 (13)	0	0	0
Catheter site inflammation	0	0	1 (6)	0	0	0
Dyspepsia	0	0	1 (6)	0	0	0
Pharyngitis	0	0	1 (6)	0	0	0
Abnormal dreams	0	1 (6)	0	0	0	0
Insomnia	0	1 (6)	0	0	0	0
Cough	0	0	0	2 (17)	0	0
Arthralgia	0	0	0	0	1 (8)	0
Dermatitis contact	0	1 (6)	0	0	0	0

Cohort 1: DTG = DTG 50 mg QD x 5 days
RPV = RPV 25 mg QD x 11 days
DTG + RPV = DTG 50 mg QD + RPV 25 mg QD x 5 days
Cohort 2: GSK1265744 = GSK1265744 30 mg QD x 12 days
RPV = RPV 25 mg QD x 12 days
GSK1265744 + RPV = GSK1265744 30 mg QD + RPV 25 mg QD x 12 days

11. Discussion and Conclusions

Dolutegravir is metabolized by different pathways including UGT1A1 and CYP3A and appears not to inhibit CYP3A to a clinically relevant extent. Rilpivirine in mainly metabolized by CYP3A and when administered as a 25 mg once daily dosage regimen, rilpivirine is not expected to impact the exposure of CYP metabolized medications according to the rilpivirine U.S prescribing information.

Based on the results from the LAI116181 trial, the following conclusions can be made:

- With 50 mg once daily dosing, the dolutegravir $AUC_{(0\text{-}24h)}$, C_{max}, and C_{τ} were increased by 12%, 13%, and 22%, respectively, when coadministered with rilpivirine 25 mg once daily
- With 25 mg once daily dosing, the rilpivirine $AUC_{(0\text{-}24h)}$, C_{max}, and C_{τ} were increased by 6%, 10%, and 21%, respectively, when coadministered with dolutegravir 50 mg once daily
- The magnitude of change in dolutegravir or rilpvirine exposure ($AUC_{(0\text{-}24h)}$, C_{max}, and C_{τ}) is not anticipated to result in any clinically relevant safety issues.

4.1.5 *In vitro* studies

Transporter interactions

07APK016
Permeability of GSK1349572 and interaction w/ P-gp in hMDR1-MDCK cells

This initial study indicated that:

- GSK1349572 is classified as having high permeability (577 nm/s)
- P-gp attenuates the (A) → (B) flux of GSK1349572 across hMDR1 MDCK cells by ~40%

Methods
The in vitro cell permeability and interaction of GSK1349572 with P-glycoprotein (P-gp) were assessed using hMDR1-MDCK cells in the presence of bio-relevant buffers. The (A) chamber contained FaSSIF, a balanced salt solution containing taurocholate and
phosphatidyl choline (pH 7.4), and the (B) chamber contained 1% (w/v) human serum albumin in transport buffer.

Amprenavir (3 μM) was included as a positive control in separate wells as a marker substrate for P-gp activity. Propranolol (3 μM) was also included in separate wells as a high permeability marker compound.

An apparent permeability coefficient (Papp) for GSK1349572 in the apical (A) to
basolateral (B) direction was calculated from the LC/MS/MS-determined concentration in the basolateral (B) compartment and the nominal (3 μM) initial concentration in the donor solution, according to the equation below (units = nm/sec).

Papp = (Creceiver x Volumereceiver)/3600sec/surface area/(3 μM)

The absorptive quotient (AQ) is a measurement of the effect of P-gp on the absorptive permeability of GSK1349572 across hMDR1 MDCK cells, and is calculated from the average (A) → (B) Papp values in the presence and absence of GF120918A (P-gp inhibitor) according to the equation below. An AQ value approaching the theoretical maximum of 1 suggests a significant decrease in the absorptive flux due to P-gp efflux of the compound, whereas a value near 0 suggests minimal P-gp influence on absorptive flux.

AQ = (Papp+918 - Papp no 918) / Papp+918

Results
The apparent permeability coefficient (Papp) of GSK1349572 in the absorptive direction (apical (A) to basolateral (B) direction) is shown in the table below. Based on its 'passive' Papp value (Papp+918) of 577 nm/s, GSK1349572 is classified as having high permeability. The absorptive quotient (AQ) value was calculated from the averaged Papp values obtained in the presence or absence of P-gp inhibitor

GF120918A. The obtained AQ value indicates that P-gp attenuates the (A) → (B) flux of GSK1349572 across hMDR1 MDCK cells by approximately 40%.

Compound	Papp (nm/s) (+918)[2]			Mass Balance (%) (+918)[3]	Permeability Classification[4]	Papp (nm/s) (-918)[5]			Mass Balance (%) (-918)	AQ[6]
	M1	M2	Avg	Avg		M1	M2	Avg	Avg	
GSK1349572	535	618	577	92	High	300	383	342	101	0.4
Lucifer Yellow CH[7]	1	2	1	ND	Low	5	5	5	ND	NR
Propranolol	521	580	551	79	High	570	601	585	96	0.0
Amprenavir	394	364	379	101	High	42	34	38	126	0.9

Conclusions

- GSK1349572 is classified as having high permeability (577 nm/s)
- P-gp attenuates the (A) → (B) flux of GSK1349572 across hMDR1 MDCK cells by ~40%

08DMR027

Membrane permeability of GSK1349572 in MDCKII-MDR1 cells

This study indicated that:

- GSK1349572 has high passive membrane permeability of 333 nm/s at pH 7.4

Methods

The passive membrane permeability of [14C] GSK1349572 was determined at pH 7.4, and the absorptive membrane permeability of [14C] GSK1349572 was determined at pH 5.5 and 7.4, using a bio-relevant buffer (FaSSIF, fasted state simulated intestinal fluid) to simulate conditions in the gastrointestinal tract. Permeabilities were measured using MDCKII-MDR1 cell monolayers in the presence of the potent P-glycoprotein inhibitor, GF120918.

The polarized Madin-Darby canine kidney MDCKII-MDR1 cell line heterologously expressing human P-gp was used for the in vitro permeability studies. In order to measure passive permeability in this system, P-gp activity was inhibited by 2 μM GF120918. Amprenavir was used as a positive control. The passive membrane permeability at pH 7.4 of [14C]GSK1349572 and [3H] amprenavir was measured in one direction (apical to basolateral [A→B]) in triplicate sets of wells. DMEM (at pH 7.4) was used as the transport medium in both compartments. To inhibit P-gp activity, both receiver and donor compartments contained 2 μM GF120918.

Results

The passive membrane permeability at pH 7.4 of [14C] GSK1349572 was high with a P7.4 of 333 nm/s. In the presence of FaSSIF, the absorptive membrane permeability of [14C] GSK1349572 was high at pH 7.4 and at pH 5.5 with a P7.4[abs] of 252 nm/s and P5.5[abs] of 265 nm/s respectively. These results indicate that pH does not affect the absorptive membrane permeability of [14C] GSK1349572 over the pH range investigated. The mass balance for [14C]GSK1349572 was considered acceptable.

Conclusions

- GSK1349572 is classified as having high permeability (333 nm/s)

08DMR028

P-gp transport of GSK1349572 in MDCKII-MDR1 cells

This study indicated that:

- GSK1349572 is a substrate for human P-gp with a moderate efflux ratio of 3.8 at a concentration of 3 μM

Methods

The polarized MDCKII-MDR1 cell line heterologously expressing human Pgp was used for the in vitro transport studies. Amprenavir was selected as the positive control. The transport of [14C] GSK1349572 and [3H] amprenavir was measured in two directions (apical to basolateral [A→B] and basolateral to apical [B→A]), with each direction performed in triplicate sets of wells.

Results

The mass balance for [14C]GSK1349572 was considered acceptable with the exception of the B to A direction with inhibitor (mass balance value of 75%), but it was not considered to affect the overall conclusion of the study.

Conclusion

- The data demonstrate that [14C] GSK1349572 was a substrate for human Pgp with a moderate efflux ratio of 3.8 at a concentration of 3 μM.

I1DMR004

BCRP transport of GSK1349572 MDCKII-BCRP cells

This study indicated that:

- GSK1349572 is a substrate for human BCRP with an efflux ratio of 3.1 at a concentration of 3 μM.

Methods

The polarized MDCKII-BCRP cell line heterologously expressing human BCRP was used for the in vitro transport studies. Cimetidine was selected as a positive control. GF120918 (2 μM) was used a BCRP inhibitor to test functionality of the system. The transport of [14C] GSK1349572 and [14C] cimetidine was measured in two directions (apical to basolateral [A→B] and basolateral to apical [B→A]), with each direction performed in triplicate sets of wells.

Results

The apical efflux ratio for [14C] cimetidine was 5.8 collapsing to 1.1 in the presence of the BCRP inhibitor, GF120918. This demonstrated the functional expression of human BCRP in the MDCKII-BCRP cell line. The mass balance for [14C]cimetidine was considered acceptable.

The apical efflux ratio of [14C]GSK1349572 at 3 μM was determined as 3.1 and 0.80 in the absence and presence of 2 μM GF120918, respectively. These results indicate that, under the assay conditions used, [14C]GSK1349572 is a substrate of human BCRP.

Conclusion

- GSK1349572 is a substrate for human BCRP with an efflux ratio of 3.1 at a concentration of 3 μM.

08DMR021

Inhibition of P-gp transport by GSK1349572 in MDCKII cells

This study indicated that:

- GSK1349572 likely would not demonstrate clinically relevant inhibition of P-gp transport (IC50 value >100 μM).

Methods

The polarized Madin-Darby canine kidney MDCKII-MDR1 cell line heterologously expressing human P-gp was used for this study. The effect of GSK1349572 on the P-gp-mediated transport of [3H] digoxin was assessed by determining the basolateral to apical ([B→A]) transport of [3H] digoxin at 90 minutes, in the absence or presence of GSK1349572 at target concentrations of 0.3 to 100 μM (applied in both apical and basolateral wells). GF120918, a potent inhibitor of P-gp, was included at a nominal concentration of 2 μM as a positive control for P-gp inhibition.

Results

The [B→A] transport rate for [3H] digoxin in the absence of inhibitor was 1.6±0.04 pmole/cm2/h and in the presence of the P-gp inhibitor GF120918 (positive control) was 0.37 ± 0.04 pmole/cm^2/h (23 % of digoxin alone transport). These results demonstrated the functional expression of human P-gp in the MDCKII-MDR1 cell line. The positive control rate is considered to represent the passive transport component of [^{3}H] digoxin.

GSK1349572 inhibited digoxin transport at concentrations >30 μM. However, the degree of inhibition over the concentration range tested was insufficient to allow calculation of the IC50 (i.e., the highest concentration tested [100 μM] did not result in 50% or greater inhibitory effect on digoxin transport). GSK1349572 inhibits transport of digoxin via human P-glycoprotein in vitro, with an IC50 value >100 μM (see table below).

The Effect of GSK1349572 on Human Pgp Mediated Transport of 30 nM [^{3}H]-Digoxin, Using MDCKII-MDR1 Cells

Compound	Conc. (μM)	Digoxin transport rate (pmole/cm²/h) ± SD	Digoxin transport rate (% control) ± SD
GSK1349572	0.3	1.7 ± 0.11	104 ± 6.5
	1.0	1.6 ± 0.04	96 ± 2.3
	3.0	1.6 ± 0.07	95 ± 4.2
	10	1.3 ± 0.13	82 ± 7.9
	30	1.4 ± 0.07	88 ± 4.2
	100	1.2 ± 0.12	71 ± 7.6
Digoxin Only	-	1.6 ± 0.04	100 ± 2.6
GF120918	2	0.37 ± 0.04	23 ± 2.4

SD is standard deviation.
Data are the mean and standard deviation from sets of three wells.
Quality control parameters were within acceptable limits (acceptable values: Lucifer yellow $P_{7.4}$ ≤ 50 nm/sec; digoxin mass balance 80 – 120 %; digoxin transport rate ≥ 1.5 pmoles transported/cm^2/h; digoxin transport rate in the presence of 2 μM GF120918 ≤ 30% of uninhibited rate).

Conclusion

- GSK1349572 likely would not demonstrate clinically relevant inhibition of P-gp transport (IC50 value >100 μM).

10DMR033

Inhibition of BCRP transport by GSK1349572 in MDCKII cells

This study indicated that:

- GSK1349572 inhibited transport of cimetidine (50% of control) via human BCRP in vitro at a concentration of 100 μM. However, the data were insufficient to calculate an IC50 value.

Methods

The polarized Madin-Darby canine kidney MDCKII-BCRP cell line heterologously expressing human BCRP was used for this study. Cimetidine was used as the probe substrate for BCRP transport while GF120918, a BCRP inhibitor, was used as the positive control.

Results

Experimental results were accepted as the quality control parameters were within the acceptable limits listed below:

- Lucifer yellow P7.4 ≤50 nm/sec
- [14C]cimetidine mass balance 80 – 120%
- [14C]cimetidine transport rate ≥1.5 pmoles transported/cm2/h
- [14C]cimetidine transport rate in the presence of 2 μM GF120918 ≤25% of uninhibited rate.

The [B→A] transport rate for [14C] cimetidine in the absence of inhibitor was 2.2±0.21 pmole/cm2/h and decreased in the presence of the BCRP inhibitor, GF120918 (positive control), to 0.43±0.025 pmole/cm2/h, (20 % of [14C] cimetidine alone transport).

GSK1349572 inhibited cimetidine transport at concentrations ≥10 μM. However, the degree of inhibition over the concentration range tested was insufficient to allow calculation of the IC50 (% of control value at the highest concentration, 100 μM, was 50).

Effect of GSK1349572 on Human BCRP Mediated Transport of 100 nM Cimetidine using MDCKII-BCRP Cells

Compound	Conc. (μM)	Cimetidine transport rate (pmole/cm^2/h) ± SD	Cimetidine transport rate (% control) ± SD
GSK1349572	0.3	2.1 ± 0.093	93 ± 4.2
	1	2.4 ± 0.15	110 ± 6.8
	3	2.1 ± 0.024	93 ± 1.1
	10	1.5 ± 0.071	66 ± 3.2
	30	1.3 ± 0.018	57 ± 0.81
	100	1.1 ± 0.017	50 ± 0.76
cimetidine only	-	2.2 ± 0.21	100 ± 9.3
GF120918	2	0.43 ± 0.025	20 ± 1.1

Data are the mean and standard deviation from three monolayers.
SD is the standard deviation.

Conclusions

- GSK1349572 inhibited transport of cimetidine (50% of control) via human BCRP in vitro at a concentration of 100 μM. However, the data were insufficient to calculate an IC50 value.

10DMR031 and 11DMR032

Inhibition of estradiol-17-β-D-glucuronide by GSK1349572 (10DMR031) and GSK1349572-glucuronide metabolite (11DMR032) in human membrane vesicles expressing MRP2

Both of these studies indicated that:

- GSK1349572 did not inhibit human MRP2 at concentrations up to 100 μM
- GSK1349572-glucuronide metabolite did not inhibit human MRP2 at concentrations up to 100 μM

Methods

Benzbromarone, a MRP2 inhibitor, was used as a positive control inhibitor in these studies and estradiol glucuronide was used as the probe substrate. MRP2 inhibition assays were performed using the assay conditions recommended by the vesicle manufacturer. Briefly, MRP2 membrane vesicles (50 μg protein) were preincubated in the presence or absence of GSK1349572 or benzbromarone. Following preincubation, reactions were initiated by the addition of 10 mM MgATP solution containing 50 μM [3H]EG. Additional incubations were performed in the absence of inhibitor and in the presence of 10 mM MgAMP solution containing 50 μM [3H]EG for passive transport.

Results

At all concentrations tested (0.1-100 μM), no discernible inhibition of [3H]EG uptake by GSK1349572 or GSK1349572-glucuronide metabolite was observed.

Conclusions

- GSK1349572 did not inhibit human MRP2 at concentrations up to 100 μM
- GSK1349572-glucuronide metabolite did not inhibit human MRP2 at concentrations up to 100 μM

08DMR016

Inhibition of OATP1B1 and OATP1B3 transport by GSK1349572

These studies indicated that:

- GSK1349572 did not inhibit human OATP1B1 or OATP1B3 in vitro at concentrations up to 100 μM

Methods

The Chinese Hamster Ovary cell lines heterologously expressing human organic anion transporting polypeptide 1B1 (CHO-OATP1B1) were used for the in vitro OATP1B1 inhibition assay. The Human Embryonic Kidney MSRII cell line, transduced with BacMam baculovirus containing the human organic anion transporting polypeptide 1B3 (OATP1B3) was used for the in vitro OATP1B3 inhibition assay.

Rifamycin (positive control) was used as an OATP1B1 and OATP1B3 inhibitor demonstrating maximal inhibition of [3H]Estradiol 17β-D-glucuronide (probe substrate) uptake. Concentrations of GSK1349572 tested were: 0.1, 1, 3, 10, 30, and 100 μM.

Results

For OATP1B1, uptake rates of 0.02 μM [3H]EG in the absence and presence of the control OATP inhibitor rifamycin were 12±0.90 fmoles/cm^2/min and 1.2±0.17 fmoles/cm^2/min, respectively, and demonstrated the functional expression of human OATP1B1 in the CHO cell line.

For OATP1B3, uptake rates of 0.02 μM [3H]EG in the absence and presence of the control OATP inhibitor rifamycin were 1.9±0.06 fmoles/cm^2/min and 0.64 fmoles/cm^2/min respectively and demonstrated the functional expression of human OATP1B3 in the HEK MRII cell line.

At all concentrations tested, no discernible inhibition of [3H]EG uptake by GSK1349572 was observed for OATP1B1 or OATP1B3. The data demonstrate that GSK1349572 is not an inhibitor of human OATP1B1 or OATP1B3 in vitro.

Conclusion

- GSK1349572 did not inhibit human OATP1B1 or OATP1B3 in vitro at concentrations up to 100 μM

OPT-2010-104 and OPT-2010-119*

Inhibition of human OCT2 mediated transport by GSK1349572 and co-administered compounds and Inhibition of human OCT2 mediated transport by GSK1349572 and co-administered compounds and IC50 determination of GSK1349572

**Two reports for the evaluation of inhibition of OCT2-mediated transport by GSK1349572 were submitted. The methods appear similar with the exception of the GSK1349572 concentrations used and a more accurate determination of the IC50 in study OPT-2010-119 (this study post-dates the OPT-2010-104 study). Thus, only the results from the -119 study are presented below.*

These studies indicated that:

- GSK1349572 produced concentration dependent inhibition of OCT2 with an IC50 value of 1.93 μM
- Co-incubation of abacavir and lamivudine or tenofovir disoproxil and emtricitabine with GSK1349572 had a nominal effect on OCT2-mediated metformin transport

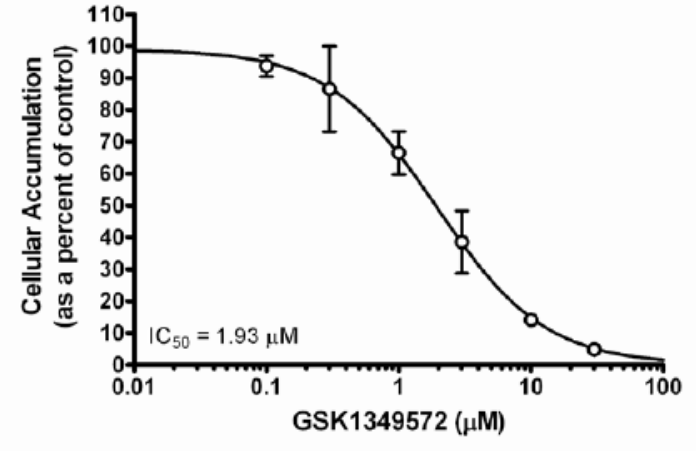
Methods

Cimetidine and quinidine were included in the study as reference inhibitors (positive controls). The purpose of the study was to determine the IC50 value for GSK1349572 against human OCT2 and assess the inhibitory effect of GSK1349572, GSK1349572 co-administered with abacavir (10 μM) and lamivudine (10 μM), and GSK1349572 co-administered with tenofovir disoproxil and emtricitabine on the transport of 10 μM 14C-metformin by OCT2. Concentrations of GSK1349572 used were: 0.1, 0.3, 1, 3, 10, 30, and 100 μM.

Results

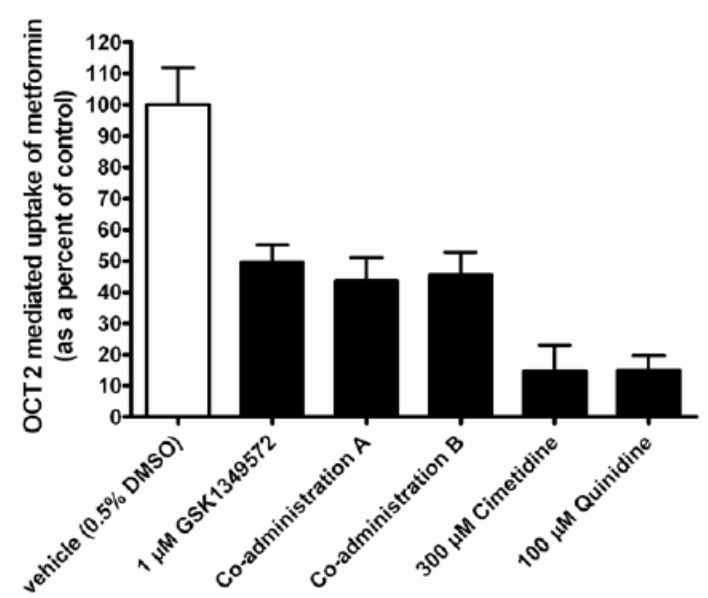
The inhibition of OCT2-mediated metformin transport by GSK1349572 was examined over a concentration range of 0.1-30 μM. The IC50 value determined from a non-linear regression analysis of the data was 1.93 μM (see figure below). A 1 μM concentration was selected for the subsequent inhibition assessment of GSK1349572 with co-administered compounds.

IC50 determination of GSK1349572 against OCT2-mediated transport of 10 μM metformin



GSK1349572, at a concentration of 1 μM inhibited OCT2-mediated transport of metformin by 50%. OCT2 inhibition results for abacavir and lamivudine or tenofovir disoproxil and emtricitabine, co-administered with GSK1349572, were similar to GSK1349572 alone. The coadministration of GSK1349572 with abacavir and lamivudine inhibited OCT2 transport by 56%, whereas the co-administration of GSK1349572 with tenofovir disoproxil and emtricitabine yielded 54% inhibition. Cimetidine, an established inhibitor of OCT2 transport, inhibited the transport of metformin. At a concentration of 300 μM, cimetidine inhibited OCT2 transport by 85.2% (see figure below).

Inhibition of OCT2 mediated transport of 10 μM metformin



Metformin transport was investigated in the presence of vehicle (0.5% DMSO), 1 µM GSK1349572, 1 µM GSK1349572 + 10 µM abacavir + 10 µM lamivudine (Coadministration A), or 1 µM GSK1349572 + 1 µM tenofovir disoproxil + 10 µM emtricitabine (Co-administration B), 300 µM cimetidine, or 100 µM quinidine. Data represent the mean and standard deviation of triplicate samples.

Conclusions

- GSK1349572 showed concentration dependent inhibition of OCT2-mediated transport of metformin in vitro with an IC50 value of 1.93 µM
- Co-incubation of abacavir and lamivudine or tenofovir disoproxil and emtricitabine with GSK1349572 had a nominal effect on OCT2-mediated metformin transport

11GSKRTPP6R1

Inhibition of [14C]Metformin uptake by GSK1349572 in HEK293-OCT1 cells

This study indicated that:

- GSK1349572A did not significantly inhibit OCT1-mediated uptake of [14C]Metformin at 10 µM (22% reduction)

Methods

Human embryonic kidney epithelial cells (HEK293) were used as the test system. Positive control inhibitors for this study were repaglinide (10 µM) and quinidine (100 µM) and the probe substrate was [14C]Metformin. The final concentration of GSK1349572A was 10 µM. The concentrations of positive OCT1 inhibitors were above their IC50 values determined internally.

Results

Inhibition of OCT1 by GSK1349572A was investigated by measuring the uptake rate of [14C]Metformin (10 μM or 1 μCi/mL) in HEK293 and OCT1-HEK293 cells in the absence and presence of 10 μM GSK1349572A or two positive OCT1 inhibitors (10 μM repaglinide and 100 μM quinidine). The net influx rate of [14C]Metformin in the OCT1-HEK293 cells was 51.2 pmol/min/mg in the absence of OCT1 inhibitor or the test compound. Repaglinide and quinidine significantly reduced the net influx rate of [14C]Metformin by 80% and 90%, respectively. The observed inhibition of [14C]Metformin influx by GSK1349572A (22% at 10 μM) did not meet the criterion for being classified as a significant OCT1 inhibitor (> 50% inhibition at the maximum steady-state plasma concentration) therefore an IC50 determination was not conducted for GSK1349572A.

Conclusions

- GSK1349572A did not significantly inhibit OCT1-mediated uptake of [14C]Metformin at 10 μM (22% reduction) and is not classified as an OCT1 inhibitor

GSK1349572 Metabolism by CYPs

The following studies demonstrated the potential for GSK1349572 to be metabolized by CYP enzymes in various test systems. A summary of findings (sponsor's description) from all studies combined is included below.

07APK019
Metabolic stability of GSK1349572 in rat, dog, cynomolgus monkey, and human liver S9, and in rat and human fresh and cryopreserved hepatocytes
07DMR124
Potential for metabolic activation of GSK1349572 in pooled rat, monkey, and human liver microsomes
07APK019
Metabolite identification of GSK1349572 in cryopreserved rat, dog, monkey, and human hepatocytes
07DMR121
Metabolism of GSK1349572 rat, monkey, and human hepatocytes
08DMR033
Investigation of human oxidative enzymology of [^{14}C]GSK1349572
07RCD8654
Metabolic production of stereoisomers of GSK1349572 in cryopreserved rat, dog, cynomolgus monkey, and human hepatocytes

Summary of CYP metabolism studies:
Preliminary investigations were conducted to evaluate the metabolic stability of dolutegravir (1 μM) in rat, dog, monkey and human liver S9 preparations and at 0.5 μM in rat and human fresh and cryopreserved hepatocytes. Dolutegravir was stable in rat, monkey and human S9 ($t_{½} \geq 90$ minutes). No conclusion could be drawn from dog S9 incubations (n=2 independent assays) due to high inter-assay variability. Dolutegravir was stable in rat cryopreserved hepatocytes and in both fresh and cryopreserved

human hepatocytes (t½ >360 minutes). In fresh rat hepatocytes, the intrinsic clearance (25 mL/min/kg body weight) and t½ (268 minutes) were determined.

Information on the likely routes of metabolism of dolutegravir across species was investigated in vitro by incubating dolutegravir (10 μM) with cryopreserved rat, dog, monkey and human hepatocytes. In a follow up study, the metabolism of [14C]-dolutegravir (50 μM) was investigated in male rat, monkey and pooled (mixed gender) human cryopreserved hepatocytes. The metabolic turnover of [14C]-dolutegravir in rat and monkey hepatocytes was low and similar to human hepatocytes (approximately 3.5 to 9.4% turnover). In human hepatocytes, the notable route of metabolism for [14C]-dolutegravir was glucuronidation. Metabolite profiles of the nonclinical species and human were qualitatively similar. The human metabolite (glucuronidation) was observed in hepatocytes from the two nonclinical species.

The oxidative enzymology of dolutegravir was investigated using pooled human liver microsomes and recombinant cytochrome P450 (CYP) enzymes. Azamulin, a selective CYP3A4 inhibitor, was used to detect potential inhibition of dolutegravir metabolism. [14C]-dolutegravir was metabolized in human liver microsomes to M7 (oxidation). M7 formation, which constituted 14 % of the metabolites generated by human liver
microsomes, was completely inhibited by azamulin. Metabolites M1 (N-dealkylation) and M7 were formed in recombinant CYP3A4 incubations. Incubations with recombinant CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 showed no metabolism. The data suggest that CYP3A4 is the primary CYP enzyme involved in the metabolism of dolutegravir in vitro.

Dolutegravir has two chiral centers, so the potential for metabolism of dolutegravir (10 μM) to its respective enantiomer and two diastereomers was investigated in incubations with cryopreserved rat, dog, monkey and human hepatocytes. (b) (4) These data indicate that no significant metabolic conversion of dolutegravir to its enantiomer or one of two possible diastereomers occurs in rat, dog, monkey or human hepatocytes.

GSK1349572 Metabolism by UGTs

The following studies demonstrated the potential for GSK1349572 to be metabolized by UGT enzymes in various test systems. A summary of findings (sponsor's description) from all studies combined is included below.

07APK024
Metabolic stability of GSK1349572 to glucuronidation by recombinant UGT1A1
08DMR067
Investigation of human UGT enzymes involved in the glucuronidation of [^{14}C]GSK1349572

06RCM8059
Potential of GSK1349572 to Form Glutathione Adducts

Summary of UGT metabolism studies:

An exploratory study to evaluate the potential of dolutegravir (0.5, 5 and 50 μM) to undergo in vitro glucuronidation by UDP glucuronosyltransferase 1A1 (UGT1A1) was investigated in incubations with pooled human liver microsomes (PHLM) and UGT1A1 supersomes (recombinantly expressed human UGT1A1 in baculovirus infected insect cells). Under optimized study conditions using recombinant UGT1A1 supersomes, 30% of dolutegravir was metabolized to an ether glucuronide (M3) at the end of the 120 minute incubation with recombinant UGT1A1.

In a follow up study, the human UDP glucuronosyltransferase (UGT) enzymology of dolutegravir was investigated in vitro using pooled human liver microsomes and recombinant human UGT enzymes. Atazanavir, a UGT1A1 inhibitor, was used to determine the potential to inhibit glucuronidation of dolutegravir.

[14C]-dolutegravir was metabolized in human liver microsomes to a single UDPGA-dependent metabolite. β-glucuronidase digestions were used to identify this metabolite as a glucuronide. Atazanavir inhibited [14C]-dolutegravir glucuronidation in human liver microsomes with a calculated IC50 value of 0.39 μM. [14C]-dolutegravir was metabolized in recombinant UGT1A1 enzymes, resulting in calculated Km and Vmax values of 21 μM and 67 pmol/min/mg, respectively. [14C]-dolutegravir glucuronidation was also observed in recombinant UGT1A3 and 1A9 incubations but to a lesser extent in comparison to UGT1A1. These data suggest that UGT1A1 is the primary UGT enzyme involved in the glucuronidation of dolutegravir in vitro, with contribution from UGT1A3 and 1A9.

Dolutegravir (100 μM) was tested in a glutathione reactive metabolite trapping assay using rat and pooled human liver microsomes with a NADPH regenerating system. The results showed in vitro evidence for formation of a metabolite consistent with addition of glutathione through oxidative defluorination, in both rat and human liver microsomes.

CYP induction by GSK1349572

RR2007/00025
Evaluation of GSK1349572 as an activator of nuclear receptor PXR

This study indicated that:

- GSK1349572B is a moderate activator of PXR in vitro and therefore could possibly cause induction of PXR target genes (e.g., CYP3A4) in vivo.

Methods

HepG2 cells were transfected with human PXR and were treated with dolutegravir (0.2 nM to 10 μM). Transcription of the reporter gene (luciferase) due to PXR activation was measured by a luminescence assay. The human PXR activator, rifampicin, was included as a positive control.

Results

Treatment of PXR transfected HepG2 cells with GSK1349572B, U23359/41/1 resulted in a maximum response that was 41.6-58.1% of the efficacious PXR activator, rifampicin.

Conclusion

- GSK1349572B is a moderate activator of PXR in vitro and therefore could possibly cause induction of PXR target genes (e.g., CYP3A4) in vivo.

07APK018

Evaluation of effect of GSK1349572 on mRNA levels of CYP genes in cultured human hepatocytes

This study indicated that:

- GSK134572 had little to no effect on the mRNA expression of CYP1A2, CYP2B6, and CYP3A4

Methods

Cultured Human hepatocytes were used as the test system. After the acclimation period, hepatocytes were treated with GSK1349572 (1, 5, 10, 20, 30, and 40 μM), vehicle control (0.1% DMSO), or prototypical inducers (35 μM β-Naphthoflavone [BNF], 1 mM phenobarbital [PB], or 20 μM rifampin [RIF]; concentrations to achieve maximal induction) once daily for two days.

Relative quantification (RQ) experiments were conducted to determine relative mRNA expression (treated versus control) of target genes. The specific mRNA level was quantitatively detected for the following genes: CYP1A2, CYP2B6, and CYP3A4 along with the housekeeping (non-inducible) gene glyceraldehydes 3-phophate dehydrogenase (GAPDH).

Results

BNF (35 μM) increased the CYP1A2 mRNA ratio of treated over control hepatocytes cultures by 6-fold. PB (1 mM) increased the CYP2B6 mRNA ration of treated over control hepatocytes cultures by 11-fold. RIF (20 μM) increased the CYP3A4 mRNA ratio of treated over control hepatocytes cultures by 7-fold. The level of induction observed following treatment with prototypical CYP inducers was consistent with the literature.

Treatment of human hepatocyte cultures with GSK1349572 had little to no effect on the mRNA expression of CYP1A2, CYP2B6, and CYP3A4 (see table below). The sample RQ calculated for each gene was <15% of the corresponding prototypical inducer RQ (8, 14, and 13% for CYP1A2, CYP2B6, and CYP3A4, respectively, [calculated using the highest RQ observed for any concentration divided by the RQ observed for the prototypical inducer]).

Effect of GSK1349572 and prototypical inducers on mRNA expression (ratio of treated over control*) following treatment of cultured human hepatocytes for 48 hours

	Fold Induction (ratio of treated over control)		
	Gene CYP1A2	Gene CYP2B6	Gene CYP3A4
1 µM GSK1349572	0.27	1.04	0.58
5 µM GSK1349572	0.50	1.27	0.74
10 µM GSK1349572	0.20	1.01	0.43
20 µM GSK1349572	0.24	1.55	0.53
30 µM GSK1349572	0.33	1.33	0.50
40 µM GSK1349572	0.26	1.00	0.86
Prototypical Inducer	6.23 (BNF)	11.34 (PB)	6.64 (RIF)
*controls are defined as 0.1% (v/v) DMSO			

Conclusion

- GSK134572 at concentrations up to 40 µM had little to no effect on the mRNA expression of CYP1A2, CYP2B6, and CYP3A4 in vitro.

CYP inhibition by GSK1349572

07APK020

Evaluation of inhibitory effect of GSK1349572 on CYP enzymes

(summary report of all preliminary studies conducted to evaluate the inhibitory potential of GSK1349572 on CYP enzymes)

These studies indicated that:

- No direct inhibition (IC50>33 µM) was observed for CYP's 2D6, 2C9, 2C19 or CYP3A4, using either the recombinant or pooled human liver microsome (PHLM) methods.
- For CYP1A2, an IC50 of 12.5 µM was observed in the recombinant assay, and an IC50 of >33 µM in the PHLM assay.
- No time-dependent inhibition for CYP3A4 was observed.

Methods

Pooled human liver microsomes (PHLM) and recombinant human enzymes were used as test systems. Tested concentrations of GSK1349572 in both systems were 0.033, 0.1, 0.33, 1, 3.3, 10, and 33 µM. The probe substrates for the recombinant enzyme system were: CYP1A2=> ethoxyresorufin, CYP2C9=> 7-Methoxy-4-trifluoromethylcoumarin-3-acetic acid, CYP2C19=> 3-Butyryl-7-methoxycoumarin,

CYP2D6=> 4-Methylaminomethyl-7-methoxycoumarin, CYP3A4=> 7-Benzyloxyquinoline. The positive controls for each CYP isoform are displayed below:

Assay	CYP1A2	CYP2C9	CY2C19	CYP2D6	CYP3A4
Positive Control and Final Conc Range (μM)	Miconazole 0-3.3 μM	Miconazole 0-3.3 μM	Miconazole 0-3.3 μM	Miconazole 0-3.3 μM	Miconazole 0-3.3 μM

The probe substrates for the PHLM system were: CYP1A2=> Phenacetin, CYP2C9=> Diclofenac, CYP2C19=> S-Mephenytoin, CYP2D6=> Bufuralol, CYP3A4=> (3 different controls) Atorvastatin, Nifedipine, Midazolam. The positive controls for each CYP isoform are displayed below:

Assay	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4	CYP3A4	CYP3A4
Positive Control and Final Range Conc. (μM)	Fluvoxamine 0-3.3 μM	Sulphaphenazole 0-3.3 μM	Ticlopidine 0-33 μM	Quinidine 0-3.3 μM	Ketoconazole 0-3.3 μM	Ketoconazole 0-3.3 μM	Ketoconazole 0-3.3 μM

Results

This report is a summary of all exploratory work performed to assess CYP inhibition potential for GSK1349572. Initial screening was performed for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 using recombinant enzymes and higher throughput fluorescence methods. At later stages, CYP inhibition was also examined using pooled human liver microsomes (PHLM) for both direct and time-dependent inhibition (TDI).

Conclusions

- No direct inhibition (IC50>33 μM) was observed for CYP's 2D6, 2C9, 2C19 or CYP3A4, using either the recombinant or pooled human liver microsome (PHLM) methods.
- For CYP1A2, an IC50 of 12.5 μM was observed in the recombinant assay, and an IC50 of >33 μM in the PHLM assay.
- No time-dependent inhibition for CYP3A4 was observed.

10DMW013

Evaluation of inhibitory effect of GSK1349572 on CYP enzymes

This study indicated that:

- There is unlikely to be clinically relevant inhibition of CYP enzymes in vivo based on the following findings:
    - GSK1349572 inhibited CYP3A4 with IC50 values of >54 μM.
    - GSK1349572 inhibited CYP2B6, 2C9, 2C19 and 2D6 with IC50 values of >100 μM.
    - GSK1349572 did not inhibit CYP1A2, 2A6 or 2C8, in vitro, up to concentrations of 100 μM.
    - Metabolism-dependent inhibition of CYP3A4 by GSK1349572 was observed, in vitro.
    - There was no metabolism-dependent inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 or 2D6.

Methods

Pooled human liver microsomes were used as the test system. Incubation conditions for the assay of the enzyme activities: CYP1A2, 2A6 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 have been described in a previous study or derived from previously published work.

Results

GSK1349572 inhibited CYP2B6, 2C9, 2C19, 2D6 in vitro but inhibition at the highest concentration tested (100 μM) was insufficient to calculate an IC50 (see table below). GSK1349572 inhibited the in vitro metabolism of the probe substrate atorvastatin by CYP3A4 with a calculated IC50 of 54 μM. Inhibition of CYP3A4 metabolism of the probe substrate nifedipine at the highest concentration tested (100 μM) was insufficient to calculate an IC50.

Target	Inhibition IC_{50} (μM)	Metabolism-Dependent Inhibition IC_{50} (μM)
CYP1A2	None	None
CYP2A6	None	None
CYP2B6	>100	None
CYP2C8	None	None
CYP2C9	>100	None
CYP2C19	>100	None
CYP2D6	>100	None
CYP3A4 (atorvastatin)	>54	33
CYP3A4 (nifedipine)	>100	65
CYP3A4 (midazolam)[a]	[a]	[a]

Conclusions

- GSK1349572 inhibited CYP3A4 with IC50 values of >54 μM.
- GSK1349572 inhibited CYP2B6, 2C9, 2C19 and 2D6 with IC50 values of >100 μM.
- GSK1349572 did not inhibit CYP1A2, 2A6 or 2C8, in vitro, up to concentrations of 100 μM.
- Metabolism-dependent inhibition of CYP3A4 by GSK1349572 was observed, in vitro.
- There was no metabolism-dependent inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 or 2D6.

UGT inhibition by GSK1349572

09DMR031

Evaluation of inhibition of UGT1A1 and UGT2B7 by GSK1349572

This study indicated that:

- GSK1349572 was not an inhibitor of UGT2B7 at concentrations up to 100 μM.
- Inhibition of UGT1A1 was observed, however, inhibition at the highest concentration tested was insufficient to calculate an IC50 value (IC50 >100 μM).

Methods

UGT1A1 and UGT2B7 Supersomes were used as the test systems. Final concentrations of GSK1349572 in the incubations were 0.1, 0.33, 1, 3.3, 10, 33 and 100 μM.

Positive control incubations with atazanavir (UGT1A1 inhibitor) or gemfibrozil (UGT2B7 inhibitor) and incubations without inhibitors (containing 1% v/v methanol only) were also performed, as well as incubations without UDPGA (at the highest concentration of GSK1349572, atazanavir, or gemfibrozil) to determine any UDPGA-independent metabolite formation.

Results

Some inhibition of human UGT1A1 activity by GSK1349572 was observed. However, at the highest concentration of GSK1349572 tested, 100 μM, the activity of UGT1A1 was 73% of the no inhibitor control, thus, the degree of inhibition was insufficient to calculate an IC50 (IC50 >100 μM). GSK1349572 did not inhibit UGT2B7 at concentrations up to 100 μM.

Conclusions

- GSK1349572 was not an inhibitor of UGT2B7 at concentrations up to 100 μM.
- Inhibition of UGT1A1 was observed, however, inhibition at the highest concentration tested was insufficient to calculate an IC50 value (IC50 >100 μM).

4.2 Pharmacogenomics Review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	204790
Submission Date	12/17/2012
Applicant Name	Viiv Healthcare
Generic Name	Dolutegravir
Proposed Indication	HIV Infection
Primary Reviewer	Jeff Kraft, PhD
Secondary Reviewer	Mike Pacanowski, PharmD, MPH

1 Background

Dolutegravir is an orally administered integrase inhibitor designed to block the action of the Human Immunodeficiency Virus (HIV) integrase, which is responsible for insertion of the viral genome into host cell DNA. Dolutegravir is being developed for the treatment of HIV infection in adults and children over 12 years of age.

Dolutegravir is primarily metabolized by UDP-glucuronosyltransferase 1A1 (UGT1A1) with minor contributions from cytochrome P450 enzymes (10-15%) such as CYP3A4 and CYP3A5. As such, the sponsor included a meta-analysis of several clinical pharmacology trials to investigate the effects of UGT1A1, CYP3A4, CYP3A5, and NR1I2 (pregnane x receptor may influence the expression of CYP3A4) on the PK of dolutegravir.

The purpose of this review is to evaluate the genotype information submitted by the sponsor regarding genotype effects on the disposition of dolutegravir.

2 Submission Contents Related to Genomics

The sponsor submitted the following reports and datasets related to the pharmacogenetic (PGx) of dolutegravir PK.

Report ID	***Title***	***Datasets***
ING116265	PGx432 Evaluation of the effect of UGT1A1 polymorphisms on dolutegravir PK: meta-analysis of Phase I studies ING111521, ING111603, ING111604,ING112934, ING113068, ING113096, ING114005, ING114819, ING113099	N/A

A summary of the clinical pharmacology studies included in the PGx meta-analysis is provided in table 1 below. Studies eligible for the meta-analysis were multiple-dose studies with intensive

PK assessments (Phase 1 or Phase 2a) that used a 50 mg dose of dolutegravir once daily (tablet formulation); other studies were excluded because formulation effects and nonlinear PK could influence the ability to identify potential PGx effects.

DNA samples were collected from subjects who consented to optional participation in PGx research during each study. A total of 104 of the 139 (75%) subjects participated, and 89 unique subjects were included in the analysis because 3 had insufficient DNA, 1 failed genotype QC, 6 participated in multiple studies (accounting for 14 total subjects), and 3 had no PK data.

Table 1: Clinical Pharmacology Studies Utilized for PGx Analysis

Study	***Description***	***Total N Dosed with 50mg Tablet QD***	***PGx N***
ING111521	Dose-ranging, 10-day, repeat dose, placebo-controlled monotherapy study in HIV-1 infected adults; fasting.	10	10
ING111603	Open-label, repeat dose, two-period, fixed-sequence, drug-drug interaction study with etravirine in healthy subjects; with moderate fat meal	16	10
ING111604	Open-label, repeat-dose, single sequence, three-period, drug-drug interaction study with tenofovir in healthy subjects; fasting	16	11
ING112934	Randomized, repeat dose, open-label, two-period, two-sequence drug-drug interaction study with etravirine, and lopinavir/ritonavir or darunavir/ritonavir in healthy subjects; with moderate fat meal	17	9
ING113068	Open-label, repeat dose, single sequence, drug-drug interaction study with fosamprenavir/ritonavir in healthy subjects; fasting	12	8
ING113096	Open-label, repeat dose, single sequence, three-period drug-drug interaction study with tipranavir/ritonavir in healthy subjects; with moderate fat meal	18	16
ING114005	Open label, repeat dose, single sequence, three period drug-drug interaction study with efavirenz in healthy subjects; fasting	12	9
ING114819	Open-label, randomized, three-arm, parallel, placebo-controlled study to evaluate the effect of DTG on GFR in healthy subjects; fasting	12	7
ING113099	Open-label, repeat dose, two-arm fixed sequence, drug-drug interaction study with rifampin and rifabutin in healthy subjects; fasting	26	24
TOTAL		**139**	**104**

DNA samples were analyzed for genetic variants in the genes encoding UGT1A1, CYP3A4, CYP3A5, and NR1I2. Table 2 lists the variants investigated and methods utilized.

For UGT1A1, subjects were classified as low (*28/*28, *28/*37, or *37/*37), reduced (*1/*28, *1/*37, *28*/*36, *36/*37), or normal UGT1A1 activity (*1/*1, *1/*36, *36/*36) and analysis was done to compare normal functioning subjects to those with either low or reduced function.

Table 2: Genes, Polymorphisms, and Genotyping Methods for the PGx Analysis

Gene	***Polymorphism***	***rs Number***	***Genotyping Method***	***Functional Effect***
UGT1A1	Promoter region TA repeat [*28, *36, *37]	rs8175347	PCR & Electrophoresis	*28 (TA)7- and *37 (TA)8 result in a reduced level of UGT1A1 activity; *36 (TA)5 results in increased UGT1A1 activity.
UGT1A1	211G>A ; Gly71Arg[*6]	rs4148323	DMET Plus Array	A *6 allele results in reduced UGT1A1 activity
CYP3A4	-392A>G [*1B]	rs2740574	DMET Plus Array	Unclear, studies showing both increased and decreased CYP3A4 activity of G (*1B) allele
CYP3A5	6986A>G [*3]	rs776746	DMET Plus Array	G (*3) allele results in severely decreased CYP3A5 activity
CYP3A5	14690G>A [*6]	rs10264272	DMET Plus Array	A *6 allele results in no, or severely decreased CYP3A5 activity
CYP3A5	27127->T [*7]	rs41303343	DMET Plus Array	T insertion (*7) allele results in severely decreased CYP3A5 activity
NR1I2	–25385C>T	rs3814055	DMET Plus Array	One study suggests T allele results in lower NR1I2 expression; second study suggests T allele results in increased NR1I2 activity following rifampicin treatment
NR1I2	7635A>G	rs6785049	DMET Plus Array	Rifampicin causes 2-fold induction of CYP3A4 activity in subjects carrying GG vs AA genotypes
NR1I2	8055C>T	rs2276707	DMET Plus Array	Rifampicin causes 2-fold higher intestinal CYP3A activity in subjects carrying CT or TT genotypes compared to those carrying the CC genotype

Comment: The reviewer verified that predicted metabolizer status was correctly assigned based on UGT1A1 genotype, but did not replicate the sponsor's analyses.

3 Key Questions and Summary of Findings

3.1 Does UGT1A1 phenotype have a clinically significant effect on the PK of dolutegravir?

No. While AUC and Cmax increased and CL/F of dolutegravir decreased in subjects with low UGT1A1 activity, the therapeutic index of dolutegravir is wide and adverse reactions are mild and not associated with higher exposures. Therefore, increased exposure of dolutegravir by conferring poor metabolizer status of UGT1A1 would not have clinically significant effects. Additionally, dolutegravir was given 50mg twice daily to ~200 subjects with raltegravir resistance and no specific safety issues were identified between cohorts despite the increased dolutegravir exposure.

The two UGT1A1 variants genotyped were used to predict UGT1A1 functional activity, the distribution of which is summarized in the table below.

Table 3: Predicted UGT1A1 Enzyme Activity

Marker rs8175347	***Marker rs8175347***	***Predicted Enzyme Activity***	***Overall (N=89)***
*1/*1	*1/*1	Normal	40 (45)
*1/*36	*1/*1	Normal	1 (1)
		Normal Subtotal	**41 (46)**
*1/*1	*1/*6	Reduced	3 (3)
*1/*28	*1/*1	Reduced	31 (35)
*1/*37	*1/*1	Reduced	1 (1)
*28/*36	*1/*1	Reduced	4 (4)
*36/*37	*1/*1	Reduced	1 (1)
		Reduced Subtotal	**40 (44)**
*28/*28	*1/*1	Low	6 (7)
*28/*37	*1/*1	Low	1 (1)
		Low Subtotal	**7 (8)**
*36/*36	*1/*1	Unknown	1 (1)

Analysis of covariance was used to evaluate the main effects of genotype and other independent variables on CL/F, Cmax or AUC using a mixed effect model with age, gender, fasting status, study, and genetic marker as fixed effects, and subject as a random effect.

ANCOVA analysis showed that CL/F decreased, while AUC(0-τ) and Cmax increased, in subjects with low and reduced UGT1A1 activity compared to subjects with normal UGT1A1 activity. In subjects with low UGT1A1 activity compared to subjects with normal UGT1A1 activity, the effect was greater. For all UGT1A1 genotype effects the maximum expected increase is less than a doubling of exposure (based on upper limit of 92% CI).

Table 4: ANCOVA Results for PK Parameters and UGT1A1 Functional Activity

PK Parameter	***Geometric LS Mean***	***Comparison***	***Geometric Mean***

	Normal Activity (N=41)	*Reduced Activity (N=40)*	*Low Activity (N=7)*		*Ration (92% CI)*
CL/F (L/hr)	1.09	0.936	0.749	Low+Reduce vs. Normal	0.765 (0.659-0.889)
				Low Vs. Normal	0.684 (0.543-0.862)
AUC (0-INF) (ug*hr/mL	45.7	53.4	66.8	Low+Reduce vs. Normal	1.307 (1.125-1.518)
				Low Vs. Normal	1.462 (1.160-1.842)
Cmax (ug/mL)	3.45	3.89	4.57	Low+Reduce vs. Normal	1.221 (1.063-1.402)
				Low Vs. Normal	1.323 (1.068-1.638)

3.2 Does CYP3A4, CYP3A5, or NR1I2 genotype have a clinically significant effect on the PK of dolutegravir?

No. Analyses exploring the effects of the number of risk alleles on PK parameters did not reveal any statistically significant results for the genes CYP3A4, CYP3A5, and NR1I2.

Genotypes for CYP3A4, CYP3A5, or NR1I2 were evaluated as numeric variables, by coding them as 0, 1, or 2, based on the number of risk alleles presented for each marker. The final ANCOVA model included genotype as the number of risk alleles, with sex and study ID as fixed effects. Results showed that no marker was significantly associated with any PK parameter tested (AUC, CL/F, or Cmax).

Table 5: ANCOVA Analysis for CYP3A4, CYP3A5, and NR1I2 and PK parameters

Gene	*Marker ID*	*PK Parameter*	*Effect Per Allele*	*95% CI*	*P Value*
CYP3A4	rs2740574	CL/F	1.005	0.901-1.120	0.913
		AUC(0-τ)	0.995	0.893-1.109	0.913
		Cmax	0.97	0.886-1.063	0.438
CYP3A5	rs776746	CL/F	0.991	0.926-1.060	0.738
		AUC(0-τ)	1.009	0.943-1.080	0.738
		Cmax	1.021	0.964-1.081	0.393
	rs10264272	CL/F	1.055	0.804-1.383	0.634
		AUC(0-τ)	0.948	0.723-1.243	0.634
		Cmax	0.889	0.705-1.121	0.249
	rs41303343	CL/F	0.976	0.663-1.437	0.878
		AUC(0-τ)	1.025	0.696-1.509	0.878
		Cmax	0.995	0.717-1.382	0.972
NR1I2	rs3814055	CL/F	0.928	0.836-1.029	0.122
		AUC(0-τ)	1.041	0.972-1.196	0.123
		Cmax	1.077	0.987-1.175	0.082

	rs6785049	CL/F	0.989	0.882-1.109	0.814
		AUC(0-τ)	1.011	0.901-1.134	0.814
		Cmax	1.042	0.946-1.148	0.325

4 Summary and Conclusions

Decreased UGT1A1 enzyme activity was associated with a decrease in CL/F and increases in both AUC (0-INF) and Cmax as compared to subjects with normal enzyme function. The exposure difference observed low/reduced function subjects was within the range of those observed for DDIs that have no dose recommendations and within the range of exposures observed with 50 BID, for which we have safety data. The therapeutic index of dolutegravir is wide and adverse reactions are mild and not associated with higher exposures, so increased exposure of dolutegravir by conferring poor metabolizer status of UGT1A1 is not expected to have clinically significant effects.
Additional secondary analyses were performed to investigate the effects of the number of CYP3A4, CYP3A5, and NR1I2 variant alleles on PK parameters did not reveal any statistically significant associations.

5 Recommendations

None.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

12.3 Pharmacokinetics
In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

Pharmacometrics Reviewer: Jeffry Florian

Pharmacometrics Team Leader: Yaning Wang

Clinical Pharmacology Reviewer: Su-Young Choi

Clinical Pharmacology Team Leader: Shirley Seo

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Does the dolutegravir (DTG) exposure-response relationship with virologic outcome (percent of subjects <50 HIV-1 copies/mL at week 48) support the selected DTG dose in treatment-naïve, treatment-experienced/integrase naïve, and treatment-experienced/integrase-experienced HIV-1 infected subjects?

Yes, the trials conducted by the applicant in treatment-naïve and treatment-experienced/integrase-naïve subjects support DTG 50 mg QD. DTG dose adjustments to 50 mg BID are recommended for subjects on regimens containing strong inducers such as efavirenz, tipranvir, and fosamprenavir (see the Clinical Pharmacology Review, Executive Summary, above). The exposure-response analysis and observations in treatment-experienced/integrase-naïve subjects support that no dose adjustment is necessary for subjects with severe renal impairment despite a predicted 46% reduction in C_{0h}.

In addition, the results of the applicant's Phase IIb and Phase III trial in treatment-experienced/integrase-experienced subjects support the use of DTG 50 mg BID in this population. It is not anticipated the higher doses of DTG (i.e., 100 mg BID) would result in substantial improvements in efficacy due to saturable absorption as well as a lack of safety DTG data at doses higher than 50 mg BID. Likewise, while coadministration with strong inducers is anticipated to lower DTG exposures, dose adjustments are not recommended in this population due to the same reasons (e.g., saturable absorption and lack of safety data at higher DTG doses [primary nonclinical toxicity was gastrointestinal related: see Pharmacology/Toxicology Review]).

Details of the exposure-response analyses for each of these populations is described in more detail below.

Treatment-naïve

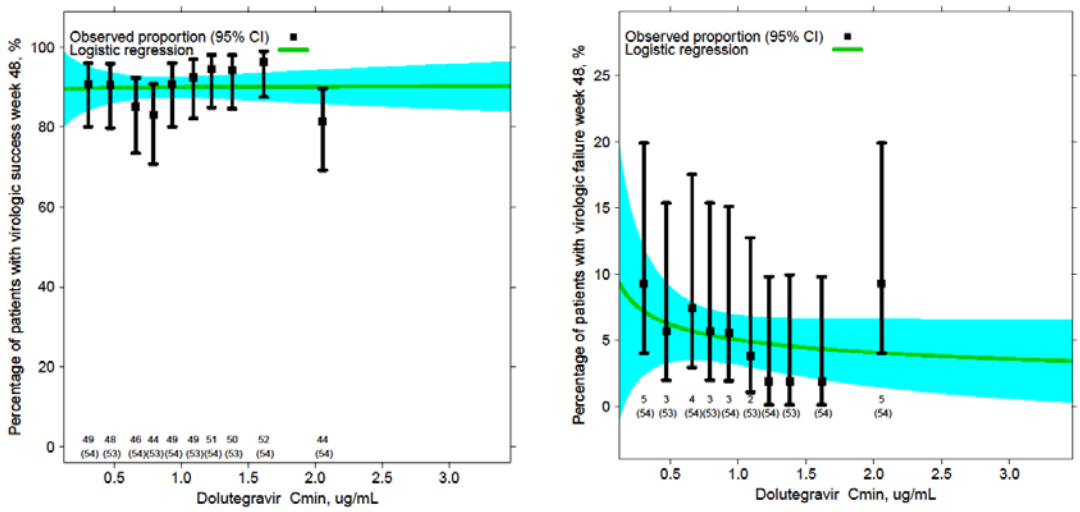
The antiviral activity and pharmacokinetics of DTG was evaluated as a short-term Monotherapy in ING111521, a Phase IIa dose-ranging study. In this study, integrase-naïve subjects who were off antiretroviral therapy were administered DTG 2, 10, or 50 QD or placebo for 10 days. A dose-response reduction in HIV-1 RNA from baseline was observed across the three doses compared to placebo. Based on this data, the EC_{90} was

estimated at 0.32 µg/mL and the geometric C_0 values for 2, 10 and 50 mg was 0.04, 0.19, and 0.83 µg/mL, respectively. The range of exposures for 50 mg QD was 0.60 to 1.17 µg/mL, all of which were above the estimated EC_{90}.

The applicant conducted three Phase IIb and III trials (ING112276, ING113086, and ING114467) in treatment-naïve HIV-1 infected subjects to support the selected DTG 50 mg QD dose. ING114467 did not collect DTG PK and was excluded from this exposure-response analysis. ING112276 included DTG PK from 141 subjects (out of 155) administered DTG 10, 25, or 50 mg QD with a background NRTI regimen of tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC). ING113086 included DTG PK from 403 subjects (out of 411) administered DTG 50 mg QD with a background NRTI regimen of TDF/FTC or ABC/3TC. Using DTG PK data from ING112276 and ING3086, a flat exposure response was observed over the DTG exposure range (Figure 1). Geometric mean C_{min} for DTG 10, 25, and 50 mg QD was 0.31, 0.53, and 1.11 µg/mL, respectively, with a model predicted response rate of 90-91% over the exposure range. These predictions are similar to those observed from the combined study results in subjects with PK data available (89-91% over DTG 10, 25, and 50 mg QD). The predicted virologic response in the lowest DTG exposure bin was 90% which was within the range of response rates for all other bins with higher DTG exposure (82-94%).

The only significant factors for predicting virologic success were baseline viral load (higher baseline viral load associated with a lower response rate) and baseline $CD4^+$ count (lower $CD4^+$ count was associated with a lower response rate); however, these are known covariates that impact response and do not necessitate any DTG dose adjustments. A flat exposure-response relationship was also identified between virologic failure and DTG C_{0h} (Figure 1). Similar flat-exposure response relationships were observed for virologic success and virologic failure when using DTG AUC as the independent variable. There was insufficient data regarding baseline DTG susceptibility (e.g., $IC_{50;}$ n=20) to evaluate relationships between IC_{50} and response from the treatment-naïve trials.

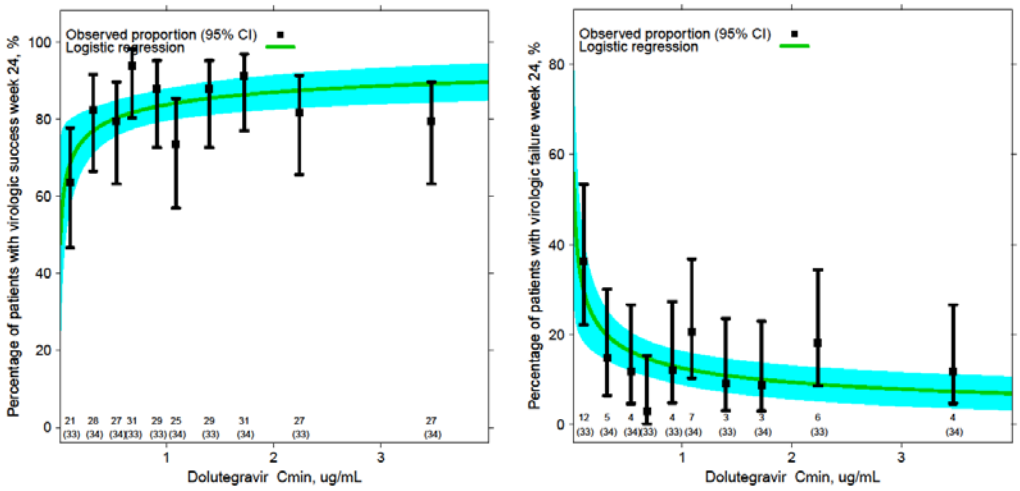
Figure 1: Percentage of Subjects Achieving Virologic Success (<50 Copies/mL, left) and Virologic Failure (right) Versus DTG C_{0h} from ING112276 and ING3086.



Treatment-experienced/integrase-naive

The applicant conducted one Phase III trial (ING111762) in treatment-experienced/integrase-naive HIV-1 infected subjects to support the selected DTG 50 mg QD dose. ING111762 included DTG PK from 335 subjects (out of 354) administered DTG 50 mg QD with an investigator selected background consisting of at least two drugs, one of which was considered fully active by susceptibility assessment. Based on initial general additive model (GAM) evaluation, subjects with one or more PK samples below the limit of quantification, baseline $CD4^+$ count, and DTG C_{0h} were identified as factors influencing virologic success. Evaluation of response with respect to IC_{50} could not be performed for this trial due to the limited number of subjects with baseline IC_{50} data available (n=22). The univariate exposure-response for virologic success and virologic failure versus DTG C_{0h} is shown below in Figure 2 and confirms the initial observation that subjects with lower exposure, primarily in the lowest exposure decile (median C_{0h} in first decile was 0.10 µg/mL), had lower response rates (64%) compared to the reminder of the population (response rates ranging between 73-94% across the remaining deciles). Similarly, there was a higher treatment failure rate in the lowest decile (36%) compared to the remaining deciles (failure rates ranging between 3-21%). Of note, the DTG C_{0h} in this first bin is less than the median DTG C_{0h} observed following DTG 10 mg QD.

Figure 2: Percentage of Subjects Achieving Virologic Success (<50 Copies/mL) Based on All Subjects Versus DTG C_{0h} from ING111762.



Closer inspection of the subjects with the lowest DTG C_{0h} indicated that such subjects were more likely to have one or more on treatment BLQ measurement or have been on a CYP3A inducer (e.g., tipranavir, fosamprenavir, efavirenz). In all, there were 28 subjects with one or more DTG PK BLQ measurements on treatment and 26 subjects on an inducer (5 subjects had a BLQ measurement and were on an inducer for a total of 49 subjects with either a BLQ measurement or on an inducer). Sixteeen of the 28 subjects (57%) were in the first two DTG exposure deciles while 20 of 26 (77%) of subjects on an inducer were in the first two DTG exposure deciles. As expected, the summary DTG PK for these subgroups was lower than that observed for the remainder of the population (Table 1). In addition, the observed geometric C_{0h} for subjects with one or more BLQ measurement (possibly indicative of a lack of adherence) was overall similar to the observed DTG exposures in subjects on a CYP3A inducer in their regimen.

Table 1: Geometric DTG C_{0h} and Response Rate for Subjects from ING111762 According to Whether the Subject was on An Inducer or Had A BLQ Measurement (19 subjects with No Concentration Measurements Were Excluded; 5 Subjects with Both BLQ Measurement and on an Inducer)

Category	Geometric Mean C_{0h}, µg/mL	Response %
DTG (all, n=335)	0.85	79%
DTG (no inducer/no BLQ, n=286)	1.04	81%
DTG (BLQ, n=28)	0.24	57%
DTG (inducer, n=26)	0.20	73%
DTG (EFV, n=13)	0.17	62%
DTG (FPV, n=11)	0.28	73%
DTG (DRV, n=135)	0.70	84%
DTG (ATV or ATV/r, n=48)	2.33	82%
DTG (no inducer/no BLQ/ATV/DRV, n=117)	1.01	81%

Based on the observed PK and response data from the trial, the applicant proposed using DTG 50 mg BID in subjects with a background regimen including an inducer such as efavirenz or tipranavir. This is supported by the PK observations and response data from ING111762. The applicant did not propose dose adjustment for fosamprenavir as the response rate in this subgroup was closer to that of the overall treatment population. However, due to the lower PK observed in this treatment group, the review team recommends increasing the DTG dose to 50 mg BID when coadministered with fosamprenavir. This recommendation is based on the PK and the slightly lower response rate observed among subjects coadministered fosamprenavir.

Also included in the summary table was the DTG PK and response when coadministered with DRV, another CYP3A inhibitor. DTG PK was slightly reduced in this group compared to the treatment population (0.70 versus 1.01 µg/mL [population C_{0h} after excluding subjects on strong or moderate inducers and inhibitors]; 30% reduction which is also similar to the 38% reduction in C_{τ} observed in the DRV/r DDI study) but there was no observed difference in the response rate (84% versus 81%). As such, the review team does not recommend an increase in DTG dose from 50 mg QD to 50 mg BID when

coadministered with DRV. These recommendations are discussed in more detail in the Executive Summary and QBR of the Clinical Pharmacology review.

Finally, the review team considered the renal impairment results from ING113125 in the context of the exposure-response analysis presented above. This single dose (50 mg) renal impairment study, performed in subjects with severe renal impairment (creatinine clearance 15-30 mL/min; n=8) demonstrated lower AUC, C_{max} and C_{24} (40%, 23%, and 43% lower) compared to matched healthy volunteers (n=8). Steady state C_{0h} values were calculated for each subject using noncompartmental apparent clearance and volume of distribution for each subject in ING113125 as well as the population mean oral absorption rate determined by the sponsor during their population PK analysis (2.24 h^{-1}). Based on the above assumptions, steady state geometric mean C_{0h} values for subjects with severe renal impairment and healthy volunteers were obtained, demonstrating a similar decrease in steady state trough concentration (46%) compared to the difference observed at 24-hours post dose from the single dose study. The anticipated decrease in C_{0h} for subjects with severe renal impairment (46%: C_{0h} 0.55 μg/mL) is between that of DRV, for which the review team recommends no dose adjustment, and the DTG exposures observed for strong inducers (decreases of 70% or more) for which the review team is recommending a dose adjustment to 50 mg BID. This predicted C_{0h} is similar to that observed from DTG 25 mg QD in ING112276 and is above the estimated EC_{90} from the monotherapy study (ING111521). In addition, the exposure-response relationship predicts only a modest difference in response for a C_{0h} of 0.55 μg/mL (80%) versus 1.01 μg/mL (84%). Finally, DTG AUC and C_{τ} predictions from the sponsor's population PK model support that subjects with normal, mild, and moderate renal impairment have similar DTG exposure (Table 2). All together, the available data supports that a DTG dose adjustment is not necessary in subjects with severe renal impairment.

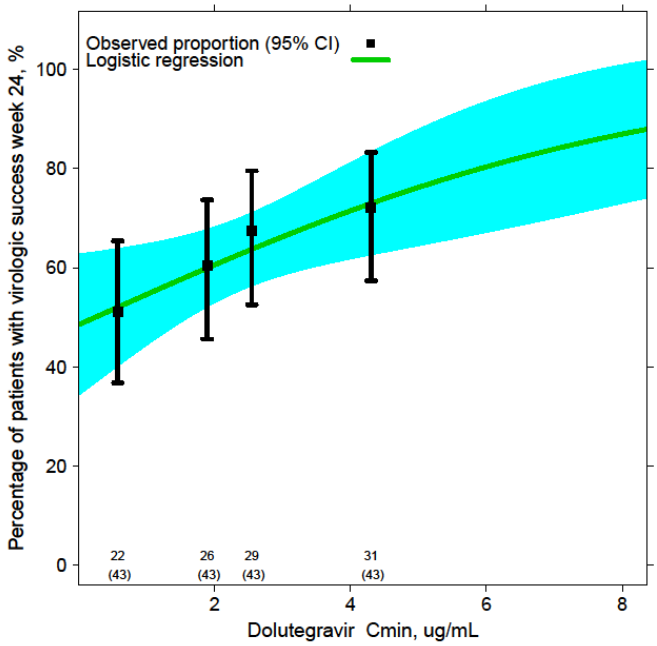
Table 2: Simulated DTG AUC, C_{max}, and C_τ Based on Baseline Creatinine Clearance in Treatment-Experienced Subjects (ING112961 and ING111762; only Subjects Administered 50 mg QD)

	Renal impairment	N	Cmax (µg/mL)	Cτ (µg/mL)	AUCτ (µg/mL·hr)
50 mg QD	Normal CrCL ≥ 90 mL/min	287	3.11 (3.02-3.20)	0.824 (0.764-0.888)	43.3 (41.5-45.2)
	Mild CrCL 60 to < 90 mL/min	71	3.43 (3.21-3.65)	0.835 (0.693-1.01)	46.6 (42.1-51.5)
	Moderate CrCL 30 to < 60 mL/min	8	3.41 (2.73-4.27)	0.794 (0.461-1.37)	45.9 (33.5– 63.1)
	Severe CrCL 15 to < 30 mL/min	1	3.64	0.857	48.7
50 mg BID	Normal CrCL ≥ 90 mL/min	152	4.10 (3.91-4.29)	2.10 (1.95-2.26)	37.1 (35.1-39.2)
	Mild CrCL 60 to < 90 mL/min	45	4.37 (4.04-4.93)	2.21 (1.94-2.51)	39.3 (35.8-43.3)
	Moderate CrCL 30 to < 60 mL/min	9	4.04 (3.34-4.88)	1.88 (1.51-2.35)	35.8 (29.5-43.5)
	Severe CrCL 15 to < 30 mL/min	1	4.23	2.36	40.2

Treatment-experienced/integrase-experienced

The applicant conducted a Phase IIb (ING112961) and III trial (ING112574) in treatment-experienced/integrase-experienced HIV-1 infected subjects to support the selected DTG 50 mg BID dose. ING112961 included DTG PK from 51 subjects (out of 51) administered DTG 50 mg QD or BID given in combination with at least one active agent in the optimized background. ING112574 included DTG PK from 183 subjects (out of 183 subjects; efficacy data was only available through week 24 for 114 subjects) administered DTG 50 mg BID in combination with at least one active agent in the optimized background. Based on initial analysis, DTG C_{0h}, baseline $CD4^+$ count (lower baseline associated with lower response), and the presence of Q148 substitutions with 2 or more additional integrase inhibitor mutations were identified as predictors of virologic response. Upon closer inspection the dependence of C_{0h} as a predictive factor for virologic response at week 24 was driven by the 50 mg QD treatment arm from ING112961. The response observed in the lowest quartile (51%) was, as would be expected, comprised of subjects predominantly from the 50 mg QD treatment arm (41%, n/N=11/27, C_{0h} 1.14 µg/mL) while a higher response rate was observed in the upper quartiles consisting of subjects administered 50 mg BID (response rate 63-68%; C_{0h} 2.29 µg/mL). This observation supports the use of 50 mg BID in the treatment-experienced/integrase-experienced population.

Figure 3: Percentage of Subjects Achieving Virologic Success (<50 Copies/mL) Versus DTG C_{0h} from ING112961 and ING112574. Two DTG Doses (50 mg QD and 50 mg BID) Were Included in This Analysis (Geometric Mean C_{0h} 1.14 and 2.29 µg/mL, Respectively)



If the subjects receiving DTG 50 mg QD are removed from the analysis, a relationship between inhibitory quotient (IQ) values [the IQ is the ratio of C_{0h} (exposure) at steady state and EC_{50} (a measurement of the ability of DTG to inhibit HIV-1 virus)] and virologic success was observed (Figure 4); however, this relationship is primarily dependent on the baseline susceptibility of the virus and to a lesser extent DTG exposure. This observation is illustrated in Table 3 where a 7-fold difference in EC_{50} was noted between the first and fourth inhibitory quotient compared to a 2-fold difference in C_{0h} across the same quartiles. A similar relationship was observed between treatment response and fold change (higher fold change values are associated with decreased susceptibility and higher EC_{50} values, which is why the relationship is inverted compared to the IQ analysis).

Figure 4: Percentage of Subjects Achieving Virologic Success (<50 Copies/mL) Versus DTG IQ (left) and Fold Change (right) from ING112961 and ING112574 (only 50 mg BID).

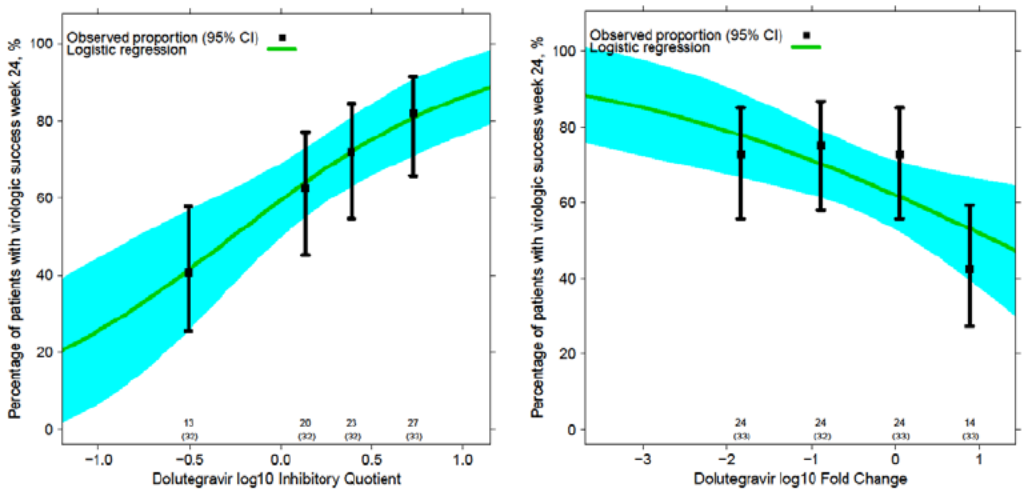


Table 3: Median DTG C_{0h} and IC_{50} for Each IQ Quartile from ING112961 and ING112574 (only 50 mg BID)

Quartile	C0h, µg/mL	EC50 µg/mL
1st	1.84	5.11
2nd	2.25	1.38
3rd	2.34	0.96
4th	3.86	0.71

This observation is further illustrated by evaluating the inhibitory quotient values for responders compared to nonresponders (1.09 versus 1.84) compared to the geometric mean C_{0h} (2.48 versus 2.31 µg/mL). Essentially, responders and nonresponders receiving DTG 50 mg BID had similar exposures, but divergent responses. A final approach for illustrating that baseline susceptibility was the determinant factor in response in this population is shown in Table 4. A decrease in overall response rate was observed between those subjects with a Q148 mutation and one or more additional integrase inhibitor mutations (19-43%) and the remaining subjects (74-83%) despite similar exposure across the treatment groups (DTG C_{0h}: 2.26-2.53 µg/mL). In contrast, a decreasing IQ trend was observed across the categories which must be driven by IC_{50} based on how IQ is defined. The observations in this table do suggest that if IQ is the primary efficacy variable to consider then increasing exposure 3-fold in subjects with a

Table 4: Geometric Mean DTG C_{0h}, IQ, and Response Based on Four Mutation Categories from ING112961 and ING112574 (only 50 mg BID)

Category	IQ	C_{0h}, µg/mL	Outcome
[1] Q148+2 or 2+ primary	0.42	2.26	19% (3/16)
[2] Q148 + 1	0.70	2.30	43% (10/23)
[3] All groups with other mutations	2.07	2.53	83% (39/47)
[4] No primary mutations	2.92	2.31	74% (28/38)

The review team evaluated the following dosing scenarios to determine if alternative DTG dosing regimens could improve the response rate in this population: i) 100 mg BID; ii) 50 mg TID; and iii) 100 mg TID. A population mean C_{0h} for each of these regimens was calculated based on the posthoc PK parameter estimates from the sponsor's population PK model, data from ING114005 that demonstrated increasing DTG from 50 mg to 100 mg resulted in only a 41% and 51% increase in AUC and C_{24}, respectively, and assuming the alterations from BID to TID dosing would not alter DTG bioavailability for a given dose. Based on these assumptions, it was identified that additional changes to the dosing frequency may be the most appropriate means of increasing exposure in subjects while limiting the cumulative total DTG dosing. DTG 50 mg TID was predicted to result in a C_{0h} of 3.53 µg/mL compared to 3.04 µg/mL for DTG 100 mg BID. Based on these increases in exposure, the above model predicts an 8-9% improvement in response for subjects with EC_{50} values between 3.48 to 8.66 µg/mL.

Table 5: Predicted C_{0h} and Response Rate in Treatment-Experience/Integrase-Experienced Subjects Based on Various Baseline Viral EC_{50} Values

	C0h	EC50=8.66 ug/mL		EC50=3.48 ug/mL		EC50=1.15 ug/mL	
		IQ	Response (%)	IQ	Response (%)	IQ	Response (%)
50 mg BID	2.01	0.23	36.8	0.58	50.8	1.75	67.7
100 mg BID	3.04	0.35	43.1	0.87	57.3	2.64	72.8
50 mg TID	3.53	0.41	45.3	1.01	59.5	3.07	74.7
100 mg TID	5.33	0.62	52.1	1.53	65.6	4.63	79.2

There are concerns with the following analysis. Specifically, it is uncertain if increasing the exposure will achieve the predicted increase in response rate given the limited available data in subjects with Q148 substitutions with 1 or more additional integrase inhibitor mutations. This analysis is based on adjusting the DTG dose to overcome the viral EC_{50}, but it is uncertain if this will be sufficient to improve the response in those

subjects at the outer end of the susceptibility distribution (i.e., subjects with Q148 substitutions). Also, the contribution from confounding factors such as baseline $CD4^+$ count could not be accounted for in the above analysis. Baseline $CD4^+$ count was identified as the strongest predictor of treatment success, and it is a known predictive factor for response for HIV treatment. However, subjects with baseline $CD4^+$ count < 50 cells/μL were also preferentially represented among subjects with Q148 substitutions with 2 or more additional integrase inhibitor mutations (10 of 15 subjects; 67%) compared to all other subjects (33 out of 114 subjects; 29%). This substitution, as previously stated, was also associated with a higher baseline EC_{50}; higher folds change values, and decreased response.

Ultimately, the review team did not recommend evaluation of a higher DTG dose in such subjects due to the limited available data in subjects with Q148 substitutions and concerns about DTG safety with local gastrointestinal exposure. While no exposure-related safety relationships were identified for DTG (see the response in Key Question 1.1.2), 50 mg BID was the highest DTG evaluated in HIV-1 infected patients. Increasing the dose to 100 mg BID or 50 mg TID was considered not to substantially improve patient response given currently available efficacy data and uncertainty in the safety with higher doses. This analysis will be reevaluated pending the submission of additional clinical data from the sponsor (VIKING-4: 40 additional treatment-experienced/integrase-experienced subjects treated with 50 mg BID).

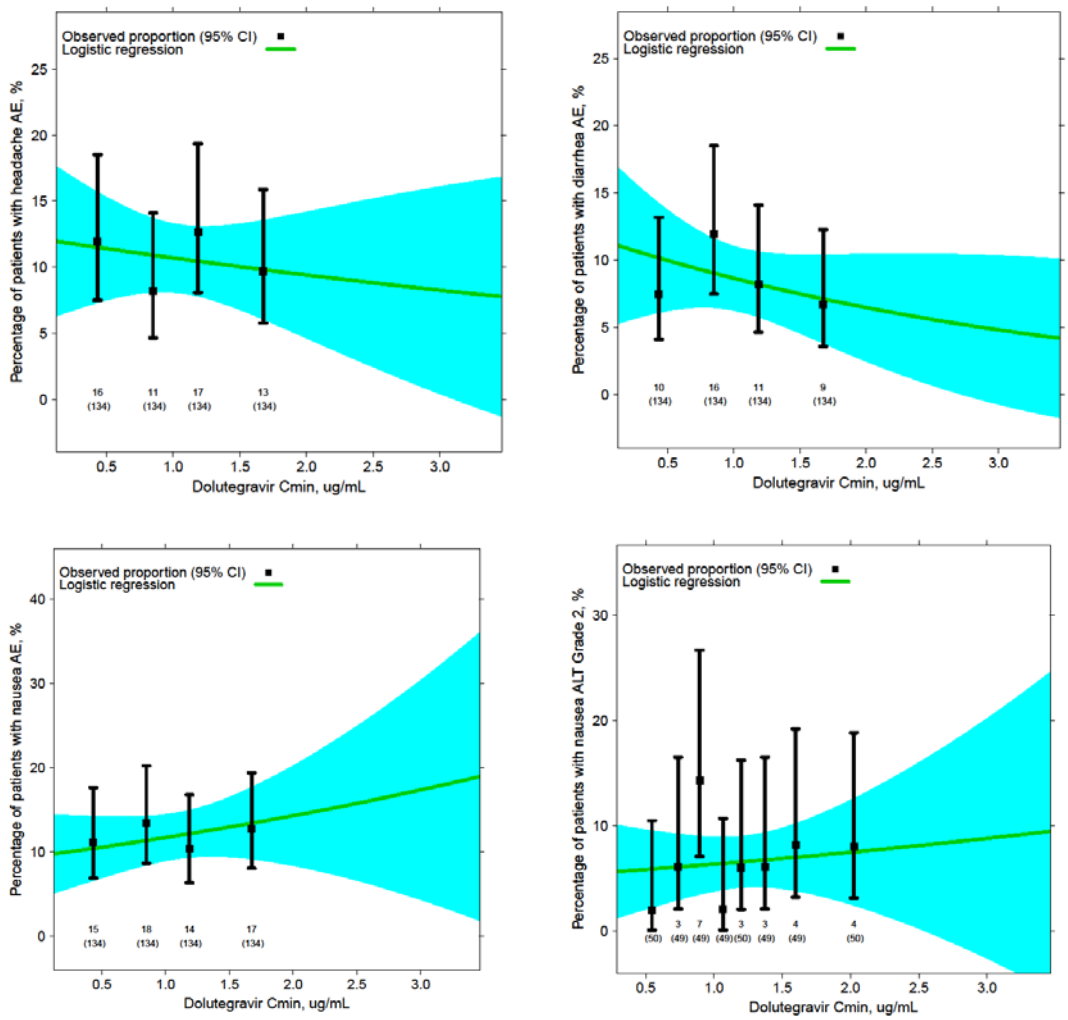
A similar rationale was used in recommending no dose adjustments in subjects on strong inducers as part of their treatment regimen in this regimen. It is anticipated that that exposures in subjects on strong inducers may be as low as that observed from 50 mg QD, which was associated with lower response in ING112961. In total, there were 15 subjects on strong inducers in ING112574 (7 on tipranvir/ritonavir in the 24-week ITT population and 1 subject who switched to efavirenz on treatment in the 24-week ITT population). In the tipranvir/ritonavir subset, geometric mean C_{0h} decreased from the day 8 assessment (2.88 μg/mL) through subsequent assessments (week 4: 1.79 μg/mL; week 24: 1.16 μg/mL), with later assessments reflecting the anticipated decrease in exposure when DTG is administered with strong inducers. Of these subjects there were only 2 treatment failures, but no conclusions can be drawn due to the small number of subjects available in this assessment. DTG dose adjustments to 50 mg TID would be one approach to overcome decreased exposure when coadministered with strong CYP3A4 inducers in this population, but such a recommendation was not concluded due to the lack of safety data at higher DTG doses and limited on treatment data in subjects on strong inducers from ING112574 where a trend of increased virologic failure was not observed. As no dose adjustment is being recommended in this population, a similar conclusion was reached for subjects with severe renal impairment who would be expected to have DTG exposures greater than that of subjects administered 50 mg BID with a strong CYP3A4 inducer.

1.1.2 Is there evidence of DTG exposure-safety relationships for headache, nausea, diarrhea, and ALT elevations (adverse events of interest from the Phase III trials)

An exposure-response relationship could not be established for headache, nausea, diarrhea, and grade 2 or higher ALT elevations and DTG exposures. Logistic regression

models were evaluated for DTG C_{max}, $C_{0h,}$ and AUC_{τ} based on data from ING112276 and ING113086 in treatment naïve subjects with no significant relationships identified. Modeling results for adverse event rates versus DTG AUC_{τ} are shown below in the reviewer's analysis.

Figure 5: Percentage of Subjects with Headache (top left), Diarrhea (top right), Nausea (bottom left), and ALT elevations (bottom right) Adverse Events Versus DTG AUC_{τ} for Treatment Naïve Subjects from ING112276 and ING3086



An exposure-response analysis on changes in renal function versus DTG exposure was also conducted as elevations in serum creatinine and subsequently, reduced estimated glomerular filtration rate (eGFR), was observed in the DTG treatment arms. No relationship between DTG dose (50 mg QD or 50 mg BID) or exposures (C_{0h}) with serum creatinine change from baseline or change in eGFR were observed based on the available DTG pharmacokinetic data. The onset of on-treatment serum creatinine increases following treatment with DTG were rapid with the largest increases occurring over the first 1-2 weeks of treatment. The mean increase in serum creatinine for DTG 50 mg QD

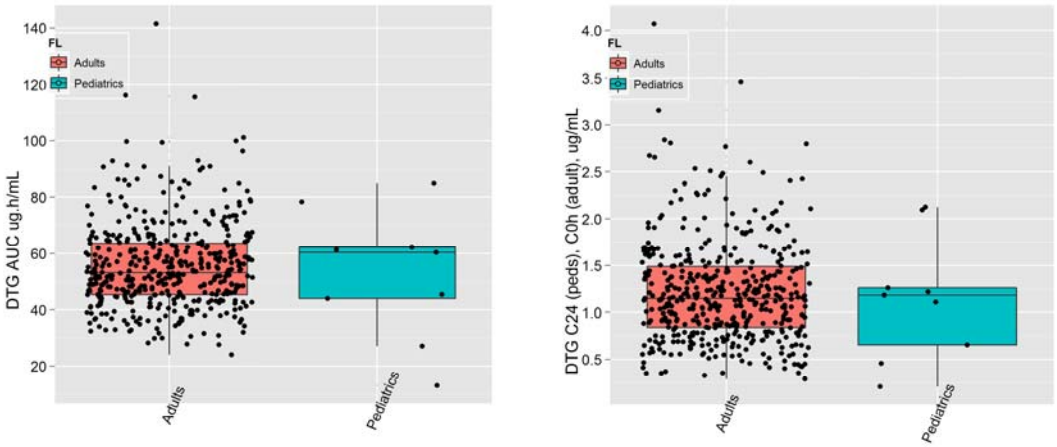
at week 2 ranged between 0.11-0.13 mg/dL (standard deviation range: 0.09-0.17 mg/dL) which was similar to the mean increase in serum creatinine for DTG 50 mg BID at week 2 (0.12 mg/dL: standard deviation: 0.13 mg/dL).

1.1.3 Does the proposed DTG dose of 50 mg QD achieve exposures in adolescents within the targeted exposure range?

Yes, the sponsor's proposed DTG dose of 50 mg QD resulted in adolescent exposures similar to the target adult (target based on Phase I/II DTG data) AUC (46 µg·hr/mL) and C_{0h} (0.96 µg·mL) and slightly lower but similar to the observed treatment-naïve adult geometric mean AUC and C_{0h} (53.6 µg·hr/mL and 1.11 µg/mL, respectively).

In all, the applicant had DTG PK data available from 10 adolescents: 9 with body weight >40 kg who were administered 50 mg QD and 1 with body weight <40 kg administered 35 mg QD from study ING112578. The overall AUC and C_{24h}in these pediatrics was 46.0 µg·hr/mL and 0.90 µg/mL, respectively.

Figure 6: Comparison of Pediatric and Adult DTG Exposures (Pediatrics: ING112578; Adults: ING112276 and ING3086).



These estimates were influenced by a single pediatric (subject ID: 290207) whose AUC and C_{24h} was 13.1 µg·hr/mL and 0.21 µg/mL, respectively, and was similarly low following a second intensive PK assessment (AUC and C_{24h} of 13.6 µg·hr/mL and 0.24 µg/mL) possibly due to the subject's background regimen. Removing this subject from the analysis (subject's AUC was less than lowest adult AUC) results in pediatric AUC and C_{24h} values of 52.9 µg·hr/mL and 1.06 µg/mL. These pediatric estimates are above the targeted exposure and only slightly lower than the observed DTG exposures in TN adults.

Table 6: Comparison of Pediatric and Adult DTG Exposures (Pediatrics: ING112578; Adults: ING112276 and ING3086) with Outlier Subjects Removed

Geometric mean	AUC, µg·h/mL (%CV)	C_{24h}, µg/mL (%CV)
Pre-defined target	46	0.96
ING112578, all included	46.0 (43)	0.90 (58)
ING112578, Subject 290207 excluded	52.9 (34)	1.06 (50)
ING112578, Subject 8503351 excluded (35 mg)	46.8 (44)	0.94 (58)
Adult Phase III Data	53.5 (26)	1.11 (44) (C_{0h})
Ratio Pediatric/Adult Data	0.86-0.99	0.81-0.95

1.2 Recommendations

The reviewer recommends that the sponsor adjust DTG dose to 50 mg BID when coadministered with strong concomitant CYP3A4 inducers, such as efavirenz, tipranavir, and fosamprenavir, in subjects receiving 50 mg QD. Similar dose adjustments in subjects already administered DTG 50 mg BID are not recommended at this time as higher DTG doses were not evaluated in the sponsor's clinical studies. No dose adjustments in subjects with severe renal impairment are recommended in any population based on available exposure-response relationships that support the decreased exposures are not predicted to result in decreased efficacy in such subjects and as a subset of drug-drug interactions resulting in similar DTG exposure decreases (i.e., darunavir) are also not receiving any recommendations for dose adjustments.

1.3 Label Statements

Please refer to the Executive Summary of the Clinical Pharmacology Review for label statements.

2 PERTINENT REGULATORY BACKGROUND

Dolutegravir (DTG) is a human immunedeficiency virus (HIV) integrase inhibitor which offers once-daily dosing without requiring coadministration with an inhibitor to increase therapeutic exposures. In addition, DTG demonstrated high antiviral activity and tolerability based on in vitro and clinical data, as well as a higher barrier to resistance. Finally, most HIV isolates with resistance to raltegravir and elvitegravir remain susceptible to DTG, making DTG an important option for many treatment-experienced patients with multi-class drug resistance.

The applicant proposed dosing of DTG in combination with other antiretroviral therapy agents for the treatment of HIV infection in adults and children ≥12 years of age (and weighting at least 40 kg). The DTG dosing recommendations were 50 mg QD in treatment-naïve and treatment-experienced, integrase inhibitor-naïve adults, 50 mg BID in integrase inhibitor resistant adults, and 50 mg QD in integrase inhibitor-naïve children 12 to <18 years of age and weighing at least 40 kg.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1 Introduction

The applicant developed a population pharmacokinetic model to explore the impact of intrinsic and extrinsic factors on DTG exposure in treatment-naïve and treatment-experienced subjects. In addition, DTG pharmacokinetic parameters were used by the applicant to explore exposure-response efficacy and safety relationships in treatment-naïve, treatment-experienced/integrase inhibitor naïve, and treatment-experienced/integrase inhibitor resistant subjects.

3.2 Population Pharmacokinetic Model

Report 5.3.3.5 Population Pharmacokinetic Analysis of Dolutegravir in HIV-1 Infected Treatment-Naïve Patients

The objectives of the analysis were: 1) to build a population PK model of DTG following once daily oral administration in HIV-infected treatment-naïve patients; 2) to identify co-factors that contribute to inter-individual variability (IIV); 3) to assess inter-occasional variability (IOV) in DTG PK; and 4) to explore the PK/PD relationship between DTG exposure and efficacy/safety endpoints.

3.2.1 Data

Dolutegravir concentration-time, dosing, demographics and covariate data from the following studies were combined: proof of concept (PoC: ING111521), Phase 2b (SPRING-1: ING112276) and Phase 3 (SPRING-2: ING113086). An overview of these clinical trials is presented in Table 7. The population PK analysis included 563 subjects from 3 studies that contributed 3357 concentrations. Demographics for these studies are summarized below in Table 8.

Table 7 Overview of Clinical Trials Included in DTG Population PK Analysis

Study/Phase	Population	N [a]	Dose/Treatment Duration	Planned PK Data
ING111521 (Proof of Concept)	ART-naïve and experienced (integrase inhibitor naïve) HIV-infected patients, not currently receiving ART therapy	19	2, 10 and 50 mg QD orally (data for the 2 mg dose was not included in this Pop PK analysis as this dose has been previously shown to have different PK to higher doses and there is no intention to commercialize the 1 mg tablet) 10 days	Days 1 and 10 at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 postdose; Days 3, 4, 7, 8 and 9 at predose
ING112276 (SPRING-1) (Phase 2b)	HIV-infected treatment-naïve patients	141	10, 25 and 50 mg DTG QD orally with either ABC/3TC (600 mg/300 mg) or TDF/FTC (300 mg/200 mg) fixed dose combination (FDC) 96 weeks	Intensive PK (N=45): Week 2 at predose, 2, 3, 4, 8 and 24 h postdose; Week 12 and 24 at predose and 2-4 h postdose Limited PK (N=96): Weeks 2, 12 and 24 at predose and 2-4 h postdose
ING113086 (SPRING-2) (Phase 3)	HIV-infected treatment-naïve patients	403	50 mg DTG QD with either ABC/3TC (600 mg/300 mg) or TDF/FTC (300 mg/200 mg) fixed dose combination (FDC) 96 weeks	Week 4: predose and 1-3 h or 4-12 h postdose; Week 24: predose; Week 48: predose and 1-3 h or 4-12 h postdose

[a] Actual number of subjects in the analysis

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Table 8 Treatment-Naïve Demographic Distribution

Covariate	Statistic or category	PoC	SPRING-1	SPRING-2	All Subjects
Age (yrs) at baseline	Median [Min-Max]	40 [22-53]	35 [20-64]	37 [18-68]	37 [18-68]
Weight (kg) at baseline	Median [Min-Max]	78.1 [60.5-106]	76.4 [49-120]	74.0 [39.0-135]*	74.5 [39.0-135]
Body mass index (kg/m^2) at baseline	Median [Min-Max]	25.5 [21.7-32.7]	24.3 [17.6-38.7]	24.1 [14.7-47.9]*	24.2 [14.7-47.9]
Body surface area (m^2) at baseline	Median [Min-Max]	1.95 [1.68-2.33]	1.94 [1.46-2.49]	1.90 [1.27-2.69]*	1.92 [1.27-2.69]
Total bilirubin (µmol/L) at baseline	Median [Min-Max]	8.55 [5.13-18.8]	10.0 [4.00-38.0]	9.00 [3.00-31.0]	9.00 [3.00-38.0]
Albumin (g/L) at baseline	Median [Min-Max]	42.0 [38.0-47.0]	44.0 [34.0-51.0]	45.0 [30.0-54.0]	45.0 [30.0-54.0]
Aspartate aminotransferase (IU/L) at baseline	Median [Min-Max]	25.0 [15.0-42.0]	24.0 [11.0-180]	24.0 [12.0-133]	24.0 [11.0-180]
Alanine aminotransferase (IU/L) at baseline	Median [Min-Max]	22.0 [12.0-41.0]	20.0 [8.00-260]	21.0 [5.00-158]	21.0 [5.00-260]
Creatinine clearance (mL/min) at baseline	Median [Min-Max]	119 [86.0-190]	116 [54.6-231]	123 [64.4-239]	121 [54.6-239]
Gender N (%)	Male	19 (100)	122 (87)	340 (84)	481 (85)
	Female	0 (0)	19 (13)	63 (16)	82 (15)
Race N (%)	Caucasian	16 (84)	113 (80)	341 (85)	470 (83)
	Black	3 (16)	16 (11)	47 (12)	66 (12)
	Asian	0 (0)	0 (0)	6 (1)	6 (1)
	Other	0 (0)	12 (9)	9 (2)	21 (4)
Ethnicity N (%)	Non-Hispanic or Latino	18 (95)	118 (84)	361 (90)	497 (88)
	Hispanic or Latino	1 (5)	23 (16)	42 (10)	66 (12)
Smoking N (%)	Never	0 (0)	72 (51)	163 (40)	235 (42)
	Current	0 (0)	54 (38)	182 (45)	236 (42)
	Former	0 (0)	15 (11)	58 (14)	73 (13)
	Unknown	19 (100)	0 (0)	0 (0)	19 (3)
CDC classification of HIV infection N (%) at baseline	A	17 (89)	120 (85)	353 (88)	490 (87)
	B	1 (5)	20 (14)	41 (10)	62 (11)
	C	1 (5)	1 (1)	9 (2)	11 (2)
Formulation N (%)	AL	19 (100)	49 (35)	0 (0)	68 (12)
	AP	0 (0)	92 (65)	0 (0)	92 (16)
	AW	0 (0)	0 (0)	403 (100)	403 (72)
Dose (mg) N (%)	10	9 (47)	49 (35)	0 (0)	58 (10)
	25	0 (0)	46 (33)	0 (0)	46 (8)
	50	10 (53)	46 (33)	403 (100)	459 (82)

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Metal-cation containing products (N=54/563, 10%) was the only concomitant medication group used by 10% or more of the population. The number of subjects taking other concomitant medications of interest (e.g. inhibitor or inducer of CYP3A4, UGT1A1/1A3 and PGP inhibitor, ginkgo biloba) was 3% or less apart from UGT1A1 inhibitors where 6% of patients were taking this concomitant medication. No subjects were taking moderate or strong CYP34A or PGP inducers.

3.2.2 Methods

The population PK model was developed using a non-linear mixed-effect modeling approach; the NONMEM VII software with the first order conditional estimation method with interaction (FOCEI) was used. The development of the population PK model consisted of building the base model followed by the development of a covariate model. Base model selection was driven by the data and was based on evaluation of goodness-of-fit plots, successful convergence, plausibility and precision of parameter estimates, and the minimum objective function value. Investigation of covariate-parameter relationships was based on range of covariate values in the dataset, scientific interest, mechanistic plausibility, and exploratory graphics. The full model approach was implemented, where all covariate-parameter relationships considered to be potentially important from the exploratory graphics were entered in the model. A backward deletion was then implemented. Insignificant or poorly estimated covariates (less than 10.83 points increase of objective function value upon covariate removal, and/or confidence interval includes the null value of the parameter, and/or the parameter is estimated with high %RSE) were eliminated from the model.

Once the final population PK model was developed, the ability of the model to describe the observed data was investigated using a predictive check procedure. Precision of the parameter estimates were evaluated using a nonparametric bootstrap procedure. The final population PK model was used to simulate plasma PK profiles of DTG in HIV-infected treatment-naïve patients to evaluate the influence of covariates on DTG AUC, C_{max}, and C_{τ}. Forest plots were created for comparison of steady-state C_{max}, AUC_{τ}, and C_{τ} among various subpopulations.

Potential exposure-response relationships were explored graphically. The following efficacy endpoints were explored:

- Plasma HIV-1 RNA <50 c/mL at Week 48 using the MSDF algorithm (categorical variable) (SPRING-2 only);
- Protocol-defined virological failure (PDVF) at Week 48 (categorical variable) (SPRING-2 only);

The following safety endpoints were explored:

- Change from Baseline in serum creatinine level, creatinine clearance, urine albumin/creatinine ratio, ALT, and total bilirubin: maximal change over 48 weeks and change at week 48 visit (continuous variable);
- Presence of the top three most common adverse events (AEs) including nausea, diarrhea, and headache (categorical variable)

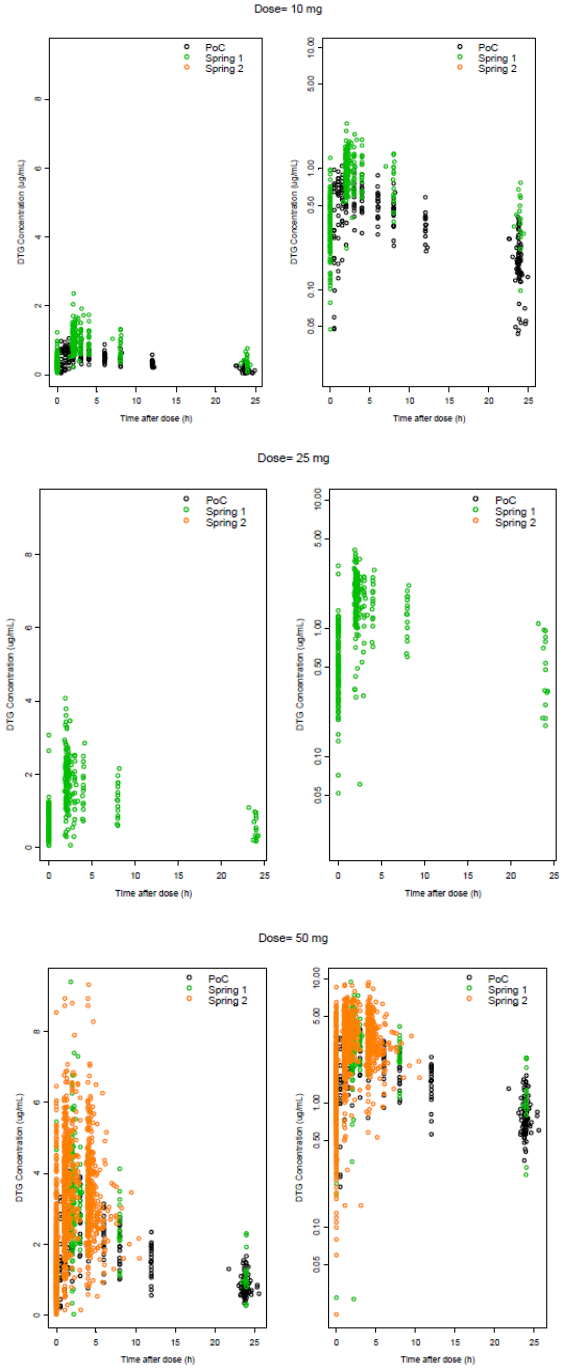
An exploratory graphical analysis of potential exposure-response relationships was performed using individual predicted DTG exposure (steady-state C_{τ}, Cmax, and AUC) obtained from the final population PK model with actual doses administered in each study assuming no IOV.

3.2.3 Results

3.2.3.1 Observed Concentration-Time Profiles

DTG concentrations vs. time since last dose for the three studies are shown in Figure 7.

Figure 7: Observed Plasma DTG Concentrations versus Time after Dose by Dose – Linear and Logarithmic Scales.



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3.2.3.2 Population PK Model Results

The PK of DTG following oral administration was adequately described by a linear one-compartment model with first-order absorption and absorption lag-time and first-order elimination, with inter-individual variability (IIV) in apparent clearance (CL/F), apparent volume of distribution (V/F) and first-order absorption (KA) and inter-occasion variability (IOV) in CL/F.

Table 9 Estimates of the Final DTG Population PK Model

Parameter [Units]	NONMEM Estimates				Bootstrap Estimates [a]	
	Point Estimate	%RSE	95% CI		Median	95% CI
CL/F [L/h]	0.901	2.11	0.864-0.938		0.901	0.866-0.940
V/F [L]	17.4	2.49	16.5-18.3		17.4	16.6-18.2
KA [h^{-1}]	2.24	15.4	1.56-2.92		2.21	1.73-3.10
ALAG [h]	0.263	32.7	0.0942-0.432		0.262	0.0833-0.393
CL/F~PoC	1.35	4.83	1.22-1.48		1.35	1.24-1.51
F~10 mg	1.24	2.92	1.17-1.31		1.24	1.17-1.31
CL/F~WT	0.438	16.9	0.293-0.583		0.440	0.290-0.582
V/F~WT	0.768	10.8	0.605-0.931		0.774	0.616-0.944
F~GEND	1.21	3.27	1.13-1.29		1.21	1.13-1.30
CL~SMOK	1.16	2.45	1.10-1.22		1.16	1.10-1.22
CL~AGE	0.193	23.7	0.103-0.283		0.195	0.105-0.283
CL~BILI	-0.211	14.0	-0.269- -0.153		-0.212	-0.267- -0.152
Inter-individual or inter-occasion variability				**CV%***		
ω^2_{CL}	0.0551	9.27	0.0451-0.0651	23.5	0.0539	0.0449-0.0652
ω^2_{V}	0.0188	29.5	0.00794-0.0297	13.7	0.0182	0.00714-0.0295
ω^2_{KA}	0.224	38.8	0.0535-0.395	50.1	0.217	0.0613-1.11
ω^2_{IOV-CL}	0.0296	15.6	0.0205-0.0387	17.2	0.0300	0.0184-0.0407
Residual variability				**CV%**	**Median**	**95% CI**
σ^2_{prop}	0.0704	7.41	0.0602-0.0806	31.3	0.0698	0.0555-0.0830

$CL/F=0.901\times1.16^{SMOK}\times1.35^{POC}\times(WT/70)^{0.438}\times(AGE/40)^{0.193}\times(BILI/9)^{-0.211}$ (SMOK=1 for smoking subjects and =0 for non-smoking subjects; POC=1 for PoC and =0 for other studies)

$V/F=17.4\times(WT/70)^{0.768}$

$F=1.21^{GEND}\times1.24^{DOSE}$ (GEND=1 for females and =0 for males; DOSE=1 for 10mg dose and =0 for other doses)

a. From 1000 completed bootstrap runs.

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100, 95% CI= 95% confidence interval on the parameter, CL/F = apparent clearance, V/F = volume of central compartment, KA = absorption rate constant, ALAG = absorption lag-time, ω^2_{CL}, ω^2_{V}, and ω^2_{KA} = variance of random effect of CL/F, V/F, and KA, respectively, CV = Coefficient of variation of proportional error (=$[\sigma^2 prop]^{0.5}$*100), $\sigma^2 prop$ = proportional component of the residual error model, IOV = Inter-occasion variability. The reference population for PK parameters CL/F and V/F are 40 year old, 70 kg male, non-current smoker, with total bilirubin of 9 µmol/L.

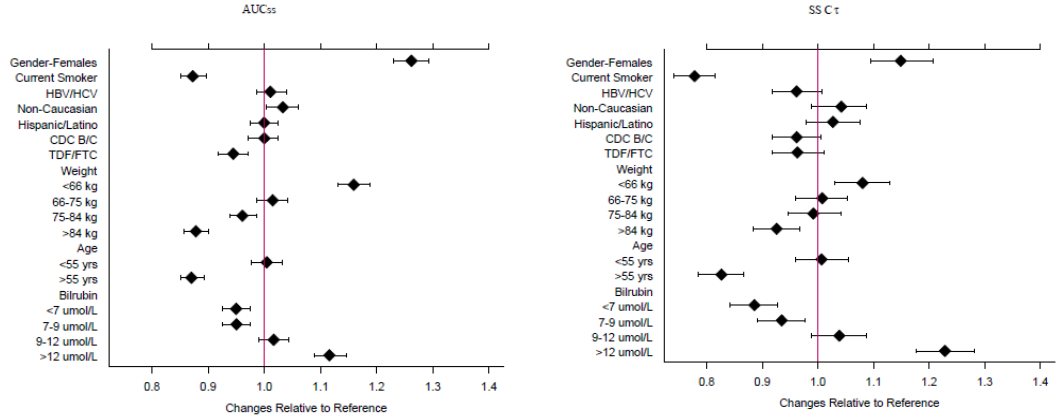
* $CV_{TV_P}=\sqrt{e^{\omega^2_P}-1}$ when ω^2_P exceeds 0.15

Sponsor's 2012n149219-poppk-report.pdf.pdf, pg 46; Model 304

Weight, smoking status, age and total bilirubin were predictors of CL/F and gender was a predictor of F. Following the same dosing regimen, females would have 21% (95% CI: 13-29%) higher F compared to males and current smokers would have 16% (95% CI: 10-22%) higher CL/F compared to non-current smokers. CL/F and V/F increased with body weight. For the range of weights in the analysis (39-135 kg), CL/F ranged from 23% lower to 33% higher and V/F ranged from 36% lower to 66% higher than for 70-kg individuals. CL/F increased with age. For the range of age in the analysis (18-68 yrs), CL/F ranged from 14% lower to 11% higher compared to a 40 yr old subject. CL/F decreased with total bilirubin. For the range of total bilirubin in the analysis (3-38 µmol/L), CL/F ranged from 26% higher to 26% lower compared to a subject with total

bilirubin of 9 µmol/L. There was a 24% higher bioavailability for the 10 mg dose compared to the 25 and 50 mg doses. The PoC studied differed to the SPRING studies, with a 35% higher CL/F for the PoC study. Inter-occasion variability was estimated to be 17% on CL/F. Forest plots describing these impact of these covariates on AUC_τ, and C_τ are shown in Figure 8.

Figure 8: Predicted Fold Change in Steady-State AUC (left) and C_τ (right) Relative to Reference Covariate Category (Fold Change in Median and 90% Confidence Interval).



Sponsor's 2012n149219-poppk-report.pdf.pdf, pg 56-57;

Race, ethnicity, HCV co-infection, CDC classification, albumin, CRCL, ALT or AST did not influence the PK of DTG in this analysis.

Steady-state AUCτ, C_{max}, t_{max} and C_τ in subjects from the two SPRING studies are summarized by dose in Table 10. A dose proportional PK is seen between 25 mg and 50 mg doses. However, a slightly higher than dose proportional PK is observed at 10 mg dose, in agreement with the model estimate that the relative oral bioavailability of 10 mg dose is approximately 24% higher than 25 mg and 50 mg doses.

Table 10 Summary of Steady-State C_{max}, T_{max}, $C\tau$, and AUCτ by Dose Following Actual Dose of DTG Administered in SPRING Studies

Dose (mg)	Statistic	$AUC_{0-\tau}$ (µg·h/mL)	C_{max} (µg/mL)	t_{max} (h)	C_τ (µg/mL)
10	N	49	49	49	49
	Geomean (95% CI)	14.3 (13.4-15.3)	0.957 (0.908-1.01)	2.00 (2.00-2.00)	0.311 (0.281-0.345)
	CV%	24.5	18.9	0.00	38.3
	Median (Min-Max)	14.6 (9.04-24.7)	0.943 (0.664-1.63)	2.00 (2.00-2.00)	0.316 (0.140-0.584)
	Percentiles				
	5%	9.89	0.743	2.00	0.158
	10%	10.5	0.756	2.00	0.194
	25%	11.9	0.837	2.00	0.248
	50%	14.6	0.943	2.00	0.316
	75%	16.8	1.09	2.00	0.410
	90%	19.9	1.20	2.00	0.487
	95%	20.6	1.25	2.00	0.555
25	N	46	46	46	46
	Geomean (95% CI)	25.7 (23.6-28.1)	1.77 (1.66-1.89)	2.00 (2.00-2.00)	0.530 (0.462-0.609)
	CV%	30.8	22.5	0.00	50.6
	Median (Min-Max)	25.0 (11.5-46.3)	1.79 (1.09-3.01)	2.00 (2.00-2.00)	0.499 (0.125-1.33)
	Percentiles				
	5%	17.1	1.28	2.00	0.290
	10%	17.4	1.36	2.00	0.308
	25%	21.4	1.53	2.00	0.362
	50%	25.0	1.79	2.00	0.499
	75%	32.3	2.01	2.00	0.777
	90%	39.3	2.42	2.00	0.930
	95%	40.9	2.59	2.00	1.02
50	N	449	449	449	449
	Geomean (95% CI)	53.6 (52.3-55.0)	3.67 (3.61-3.74)	2.00 (2.00-2.00)	1.11 (1.06-1.15)
	CV%	26.9	19.7	0.00	46.3
	Median (Min-Max)	53.2 (24.1-142)	3.61 (2.15-7.92)	2.00 (2.00-2.00)	1.15 (0.290-4.07)
	Percentiles				
	5%	35.1	2.74	2.00	0.532
	10%	38.5	2.94	2.00	0.625
	25%	45.4	3.22	2.00	0.842
	50%	53.2	3.61	2.00	1.15
	75%	63.6	4.17	2.00	1.49
	90%	74.9	4.75	2.00	1.90
	95%	84.9	5.19	2.00	2.24

Sponsor's 2012n149219-poppk-report.pdf.pdf, pg 51;

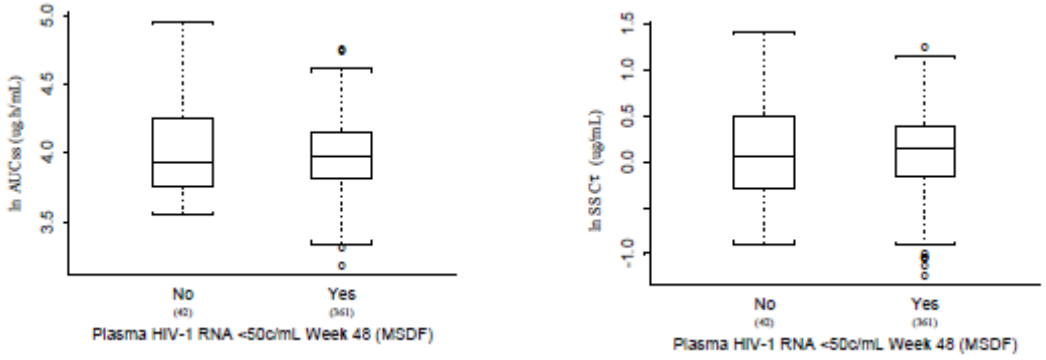
Reviewer's Comments: The sponsor identified multiple significant factors during their population PK analysis, including body weight, smoking status, age, and bilirubin on clearance, body weight on age, and gender on bioavailability. Other identified covariate estimates, such as a higher bioavailability for the 10 mg DTG dose and higher DTG clearance for the proof-of-concept study, while numerically significant, are not necessary to inform dosing in the treatment-naïve HIV-1 infected population.

None of the identified covariates during the sponsor's analysis were of significant magnitude to necessitate dose adjustments in treatment-naïve, HIV-1 infected adults. The identification of a body weight effect on clearance and volume of distribution is being used by the sponsor to evaluate appropriate dosing in pediatrics and will be reviewed as additional data becomes available. The identification of a gender effect on bioavailability, which was also identified by the reviewer during repetition of the sponsor's analysis, may be related to the already identified body weight effect on clearance and volume of distribution. A mechanism to support increased bioavailability in women compared to men for DTG was not provided by the sponsor, though the magnitude of the difference does not warrant any dose adjustment..

3.2.3.3 Exploratory PK/PD Results

No relationship was evident between any of the efficacy endpoints and DTG exposure. Steady-state DTG exposure (C_τ and AUC_τ) from subjects in SPRING-2 plotted against plasma HIV-1 RNA (<50 c/mL or ≥50 c/mL) is shown in Figure 9. PDVF, similarly, displayed no trend between responders and nonresponders.

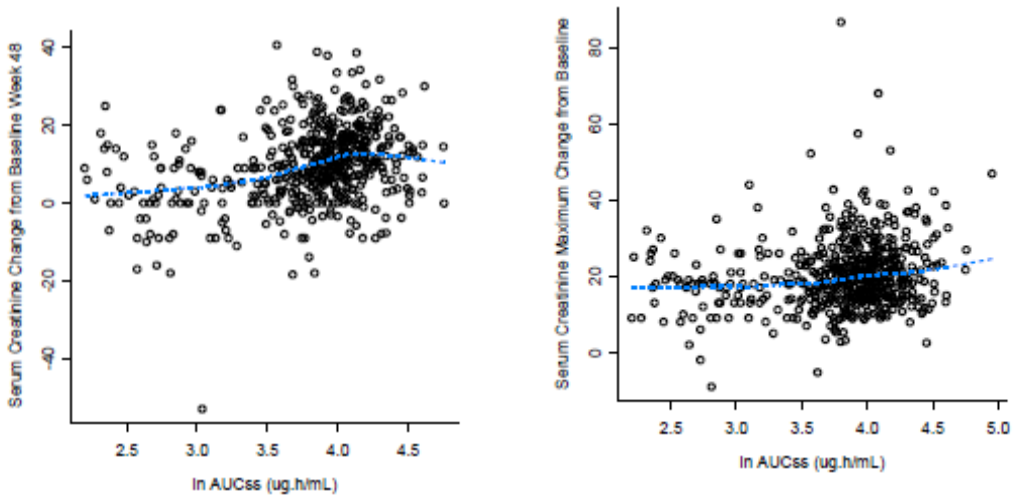
Figure 9: Plasma HIV-1 RNA < 50 c/mL at Week 48 versus DTG exposure (C_τ and AUC_τ)-SPRING-2.

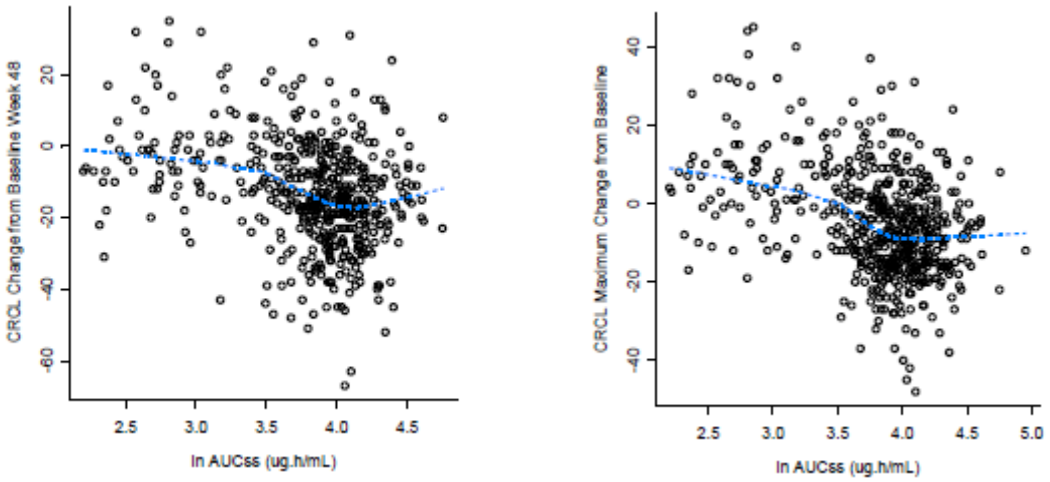


Sponsor's 2012n149219-poppk-report.pdf.pdf, pg 230;

The change from baseline and maximum change from baseline at week 48 for serum creatinine versus DTG exposure (AUC_τ) are shown in Figure 10. Serum creatinine change from baseline both at week 48 and maximum value increased with increasing DTG exposure. This increase reached a plateau for serum creatinine change from baseline at week 48 at ~70 µg·h/mL for AUC_τ (ln AUC: 4.3). Similarly, creatinine clearance change from baseline at week 48 and maximum creatinine clearance decreased with increasing DTG exposure up to ~70 µg·h/mL for AUC_τ.

Figure 10: Serum Creatinine (top) and Creatinine Clearance (bottom) Change from Baseline (left) and Maximum Change from Baseline (right) versus DTG exposure (AUC).





Sponsor's 2012n149219-poppk-report.pdf.pdf, pg 230;

No relationship was evident for urine albumin/creatinine ratio, ALT, total bilirubin, nausea, diarrhea and headache versus DTG exposure.

Reviewer comments: The sponsor identified a relationship between DTG exposure and increase in serum creatinine from baseline, which the sponsor hypothesizes as related to inhibitions of OCT2 (a description of the dedicated renal study to evaluate this hypothesis is discussed in detail in the Clinical Pharmacology Review). These increases were related to both AUC and C_{0h}, and the reviewer selected the AUC plots for further discussion. The sponsor identified a saturating relationship between DTG AUC and change from baseline in serum creatinine/creatinine clearance at week 48 that plateaued at DTG exposures similar to that achieved with 50 mg QD. There were no identified renal safety signals from the sponsor's Phase III trials which used 50 mg QD to suggest the increase in serum creatinine was related to kidney injury. In addition, the reviewer's independent analysis that included 50 mg BID supports the sponsor's creatinine clearance plateau relationship as similar maximum changes in creatinine clearance were observed on for DTG 50 mg QD (-26.3, -27.1, and -26.9 mL/min from ING113086, ING114467, and ING111762) and DTG 50 mg BID (-22.4 mL/min for ING111762; this regimen assessment was at 24 weeks). As such, the available data supports that the serum creatinine changes observed with DTG doses of 50 mg QD and 50 mg BID are of similar magnitude.

3.3 Population Pharmacokinetic Model

Report 5.3.3.5 Population Pharmacokinetic Analysis of Dolutegravir in HIV-1 Infected Treatment-Experienced Adults

The main objective of the analysis was to build a population pharmacokinetic (PopPK) model of dolutegravir (DTG) after oral administration in HIV-1 infected treatment-experienced adults, to identify co-factors that contribute to inter-individual variability (IIV) in DTG PK, and to assess inter-occasion variability (IOV) in DTG PK.

3.3.1 Data

DTG concentration-time, dosing, demographics and covariate data from the following studies were combined: ING112961 (VIKING, Phase 2b raltegravir-resistant), ING112574 (VIKING-3, Phase 3 integrase inhibitor-resistant) and ING111762 (SAILING, Phase 3, treatment-experienced and integrase inhibitor-naïve). An overview of these clinical trials is presented in Table 11. The population PK analysis included 574 subjects from 3 studies that contributed 2289 plasma DTG concentrations. Demographics for these studies are summarized below in Table 12.

Table 11 Overview of Clinical Trials Included in DTG Treatment-Experienced Population PK Analysis

Study (Phase)	Population and No. Subjects[a]	DTG Dose/Treatment Duration	Planned PK Data	PK Data Included in the Analysis
ING112961 (VIKING) (Phase 2b)	Population: HIV-1 infected, ART-experienced adults with RAL resistance N=51 (27 on 50 mg QD and 24 on 50 mg BID)	50 mg QD and BID with continuation of the current failing antiretroviral regimen for 10 days, then in combination with OBT for a minimum of 24 weeks	• Intensive PK on Day 10 at pre-dose, 2, 3, 4, 8, 12 (BID only after PM dose) and 24 hr (QD only) post-dose • Sparse PK on Weeks 4 and 24 at pre-dose and 2-4 hr post dose	• All final PK data collected in the trial
ING112574 (VIKING-3) (Phase 3)	Population: HIV-1 infected, ART-experienced adults with INI resistance N=183	50 mg BID with continuation of the current failing anti-retroviral regimen for 7 days, then in combination with OBT for a minimum of 24 weeks	• Sparse PK on Day 8 at pre-dose and 1-3 hr post-dose • Sparse PK on Week 4 at pre-dose and 1-3 hr (or 4-12 hr post-dose • Sparse PK on Week 24 at pre-dose and 4-12 hr (or 1-3 hr) post-dose	• All QC'ed PK data available in GSK PK database (SMS2000) on June 28, 2012
ING111762 (SAILING) (Phase 3)	Population: HIV-1 infected, ART-experienced, INI-naïve adults N=340	50mg QD with an investigator selected regimen for 48 weeks	• Sparse PK on Week 4 at pre-dose and 1-3 hr (or 4-12 hr) post-dose • Sparse PK on Week 24 at pre-dose • Sparse PK on Week 48 at pre-dose and 4-12 hr (or 1-3 hr) post-dose	• All QC'ed PK data available in GSK PK database (SMS2000) on June 28, 2012

[a] Actual number of subjects involved in the analysis

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Table 12 Overview of Demographics of Treatment-Experienced Subjects in the DTG Population PK Analysis

Covariate	Statistic or category	VIKING[a] (N=51)	VIKING-3[b] (N=183)	SAILING[c] (N=340)	All Subjects (N=574)
Age (yrs) at baseline	Median [Min-Max]	47 [19-68]	48 [19-67]	42 [21-69]	45 [19-69]
Weight (kg) at baseline	Median [Min-Max]	72.5 [45.0-119]	72.6 [39.0-163]	71.0 [32.0-152]	72.0 [32.0-163]
Body mass index (kg/m^2) at baseline	Median [Min-Max]	24.1 [15.8-38.9]	24.8 [14.9-53.6]	24.2 [12.7-44.8]	24.4 [12.7-53.6]
Body surface area (m^2) at baseline	Median [Min-Max]	1.89 [1.42-2.46]	1.89 [1.30-3.01]	1.85 [1.17-2.88]	1.87 [1.17-3.01]
Total bilirubin (µmol/L) at baseline	Median [Min-Max]	10.0 [6.00-58.0]	8.00 [4.00-100]	6.00 [3.00-56.0]	8.00 [3.00-100]
Albumin (g/L) at baseline	Median [Min-Max]	44.0 [35.0-50.0]	44.0 [29.0-53.0]	43.0 [30.0-55.0]	43.0 [29.0-55.0]
Aspartate aminotransferase (IU/L) at baseline	Median [Min-Max]	27.0 [13.0-282]	27.0 [11.0-382]	26.0 [9.00-324]	27.0 [9.00-382]
Alanine aminotransferase (IU/L) at baseline	Median [Min-Max]	26.0 [9.00-210]	25.0 [7.00-363]	22.5 [5.00-164]	24.0 [5.00-363]
Serum creatinine (mg/dL) at baseline	Median [Min-Max]	0.996 [0.532-2.00]	0.850 [0.509-2.86]	0.786 [0.420-2.68]	0.820 [0.420-2.86]
Creatinine clearance (mL/min) at baseline	Median [Min-Max]	97.0 [43.9-161]	103 [25.3-255]	117 [23.0-285]	111 [23.0-285]
Gender N (%)	Male	43 (84)	141 (77)	238 (70)	422 (74)
	Female	8 (16)	42 (23)	102 (30)	152 (26)
Race N (%)	Caucasian	43 (84)	130 (71)	172 (51)	345 (60)
	Black	8 (16)	49 (27)	139 (41)	196 (34)
	Asian	0 (0)	1 (1)	7 (2)	8 (1)
	Other	0 (0)	3 (2)	21 (6)	24 (4)
	Unknown	0 (0)	0 (0)	1 (<1)	1 (<1)
Ethnicity N (%)	Non-Hispanic or Latino	43 (84)	163 (89)	211 (62)	417 (73)
	Hispanic or Latino	8 (16)	20 (11)	129 (38)	157 (27)

Smoking N (%)	Never	23 (45)	79 (43)	174 (51)	276 (48)
	Current	17 (33)	67 (37)	119 (35)	203 (35)
	Former	11 (22)	37 (20)	47 (14)	95 (17)
Hepatitis co-infection at baseline N (%)	None	34 (67)	144 (79)	280 (82)	458 (80)
	Hepatitis B only	2 (4)	10 (5)	14 (4)	26 (5)
	Hepatitis C only	8 (16)	26 (14)	28 (8)	62 (11)
	Hepatitis B and C	0 (0)	2 (1)	1 (<1)	3 (1)
	Unknown	7 (14)	1 (1)	17 (5)	25 (4)
CDC classification of HIV infection at baseline N (%)	A	14 (27)	44 (24)	104 (31)	162 (28)
	B	13 (25)	37 (20)	67 (20)	117 (20)
	C	24 (47)	102 (56)	169 (50)	295 (51)
Renal impairment classification at baseline N (%)	Normal (CRCL≥90)	30 (59)	138 (75)	271 (80)	439 (76)
	Mild (60≤CRCL<90)	17 (33)	36 (20)	63 (19)	116 (20)
	Moderate to Severe (CRCL<60)	4 (8)	9 (5)	6 (2)	19 (3)
Dosing regimen N (%)	50 mg QD	27 (53)	0 (0)	340 (100)	367 (64)
	50 mg BID	24 (47)	183 (100)	0 (0)	207 (36)
Metal-cation containing products N (%)	Present, visit 1	7 (14)	25 (14)	25 (7)	57 (10)
	Present, visit 2	5 (11)	22 (12)	9 (4)	36 (8)
	Present, visit 3	4 (10)	10 (11)	4 (7)	18 (10)
CYP3A inhibitors N (%)	Present, visit 1	36 (73)	154 (87)	287 (85)	477 (85)
	Present, visit 2	43 (98)	154 (87)	176 (86)	373 (88)
	Present, visit 3	38 (97)	75 (85)	50 (86)	163 (88)
CYP3A inducers N (%)	Present, visit 1	18 (37)	89 (50)	61 (18)	168 (30)
	Present, visit 2	25 (57)	72 (41)	33 (16)	130 (31)
	Present, visit 3	22 (56)	33 (38)	10 (17)	65 (35)
P-gp inhibitors N (%)	Present, visit 1	14 (29)	54 (30)	115 (34)	183 (32)
	Present, visit 2	14 (32)	50 (28)	68 (33)	132 (31)
	Present, visit 3	12 (31)	21 (24)	11 (19)	44 (24)
UGT1A1 inhibitors N (%)	Present, visit 1	23 (47)	70 (39)	155 (46)	248 (44)
	Present, visit 2	22 (50)	60 (34)	96 (47)	178 (42)
	Present, visit 3	17 (44)	29 (33)	15 (26)	61 (33)
UGT1A3 inhibitors N (%)	Present, visit 1	13 (27)	34 (19)	145 (43)	192 (34)
	Present, visit 2	14 (32)	23 (13)	87 (42)	124 (29)
	Present, visit 3	10 (26)	9 (10)	14 (24)	33 (18)
Background ART as inhibitors[d] N (%)	Present, visit 1	6 (12)	5 (3)	49 (15)	60 (11)
	Present, visit 2	5 (11)	3 (2)	29 (14)	37 (9)
	Present, visit 3	4 (10)	2 (2)	6 (10)	12 (6)
Background ART as inducers[e] N (%)	Mild, visit 1	25 (51)	139 (78)	141 (42)	305 (54)
	Mild, visit 2	35 (80)	119 (67)	92 (45)	246 (58)
	Mild, visit 3	32 (82)	61 (69)	39 (67)	132 (71)
	Moderate, visit 1	5 (10)	10 (6)	16 (5)	31 (5)
	Moderate, visit 2	1 (2)	15 (8)	5 (2)	21 (5)
	Moderate, visit 3	1 (3)	8 (9)	0 (0)	9 (5)

[a]Visit 1= Day 10, visit 2 = Week 4, visit 3 = Week 24
[b]Visit 1 = Day 8, visit 2 = Week 4, visit 3 = Week 24
[c]Visit 1 = Week 4, visit 2 = Week 24, visit 3 = Week 48
[d]Background ART as inhibitors include atazanavir and atazanavir-ritonavir.
[e]Background ART as mild inducers represent any combination therapy containing darunavir-ritonavir or fosamprenavir-ritonavir.
Background ART as moderate inducers represent any combination therapy containing etravirine without ritonavir-boosted protease inhibitors, efavirenz without ritonavir-boosted protease inhibitors, or tipranavir-ritonavir.

Sponsor's 2012n149456-poppk-report.pdf, pg 5-7

3.3.2 Methods

A Pop PK model for DTG has been developed in HIV-1 infected treatment-naïve adult subjects. The predictive performance of this previous model was evaluated by applying the final model to the current analysis population and re-estimating all model parameters. Backward deletion was performed to retain covariates that were significant in the current population. Structural model was also refined to ensure parameter identifiability in the current population.

Investigation of additional covariate-parameter relationships was based on range of covariate values in the dataset, scientific interest, mechanistic plausibility, and exploratory graphics. The full model approach was implemented in stages, where time-varying concomitant medications (metal-cation containing products, ginko biloba, CYP3A inducers/inhibitors, P-gp inhibitors/inducers, UGT1A1 inhibitors/inducers, and background treatment with inhibitors/inducers) considered to be potentially important from the exploratory graphics were entered in the model first.

A backward deletion was once again implemented. Insignificant or poorly estimated covariates (less than 10.83 points increase of objective function value upon covariate removal, and/or confidence interval includes the null value of the parameter, and/or the parameter is estimated with high relative standard error) were eliminated from the model. Once the final population PK model was developed, the ability of the model to describe the observed data was investigated using a predictive check procedure. Precision of the parameter estimates were evaluated using a nonparametric bootstrap procedure.

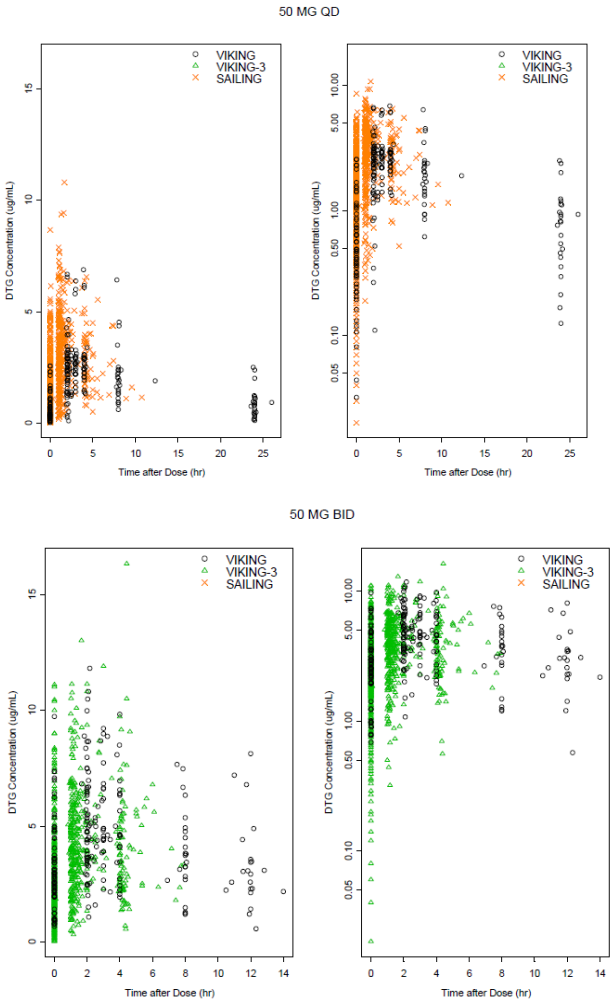
Once the final population PK model was developed, the ability of the model to describe the observed data was investigated using a predictive check procedure. Precision of the parameter estimates were evaluated using a nonparametric bootstrap procedure. The final population PK model was used to simulate plasma PK profiles of DTG in HIV-infected treatment-experienced patients to evaluate the influence of covariates on DTG AUC, C_{max}, and C_{τ}. Forest plots were created for comparison of steady-state C_{max}, AUC_{τ}, and C_{τ} among various subpopulations.

3.3.3 Results

3.3.3.1 Observed Concentration-Time Profiles

DTG concentrations vs. time since last dose for the three studies are shown in Figure 11.

Figure 11: Observed Plasma DTG Concentrations versus Time after Dose by Dose – Linear and Logarithmic Scales.



Sponsor's 2012n149456-poppk-report.pdf,f, pg 91;

3.3.3.2 Population PK Model Results

The PK of DTG following repeat-oral administration in HIV-1 infected treatment-experienced adults were adequately described by a one-compartment model with first-order absorption, absorption lag-time and first-order elimination.

Table 13 Parameter Estimates of the Final DTG Treatment-Experienced Population PK Model

Parameter [Units]	NONMEM Estimates				Bootstrap Estimates[a]	
	Point Estimate	%RSE	95% CI		Median	95% CI
CL/F [L/hr]	1.05	3.25	0.983-1.12		1.04	0.974-1.12
V/F [L]	19.9	2.60	18.9-20.9		19.8	18.3-21.2
Ka [hr^{-1}]	2.35	11.2	1.83-2.87		2.30	1.81-3.16
ALAG [hr]	0.333 FIX	-	-		-	-
CL/F~WT	0.395	20.1	0.240-0.550		0.398	0.236-0.567
V/F~WT	0.697	12.3	0.530-0.864		0.716	0.496-0.953
CL/F~SMOKC	1.16	3.35	1.08-1.24		1.16	1.08-1.24
F~GEND	1.18	3.67	1.10-1.26		1.17	1.09-1.27
F~MCAT	0.846	6.57	0.737-0.955		0.841	0.752-0.955
CL/F~INDMI	1.26	3.16	1.18-1.34		1.26	1.18-1.34
CL/F~INDMO	1.73	7.46	1.48-1.98		1.73	1.50-2.01
CL/F~INH	0.576	4.64	0.524-0.628		0.578	0.521-0.630
CL/F, V/F~ALBU	-0.592	29.2	-0.931 - -0.253		-0.596	-0.944 - -0.249
Inter-individual or inter-occasion variability				**CV%**		
ω^2_{CL}	0.0823	11.8	0.0632-0.101	28.7	0.0798	0.0609-0.100
ω^2_{IOV-CL}	0.0838	10.8	0.0661-0.101	28.9	0.0843	0.0642-0.105
Residual variability				**CV%**		
σ^2_{prop}	0.0992	5.64	0.0882-0.110	31.5	0.0981	0.0881-0.110

$CL/F = 1.05 \times 1.16^{SMOKC} \times 1.26^{INDMI} \times 1.73^{INDMO} \times 0.576^{INH} \times (WT/70)^{0.395} \times (ALBU/43)^{-0.592}$ (SMOKC=1 for current smokers and =0 for non-current smokers; INDMI=1 for background ART containing mild inducers and =0 for none; INDMO=1 for background ART containing moderate inducers and =0 for none; INH=1 for background ART containing atazanavir or atazanavir-ritonavir and =0 for none)

$V/F=19.9 \times (WT/70)^{0.697} \times (ALBU/43)^{-0.592}$

$F=1.18^{GEND} \times 0.846^{MCAT}$ (GEND=1 for females and =0 for males; MCAT=1 for metal-cation containing products and =0 for none)

[a] From 1000 bootstrap runs.

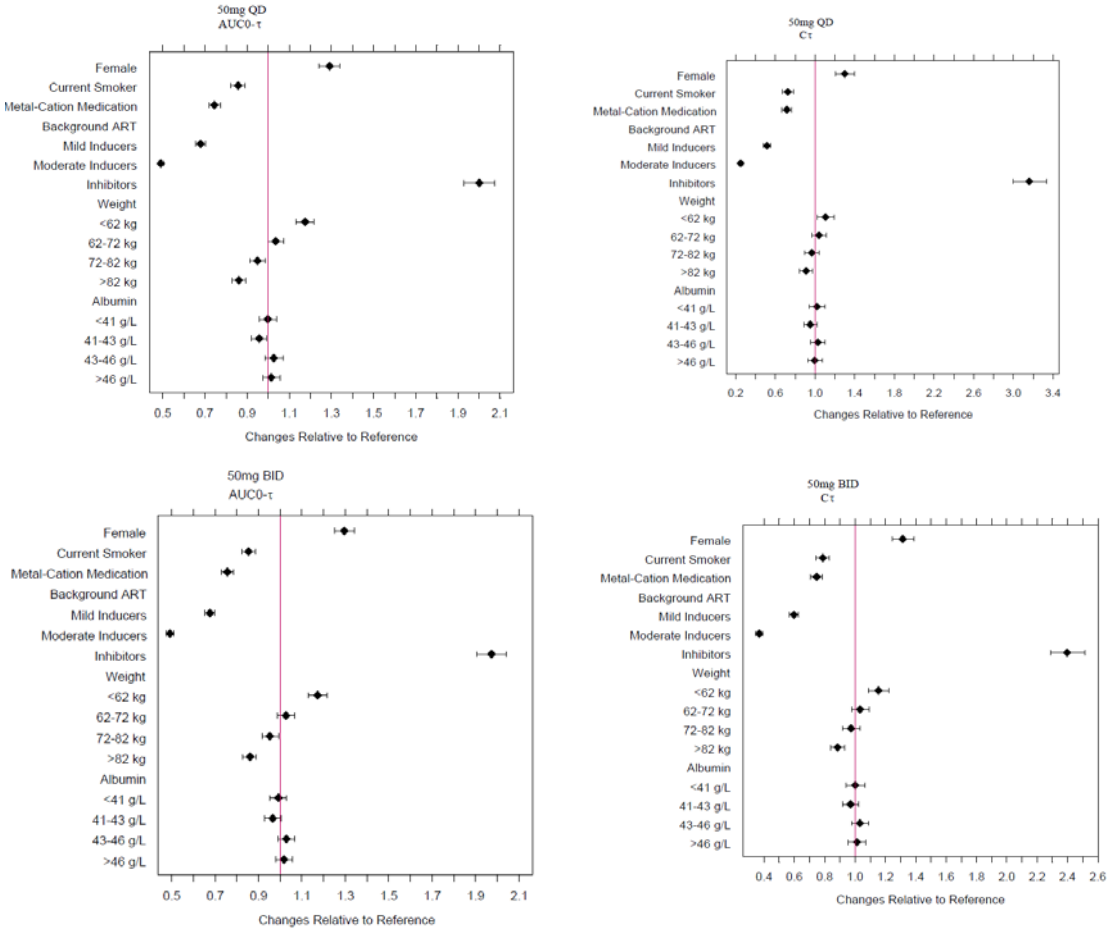
Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100, 95% CI= 95% confidence interval on the parameter, CL/F = apparent clearance, V/F = apparent volume of central compartment, Ka = absorption rate constant, ALAG = absorption lag time, ω^2_{CL}= variance of random effect of CL/F, CV = coefficient of variation of proportional error (=$[\sigma^2 prop]^{0.5}$*100), σ^2prop = proportional component of the residual error model, IOV = Inter-occasion variability, WT = baseline weight (kg), ALBU = baseline albumin (g/L). The reference population for PK parameters CL/F and V/F is 70 kg male, non-current smoker, not currently taking metal-cation containing medications, not receiving metabolic inducers as part of background ART, not receiving metabolic inhibitors as part of background ART, with albumin of 43 g/L.

Sponsor's 2012n149456-poppk-report.pdf, pg 7, Model 048

Weight, smoking status, use of metabolic inducers as part of background ART classified by their level of induction, use of atazanavir or atazanavir-ritonavir as part of background ART, and albumin level were predictors of CL/F; weight and albumin level were predictors of V/F; and gender and concomitant use of metal-cation containing products were predictors of relative bioavailability (F). CL/F of DTG was, on average, 16% (95% CI: 8-24%) higher in current smokers than non-current smokers. Use of metabolic inducers as part of background ART within two weeks of PK sampling resulted in 26% (95% CI: 18-34%) and 73% (95% CI: 48-98%) increase in CL/F for mild (darunavir-ritonavir or fosamprenavir-ritonavir) and moderate (etravirine without ritonavir-boosted protease inhibitors, efavirenz without ritonavir-boosted protease inhibitors, or tipranavir-ritonavir) inducers, respectively, compared to non-users. On the contrary, use of metabolic inhibitors (atazanavir or atazanavir-ritonavir) as part of background ART on the day of PK sampling resulted in a 42% (95% CI: 37-48%) decrease in CL/F compared to non-users. CL/F and V/F increased with body weight. For the range of weights in the

analysis (32-163 kg), CL/F ranged from 27% lower to 40% higher and V/F ranged from 42% lower to 80% higher than for 70 kg individuals. CL/F and V/F decreased with albumin to the same extent. For the range of albumin levels in the analysis (29-55 g/L), CL/F and V/F ranged from 14% lower to 26% higher compared to subjects with albumin of 43 g/L. On average, F was 15% (95% CI: 4-26%) lower in subjects who were on metal-cation containing medications compared to those not on these medications, and F was 18% (95% CI: 10-26%) higher in female subjects compared to males. Forest plots describing these impact of these covariates on AUC_τ, and C_τ on DTG 50 mg QD and 50 mg BID are shown in Figure 12.

Figure 12: Predicted Fold Change in Steady-State AUC (left) and C_τ (right) Relative to Reference Covariate Category (Fold Change in Median and 90% Confidence Interval) (Treatment-Experienced Subjects, 50 mg QD [top]; 50 mg BID [bottom]).



Sponsor's 2012n149219-poppk-report.pdf.pdf, pg 59, 61;

Steady-state AUCτ, C_{max}, t_{max} and C_τ in subjects from the treatment-experienced studies are summarized by dose in Table 14. On average, Cmax and C_τ were 31% and 157%, respectively, higher for the 50 mg BID regimen than the 50 mg QD regimen. AUC0-τ was 15% lower in the BID group.

Table 14 Summary of Steady-State C_{max}, T_{max}, $C\tau$, and AUCτ by Dose in Treatment-Experienced Subjects

Dose	Statistic	C_{max} (µg/mL)	C_{τ} (µg/mL)	$AUC_{0-\tau}$ (µg·h/mL)	AUC_{0-24} (µg·h/mL)
50 mg QD	N	367	367	367	367
	Geomean (95% CI)	3.18 (3.10-3.26)	0.826 (0.770-0.885)	44.0 (42.3-45.8)	44.0 (42.3-45.8)
	CV%	26.4	76.5	40.3	40.3
	Median (Min-Max)	3.13 (1.53-7.20)	0.867 (0.0807-3.82)	43.5 (15.6-130)	43.5 (15.6-130)
	Percentiles				
	5%	2.14	0.254	23.6	23.6
	10%	2.33	0.323	26.7	26.7
	25%	2.68	0.550	33.5	33.5
	50%	3.13	0.867	43.5	43.5
	75%	3.79	1.26	56.4	56.4
	90%	4.42	2.07	75.1	75.1
	95%	4.95	2.58	88.0	88.0
50 mg BID	N	207	207	207	207
	Geomean (95% CI)	4.15 (4.00-4.32)	2.12 (1.99-2.25)	37.5 (35.8-39.3)	75.1 (71.6-78.6)
	CV%	29.2	47.1	35.1	35.1
	Median (Min-Max)	4.14 (2.19-10.3)	2.13 (0.455-7.39)	37.3 (15.6-107)	74.7 (31.2-213)
	Percentiles				
	5%	2.61	0.954	20.1	40.2
	10%	2.98	1.18	25.0	50.0
	25%	3.34	1.63	29.1	58.3
	50%	4.14	2.13	37.3	74.7
	75%	5.00	2.87	47.3	94.5
	90%	5.93	3.68	57.3	115
	95%	6.69	4.19	65.4	131

Sponsor's 2012n149219-poppk-report.pdf.pdf, pg 51;

Reviewer's Comments: The sponsor performed a separate population PK analysis for treatment-experienced to assist in identifying relevant covariates for dose adjustments in this population. The sponsor used the previously development DTG population PK model in treatment naïve subjects as the base model for the updated analysis.

The sponsor identified weight, smoking status, use of inducers/inhibitors in the background regimen, and albumin levels as predictors of clearance, body weight and albumin as predictors of volume of distribution, and gender and use of metal-cation products on bioavailability. Body weight and gender were identified, as before, but neither resulted in significant changes to DTG PK to necessitate dose adjustment. The implications of the body weight relationship will be reassessed as pediatric data becomes available.

The use of concomitant strong inducers in the background regimen results in substantial changes on DTG CL (73% increase) and on DTG AUC and C_{τ}. A lower virologic response rate was observed in subjects on concomitant inducers in the treatment-experienced/integrase-naïve trial, and the review team recommends an increase in dose from 50 mg QD to 50 mg BID (highest dose evaluated by the sponsor during the Phase II/III trials). A similar impact on DTG exposure may be expected for treatment-experienced/integrase-experienced subject administered 50 mg BID; however, the available data from the sponsor's Phase III data did not demonstrate increased virologic failure in the 8 subjects (n=114) on concomitant strong inducers. Combined with potential safety concerns with higher DTG dosing, the recommendation is to not dose adjust in treatment-experienced/integrase-experienced subjects administered 50 mg BID who are also on a strong inducer.

Higher exposures (1.9-fold increase in AUC) were observed in subjects administered a strong inhibitory such as atazanavir. No clear DTG exposure-related safety signal was identified during Phase III and the sponsor included 53 subjects in their treatment-experienced studies with atazanavir as part of their background regimen. Given the lack of a safety signal in this subgroup, there was no recommended dose adjustment for subjects on concomitant atazanavir.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The purpose of this review was to evaluate the exposure-response efficacy relationships for dolutegravir in HIV-1 infected treatment-naïve, treatment-experienced/integrase-naïve, and treatment-experienced/integrase-experienced patients and assess the adequacy of the proposed dosing. In addition, overall exposure-response safety relationships between dolutegravir and key adverse events of interest (headache, nausea, and diarrhea), serum creatinine elevations, and ALT elevations were also evaluated.

4.2 Objectives

Analysis objectives are:

1. Evaluate exposure-response efficacy relationships for dolutegravir in treatment-naïve, treatment-experienced/integrase-naïve, and treatment-experienced/integrase-experienced subjects to inform dosing in each population
2. Evaluate relevant exposure-response safety relationships between dolutegravir and adverse events of interest

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 15.

Table 15. Analysis Data Sets

Study Number	Name	Link to EDR
ING112276, ING113086, ING114467, ING111762, ING112961, ING112574	Renal.xpt, liver.xpt, pkpd.xpt, pkcnc.xpt, pkpop.xpt, resist.xpt, adeffout.xpt (all studies except ING114467 had pkpd.xpt, pkcnc.xpt, and pkpop.xpt datasets)	\\Cdsesub1\evsprod\NDA204790\0000\m5\datasets
ING112578	Pediatric_PK_ING112578.csv (copied from study report)	
Population PK	Pk3.xpt, pkpd.xpt	\\Cdsesub1\evsprod\NDA204790\0000\m5\datasets

4.3.2 Software

Estimation and simulation were performed NONMEM 7.2 on the Pharmacometrics Group Linux cluster using the front end manager Perl Speaks NONMEM (PsN).

Diagnostic graphs, model comparison, and statistical analysis were performed in R (version 10.1).

4.3.3 Models

4.3.3.1 Logistic Regression: Efficacy and Safety Exposure-Response Relationships

Logistic regression models for efficacy (HIV-1 <50 copies/mL at week 48 (treatment naïve subjects) and week 24 (treatment experienced subjects)) and common adverse events were performed using the applicant's Phase II/III trial data. Three independent variables were used for developing logistic regression plots: steady-state AUC (AUC_τ), maximum concentration (C_{max}), and trough concentration (C_{0h}). AUC_τ was calculated for each subject using empirical Bayes' estimates from the population PK model. C_{max} was obtained from subjects with intensive PK sampling during Phase III. C_{0h} was calculated using the average of on treatment C_0 measurements collected for each subject.

4.4 Results

4.4.1 Exposure-Response for Efficacy (Virologic Response)

Detailed discussion of the efficacy analyses and dosing recommendations for treatment naïve, treatment-experienced/integrase-naïve, and treatment-experienced/integrase-experienced subjects are above in Key Question 1.1.

4.4.2 Exposure-Response for Safety: Adverse Events

Detailed discussion of the safety analyses for adverse events is above in Key Question 1.2.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
DTG_ER_Analysis.R	DTG exposure-response and safety analyses for the Phase II/III studies	Ongoing PM Reviews\Dolutegravir_NDA204790_JAF\ER Analyses
ER_Safety_Analysis.R	Analyses for DTG serum creatinine, liver enzyme, and other laboratory Aes	Ongoing PM Reviews\Dolutegravir_NDA204790_JAF\ER Analyses
ConMeds_HepB.R	Summary information of the concomitant medications subjects coinfected with hepatitis B were on during treatment	Ongoing PM Reviews\Dolutegravir_NDA204790_JAF\PPK Analyses
Pediatric_PK_ING112578	Pediatric PK and dosing analyses	Ongoing PM Reviews\Dolutegravir_NDA204790_JAF\PPK Analyses

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