CLINICAL REVIEW

Application Type	NDA
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Division / Office	Division of Antiviral Products/ Office of Antimicrobial Products
Reviewer Names	Charu Mullick MD Wendy Carter DO Yodit Belew MD
Review Completion Date	May 17, 2013
Established Name	Dolutegravir
Proposed Trade Name	Tivicay
Therapeutic Class	Integrase Inhibitor
Applicant	GSK
Formulation	50 mg tablet
Dosing Regimen	One tablet once or twice daily
Indication	Treatment of HIV-1 infection
Intended Population	HIV-1 infected adults and adolescents

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Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of NDA 204790 supporting the use of dolutegravir (DTG) for the treatment of HIV infection in adults and pediatric patients ages 12 years and older. This recommendation is based on data from four phase 3 adult clinical trials and one pediatric trial. Findings from these trials support an acceptable risk-benefit assessment for DTG use in the following HIV-infected populations: 1) treatment naïve adults, 2) treatment experienced, integrase strand transferase inhibitor (INI) naïve adults, 3) treatment experienced, INI experienced adults, and 4) treatment-naïve and treatment experienced INI naïve adolescents.

The efficacy of DTG 50 mg once daily (QD) in the treatment naïve population was demonstrated in two adequate and well-controlled trials. Dolutegravir, in combination with other antiretroviral (ARV) agents, was superior to an efavirenz containing regimen in study ING114467 at week 48. Virologic response, defined as the proportion of subjects with HIV RNA < 50 copies/ml, was 88% for DTG and 81% for EFV. In the second treatment naive trial ING113086, DTG containing regimen was non-inferior to raltegravir (RAL) containing regimen at week 48. Virologic response at week 48 was observed in 88% and 86% subjects in the DTG and RAL arms, respectively. Lastly, efficacy in the treatment experienced, INI naïve population was demonstrated in trial ING111762, comparing DTG 50 mg QD to RAL, each in combination with an optimized background regimen (OBR). Superiority of DTG was demonstrated at Week 24 with virologic response observed in 79% and 70% subjects in the DTG and RAL arms, respectively.

The efficacy of DTG 50 mg twice daily in treatment experienced, INI experienced subjects was demonstrated in study ING112574. In a population with advanced HIV disease, limited viable ARV options, and with evidence of failure to an INI containing regimen; the addition of DTG resulted in mean viral load decline of 1.4 $\log_{10}$ from baseline by study day 8. DTG administered with an OBR resulted in virologic response of 63% at week 24 and increases in CD4 count. Response to DTG was primarily influenced by presence of INI substitutions involving Q148 pathway and baseline susceptibility to DTG. Although data are from limited subjects in a non-comparative, open-label trial; day 8 and week 24 results taken together provide substantial evidence of DTG activity and efficacy of a DTG containing regimen over 24 weeks in a highly treatment experienced population with limited ARV options.

In all adult trials, DTG treatment resulted in immunologic benefit with mean increases in CD4 cell counts from baseline. Virologic responses to DTG were comparable by race and gender.

The primary safety concerns with DTG include risk for hypersensitivity reactions and risk for elevated liver chemistries in the setting of hepatitis B and/or C coinfection. Hypersensitivity reactions characterized by rash, constitutional findings and in some cases with evidence of liver involvement were observed in clinical trials. Overall, these events were observed in 1% or fewer subjects in adult trials. Given the severity and life-threatening potential, the Applicant's proposal to convey the risk in the label Warnings/Precautions section is acceptable.

The hepatic adverse event and laboratory profile of DTG 50 mg QD was generally similar to comparator drugs, RAL or Atripla. Graded ALT or AST increases in the DTG arms were more frequent in HBV/HCV coinfected groups compared to mono-infected group, a finding consistent with each comparator drug and also consistent with observations in the general HIV population treated with antiretroviral agents. The hepatic events and laboratory profile for DTG 50 mg QD dose and BID dose was generally comparable. Potentially concerning cases with at least grade 3 ALT increases were confounded by HBV/HCV, or with evidence of pre-existing liver disease, or confounded by concurrent use of known hepatotoxic medications; and no definitive case of hepatoxicity was identified. Notably, more cases of HBV/HCV reactivation or immune reconstitution inflammatory syndrome (IRIS) were observed in DTG treated subjects compared to controls across trials. Although viral reactivation and/or IRIS were plausible diagnoses, hepatotoxicity could not be conclusively excluded in these cases. Based on severity of liver chemistry elevations, a Warning for liver biochemistry elevations and recommendation for monitoring of liver enzymes for hepatotoxicity is warranted HBV/HCV coinfected patients

Other safety issues of interest include the renal safety, psychiatric events and musculoskeletal events of interest. Renal failure events in phase 3 trials occurred in 1% or fewer subjects, at a frequency similar to the controls, and all events were confounded by ongoing renal disease or concurrent use of nephrotoxic medication. Dolutegravir inhibits renal transport of creatinine by blocking renal organic cation transporter 2 proteins (OCT2). Dolutegravir therefore results in small increases in mean serum creatinine from baseline of magnitude 0.1 mg/dL. The increases appeared by week 1 of treatment and remained at a plateau throughout the dosing period. Dolutegravir had no effects on the glomerular filtration rate or renal plasma flow measured using highly specific markers. Dolutegravir effects on serum creatinine were similar for the 50 mg QD and BID dose. The psychiatric event profile of DTG was notable for a high frequency of insomnia observed relative to the control in one phase 3 trials. Increase serum creatine kinase was mostly asymptomatic and observed at a frequency comparable to controls.

Overall, the safety profile of DTG dosed either 50 mg QD or BID was generally similar and acceptable.

Finally, the proposed adolescent dose 50 mg QD achieves exposures in adolescents within the targeted exposure range from adult data in a similar population. Efficacy at week 24 in the adolescent trial subjects was 65%, with associated improvements in mean CD4 count from baseline which provide additional supportive evidence. Safety analysis in adolescent subjects suggested DTG administered 50 mg QD is generally safe and well tolerated in this population, with no unexpected safety concerns compared to adult trial findings.

1.2 Risk Benefit Assessment

Risk-Benefit Assessment for Adults

Dolutegravir, in combination with other ARV drugs, was shown to be efficacious in a broad population of HIV-infected adults in phase 3 trials.

At week 48 in treatment naïve trials, efficacy of DTG 50 mg QD was demonstrated compared to EFV or RAL containing regimens, each a preferred agent for combination therapy in treatment naïve patients recommended by DHHS adult HIV treatment guidelines. In treatment experienced INI naive subjects, the regimens containing DTG, again dosed 50 mg QD were shown to be superior to RAL at week 24. Lastly, in treatment-experienced INI experienced subjects, DTG dosed 50 mg BID with an OBR resulted in virologic response defined as HIV RNA < 50 copies/ml in 63% at week 24. In all trial populations, virologic response to DTG was accompanied by increases in CD4 cell counts.

The chief safety concerns with DTG include risks for hypersensitivity reaction and risk for elevated liver chemistries in the setting of hepatitis B and/or C coinfection. Hypersensitivity reactions were observed in 1% or fewer subjects in clinical trials. Hypersensitivity reactions characterized by rash, constitutional findings and in some cases with evidence of liver involvement were observed in clinical trials. Labeling for this serious condition including possible presentations and recommendation to discontinue treatment proposed by the Applicant in the Warnings/Precautions is acceptable.

The hepatic adverse event and laboratory profile of DTG 50 mg QD was generally similar to comparator drugs, RAL or Atripla. The adverse event and laboratory profile for DTG 50 mg QD dose and BID dose was also generally comparable. Potentially concerning cases with at least grade 3 ALT increase were confounded by HBV/HCV, or with evidence of pre-existing liver disease, or confounded by concurrent use of known hepatotoxic medications; and no definitive case of hepatoxicity was identified. More cases of HBV/HCV reactivation or IRIS were observed in DTG treated subjects compared to controls across trials. Although viral reactivation and/or IRIS were plausible diagnoses, hepatotoxicity could not be conclusively excluded in these cases. Based on severity of liver chemistry elevations, a Warning for liver biochemistry elevations and

recommendation for monitoring of liver enzymes for hepatotoxicity is warranted HBV/HCV coinfected patients

Other safety issues include small non-progressive increase in serum creatinine considered non-pathologic and secondary to DTG inhibition of OCT2 renal transporter. No excess of renal failure events were observed with DTG 50 mg QD compared to EFV or RAL; and DTG events were confounded by pre-existing renal disease or concurrent use of another nephrotoxic agent. The renal adverse event and laboratory profile was generally similar between DTG 50 mg QD and BID dose. Psychiatric adverse event profile of DTG was notable for a relatively high frequency of insomnia reported in one phase 3 trial. No unusual trends or new safety issues were observed with DTG twice daily dose; and the overall safety profile was generally similar to observations with QD dosing. Graded increase in serum creatine kinase was mostly asymptomatic and observed at a frequency comparable to controls.

In addition to the above-mentioned favorable efficacy and safety profile, DTG offers advantages over approved in-class agents including QD dosing and a more favorable renal safety profile compared to RAL and elvitegravir/cobicistat/ emtricitabine/tenofovir, respectively. Another advantage of DTG is a higher barrier to resistance development. While resistance to background drug class or INI/NNRTI class emerged in subjects failing RAL or EFV in treatment-naïve trials, no background drug class resistance or INI substitutions with decrease in DTG susceptibility was observed in subjects failing DTG.

For the proposed DTG dose 50 mg BID, the risk-benefit assessment should be considered in the context of the intended target population of highly treatment experienced patients with INI experience. Although safety and efficacy for this dose are from limited subjects in an open-label non-comparator trial, there is substantial evidence of DTG antiviral effect observed as early as day 8 (1.4 $\log_{10}$ decline in HIV RNA) and of DTG efficacy in combination with other ARVs at 24 weeks (63% response rate) in subjects. Overall, the safety profile for DTG 50 mg BID was comparable to the 50 mg QD dose in relatively similar population of treatment-experienced subjects. No new or unique safety findings were observed with the BID dose. Further, no relationships between DTG exposures and key safety concerns were identified. These findings taken together demonstrate DTG dosed 50 mg BID has an acceptable safety profile for the intended population.

In conclusion, data support a favorable risk/benefit assessment for DTG 50 mg QD for treatment naïve and treatment experienced INI naïve populations. Data also support a favorable risk/benefit assessment for DTG 50 mg BID for the intended population of treatment-experienced, INI experienced patients.

Risk-Benefit Assessment for Pediatrics

HIV pediatric trials are predominately single-arm, uncontrolled trials with the primary aim of showing comparable PK with adults, provide 24 week or longer safety data and demonstrate the activity of the drug is generally within the range observed for adults. The required data to support an indication in HIV-1 infected pediatrics subjects is the pharmacokinetic and safety data. Efficacy data are considered supportive. The effectiveness in pediatrics is extrapolated based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects. Thus, the pharmacokinetic data are sufficient to extrapolate efficacy; that is, if the effective exposures (AUC24, C24) from the adult trials are reached in the pediatric trials, it can be presumed, the new drug is also effective in pediatric population.

The Applicant's effort to provide pediatric (adolescent) data at the time of NDA application for an NME, dolutegravir, is commendable. The submitted data provides complete pharmacokinetic data to allow the review team to conclude that the proposed DTG dose of 50 mg QD achieves exposures in adolescents within the targeted exposure range. Thus the applicant has shown that the selected dose meets the trial's primary endpoint. One can therefore conclude that extrapolation of efficacy for DTG can be made for the adolescent population with HIV-1 infection. Supportive efficacy data, from 23 treatment-experienced INI naïve subjects ages 12-17 years was also provided This number only represents a subset of subjects (adolescents) from the overall pediatric trial P1093, and it is comparable to the number of adolescent subjects enrolled in other, HIV-1 pediatric trials. The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 was 65% (15/23). The response rate in adolescents was not markedly different from the adult trial in treatment-experienced INI naïve subjects (79%), albeit numerically lower response rate. The response rate is comparable to other trials in treatment-experienced adolescent subjects.

As mentioned, safety of DTG in pediatric (adolescent) subjects cannot be extrapolated. Safety data from a pediatric study is required to demonstrate that the selected dose and exposures (AUC) are generally safe and tolerated when used in the pediatric subjects. The Applicant submitted a 24-Week safety data for the 23 subjects. Longer-term data (up to 72-weeks) was available for a subset of subjects. Overall, the safety analysis suggests that DTG is generally safe and well tolerated in adolescent subjects. There were no deaths, SAE, Grade 3 or higher clinical events or discontinuations due to adverse events. No new or unique safety findings compared to adults were observed. Overall, DTG has a favorable benefit-risk profile for the intended adolescent population.

Although DTG was evaluated in treatment-experienced, INI-naive adolescent subjects, the indication may be extended to include treatment-naïve adolescent subjects for several reasons. First, the dose, 50 mg QD, has been shown to be generally safe and tolerated in treatment-experienced adolescent subjects, thus a reasonably safe drug to recommend in treatment-naïve adolescent patients. Second, the effectiveness of 50 mg

QD was demonstrated in both treatment-naïve and treatment-experienced, INI-naïve adults. In fact, as expected, DTG 50 mg QD demonstrated higher efficacy rate in naives compared to treatment-experienced, INI-naive adult subjects. Therefore, since the dose remains unchanged, it is reasonable to expect that DTG 50 mg QD would be as effective, if not more effective, in treatment-naïve adolescent patients compared to treatment-experienced, INI-naïve adolescent subjects. Finally, for those naïve adolescent patients who may initiate HIV treatment with INI-based regimen, DTG may be a preferred option as it is a QD regimen.

In sum, data in this NDA support a favorable risk-benefit assessment for DTG in the different studied adult and adolescent populations.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A risk management plan indicates routine monitoring of the safety profile for events such as hypersensitivity reactions, hepatic, renal and psychiatric safety in ongoing and planned clinical trials and routine pharmacovigilence activities. The clinical data from the Phase 3 trials supports the proposed plan to conduct routine pharmacovigilence monitoring. The Division agrees no additional risk management activities are required at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time of action for this NDA, the following PMR/PMCs should be issued. At the time of this review, dates for study completion and final study report submission for the clinical/PREA PMC/PMRs are pending and will be discussed with the Applicant during PMR/labeling negotiations.

1. Submit the final study reports for 48 week data analyses from the ongoing Phase 3 studies ING111762 and ING112574.

2. Submit the final study report for 24 week data analyses for the safety, efficacy, and resistance evaluation from the ongoing study ING116529 (Viking-4 evaluating dolutegravir 50 mg twice daily).

3. Deferred pediatric study under PREA for the treatment of HIV-infection in pediatric subjects (b) (4) to <12 years of age. Conduct a pediatric safety and antiviral activity study of dolutegravir in HIV-1 infected pediatric subjects (b) (4) to less than 12 years old. The safety of dolutegravir in pediatric subjects should be evaluated for a minimum of 24 weeks.

4. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects 2 to less than (b) (4) years of age. Conduct a pediatric study to evaluate the safety and antiviral activity of dolutegravir in HIV-1 infected pediatric subjects 2 to less than (b) (4) years old. The safety of dolutegravir in pediatric subjects should be evaluated for a minimum of 24 weeks.

5. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects 4 weeks to less than (b) (4) years of age. Conduct a pediatric study to evaluate the safety and antiviral activity of dolutegravir in HIV-1 infected pediatric subjects 4 weeks to less than (b) (4) years old. The safety of dolutegravir in pediatric subjects should be evaluated for a minimum of 24 weeks.

6. Conduct the requested (b) (4) testing for drug substance to target (b) (4) degradation, evaluate both drug substance and drug product impurities methods using these conditions, and submit the data as a Changes Being Effected in 0 Days Supplement to be filed within 6 months from the date of NDA action.

2 Introduction and Regulatory Background

2.1 Product Information

Dolutegravir (DTG, dolutegravir sodium) is an integrase strand transfer inhibitor of human immunodeficiency virus type-1. Dolutegravir inhibits viral replication by blocking the integrase enzyme responsible for insertion of viral genome into host cell DNA. Two other INIs, raltegravir and elvitegravir, are currently marketed for HIV treatment. Dolutegravir, a new molecular entity, will be the third INI added to this mechanistic class.

Established name:	Dolutegravir (GSK 1349572)
Trade name:	Tivicay™ (under review)
Chemical class:	New molecular entity
Pharmacologic class:	Integrase strand transfer inhibitor

Proposed indication:	Dolutegravir in combination with other antiretroviral agents indicated for the treatment of HIV-1 infection in adults and children ages 12 years and older	
Dosage form:	50 mg tablet	
Dose and regimen:	Adults	
	50 mg once daily:	treatment-naive
	50 mg once daily:	treatment-experienced, INI-naïve
	50 mg twice daily:	treatment-experienced, INI-experienced
	Pediatric	
	50 mg once daily:	INI-naïve (treatment-naïve or treatment-experienced) patients ages 12 years or older and at least 40 kg body weight

2.2 Table of Currently Available Treatments for Proposed Indications

Currently 27 agents are approved for the treatment of HIV infection in the adult populations (not including all approved fixed dose combinations). As shown in Table 1, approved drugs belong to six mechanistic classes namely, nucleos(t)ide reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), INI, CCR5 antagonist, and fusion/entry inhibitor. Two approved INIs are raltegravir which is approved for both treatment naïve and treatment-experienced patients. The second INI, elvitegravir, is currently approved only as part of the FDC Stribild. Stribild, comprising of EVG, cobicistat, tenofovir, emtricitabine; is approved for treatment-naïve HIV-infected adults.

Table 1: **Currently approved antiretroviral drugs for adults**

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx/Videx EC®
	Zalcitabine (ddC)	Hivid®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir (ABC)	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavirdine	Rescriptor®
	Nevirapine (NVP)	Viramune®
	Efavirenz (EFV)	Sustiva®
	Etravirine (ETR)	Intelence®
	Rilpivirine	Edurant®
PI	Indinavir (IDV)	Crixivan®
	Ritonavir	Norvir®
	Nelfinavir	Viracept®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel	Fortavase®
	Amprenavir	Agenerase®
	Fosamprenavir (FPV)	Lexiva®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Atazanavir (ATV)	Reyataz®
	Darunavir (DRV)	Prezista®
	Tipranavir	Aptivus®
Integrase Inhibitor	Raltegravir (RAL)	Isentress®
	Elvitegravir/cobicistat/ emtricitabine/tenofovir	Stribild®
CCR5 receptor antagonist	Maraviroc (MVC)	Selzentry®
Fusion/entry Inhibitor	Enfuvirtide (T-20)	Fuzeon®

For the pediatric population, treatment of HIV infection relies on several drugs mentioned above. The following table summarizes currently approved ARVs for use in pediatric population.

Table: Currently approved pediatric antiretroviral drugs

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT or ZDV)	Retrovir®
	Didanosine (ddI)	Videx®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir (ABC)	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Nevirapine (NVP)	Viramune®
	Efavirenz (EFV)	Sustiva®
PI	Ritonavir (rtv)	Norvir®
	Nelfinavir	Viracept®
	Fosamprenavir	Lexiva®
	Lopinavir/ritonavir (LPVR/rtv)	Kaletra®
	Atazanavir (ATV)	Reyataz®
	Darunavir (DRV)	Prezista®
	Tipranavir	Aptivus®
Integrase Inhibitor	Raltegravir (RAL)	Isentress®
CCR5 inhibitor	Maraviroc (MVC)	Selzentry®
Fusion Inhibitor	Enfuvirtide (T-20)	Fuzeon®

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is not marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

No specific class-related toxicities have been identified to-date with the INI class. Raltegravir is associated with development of serious skin reactions as well as psychiatric events including suicidal ideation. Myopathy, rhabdomyolysis, and creatinine kinase elevations have also been reported with raltegravir use. Elvitegravir, marketed as part of the FDC Stribild, is associated with gastrointestinal side-effects chiefly diarrhea and nausea. Proximal renal tubulopathy observed in Stribild clinical trials was attributed to tenofovir and cobicistat in the FDC, and not EVG. Other events observed in Stribild clinical trials were musculoskeletal events and sleep disorders. Potent antiretroviral therapy, regardless of ARV class, can lead to immune reconstitution syndrome with paradoxical worsening of subclinical infection secondary to treatment-related immune restoration.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Investigational New Drug application (IND 75382) for DTG was submitted on 24 October 2007. The Applicant met with the Agency to discuss the DTG development program on several occasions. Major regulatory milestones include a Type C Meeting (February 2009) to agree Phase 2 and 3 development plans, Type B, End of Phase 2 Meetings [clinical and chemistry, manufacturing and controls (CMC), July 2010] and Pre-NDA Meetings (CMC, July 2012; Clinical, September 2012).

2.6 Other Relevant Background Information

The DTG IND was transferred by GlaxoSmithKline to ViiV Healthcare during the course of DTG clinical development in August 2010. Dolutegravir is owned by Viiv Healthcare; GSK is the Applicant for this NDA.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

FDA's Division of Scientific Investigations (DSI) performed clinical site inspections of five clinical trial sites enrolling subjects in phase 3 trials. The DSI inspections of medical records did not raise concern regarding data integrity and data from these sites were determined as acceptable. Please refer to the DSI clinical inspection summary for NDA 204790 for details. Pharmacokinetic data obtained in the pediatric trial P1093 are pivotal because the primary study endpoint is based on pharmacokinetic parameters. Bioanalytical site inspections for these pediatric samples were therefore performed. FDA manufacturing site inspections were also performed. Outcomes of the bioanalytical and manufacturing site inspections are pending at the time of this review.

Although the Applicant confirmed lack of data integrity issues at clinical sites in the DTG development program, two phase 3 sites were closed by the Applicant. The Agency was informed about one site closure with the NDA submission; notification of the second closure occurred during the NDA review cycle. For each issue, the review team collaborated with Antoine El-Hage from the DSI to review the Applicant's information and to determine handling of data from these sites.

Volvograd site
One site located in Volvograd, Russia was closed by the Applicant after Good Clinical Practices (GCP) violations were identified at this site in another Viiv-sponsored trial A4001101, a non-IND study of maraviroc. The site, Volgograd Regional Center for AIDS, enrolled subjects in two DTG phase trials ING111762 and ING113086. Briefly, GCP violations at this site were related to validity of biological samples collected in the maraviroc trial. An investigation by the sponsor revealed mismatched plasma samples by DNA testing for 13 participants at the site. As a result, the Applicant closed the site

for all DTG trials, and reported the site and investigator to DSI. The Applicant also excluded subjects enrolled at this site from efficacy analysis for ING111762. Of note, the Applicant did not exclude the implicated site from efficacy analysis for study ING113086 because non-compliance issues were reported after statistical analyses were completed for this trial. In lieu of excluding the site from the overall efficacy analysis, the Applicant chose to conduct sensitivity analysis for the primary efficacy endpoint.

The review team, in agreement with DSI, determined that the site be excluded from all safety and efficacy analyses for each trial based on the serious nature of GCP violations and to remain consistent with the overall approach for handling data from this site. During this investigation, the review team expressed concern whether noncompliance was site-specific or a region/country–specific issue. In response, the Applicant provided assurance that noncompliance findings were site-specific and similar irregularities were not noted at monitoring visits in any of the other Russian Federation sites. Additional independent audits of two other Russian sites performed by GSK or on behalf of GSK also did not reveal non-compliance issues. A sensitivity analysis performed by FDA excluding sites located in Russia did not affect the overall efficacy outcome in either study. The review team, again in collaboration with DSI, determined inspection of any Russian Federation sites was not necessary because 1) data from the Volvograd site was excluded from all FDA analyses, 2) the Applicant provided written assurance supporting integrity of data collected at other Russian Federation sites, and 3) findings from above-mentioned FDA sensitivity analyses supporting limited impact of these data on overall efficacy outcomes. Also, refer to section 5.2 Review Strategy for specific details regarding handling of data from this site.

Houston site
One US clinical site located in Houston, Texas was closed by the Applicant because the site principal investigator did not comply with corrective actions instituted by the Applicant. This site enrolled 23 subjects in phase 3 DTG trials. The Applicant considered data from the site to be reliable. Site closure was described by the Applicant as “deterioration of working relationship” with the site principal investigator. Specifically, the investigator did not comply with remedial measures to address issues identified in an audit, and did not provide assurance of corrective action or improvement. The site was closed in April 2013 following which the Agency was informed of the decision. The review team assessed this issue with DSI. It was determined to include data from the site in FDA analyses based on 1) Applicant’s assurance of data integrity from this site, and 2) results from a recent DSI inspection of this site conducted as part of routine FDA site inspection for another NDA application which did not raise concerns for noncompliance.

3.2 Compliance with Good Clinical Practices

The Applicant states DTG clinical trials were conducted in accordance with the Declaration of Helsinki. Studies followed guidelines prescribed by the International Conference on Harmonization of Good Clinical Practices (GCP). According to the Applicant, GCP noncompliance issues were not identified in DTG trials. GCP violations at one site reported in a study of maraviroc resulted in exclusion of this site from FDA analysis as discussed in detail in section 3.1. The DTG trials were conducted under IND 75382 according to FDA requirements. Lastly, FDA site inspections did not reveal evidence of GCP non compliance at the inspected sites.

3.3 Financial Disclosures

The majority of investigators participating in phase 3 DTG trials did not have financial interests in GSK or ViiV Healthcare, as described in 21 CFR 54.2 (a), (b), or (c). Four investigators, each enrolling (b) (6) subjects in individual phase 3 trials entered into financial arrangement with the Applicant. One investigator enrolled (b) (6) subjects (b) (6); the investigator received $25,250 as honoraria for each study. The second investigator enrolled (b) (6) subjects (b) (6); this investigator received up to $93,215 as honoraria for each study. A third investigator enrolled (b) (6) subjects (b) (6) the investigator received up to $40,650 honoraria for each study. The fourth investigator enrolled (b) (6) subjects (b) (4); the investigator received $53,700 as honoraria in each study. This financial disclosure information is not likely to affect the overall results because each investigator enrolled (b) (6) subjects in each trial. In addition, efficacy for the pursued HIV treatment indication relies on an objective endpoint, HIV viral load, based on laboratory results and not subjective investigator-based endpoints, thereby limiting ability of investigators to impact the efficacy results. Lastly, any investigator related bias is unlikely to influence overall outcomes because phase 3 trials supporting this NDA were large, multicenter, double-blind trials.

Additionally, refer to the Clinical Investigator Financial Disclosure Review Template in section 10.4 of this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Dolutegravir sodium is [redacted] slightly soluble in water, with solubility varying across physiological pH ranges. The proposed tablet formulation is composed of [redacted] Each film-coated tablet contains 52.6 mg of DTG sodium.

A [redacted] formulation was developed during phase 1 clinical development. The 50 mg formulation, evaluated in phase 2b and 3 trials, was supported by bioavailability and dissolution data. The to-be-marketed formulation will be identical to the formulation evaluated in phase 2b/3 clinical trials, with slight difference in the tablet color and degree of concavity. Refer to CMC reviews by Drs. Lin Qi and Zhou Maotang for details.

No separate formulation is proposed for adolescent use. The same 50 mg tablet, proposed for adults, is also proposed for adolescents.

4.2 Clinical Microbiology

Please refer to the virology review by Dr. Lisa Naeger for details.

Antiviral Activity in Cell Culture
Dolutegravir exhibited activity against HIV-1 reference strains with EC50 values ranging from 0.5 nM to 2.1 nM in PBMCs and MT-4 cells. Dolutegravir demonstrated activity against a diverse panel of clade B isolates, group M clades A, C, D, E, F, G and group O isolates with EC50 values ranging from 0.02 nM to 2.1 nM.

Dolutegravir also had sub-nanomolar activity against HIV-2 clinical isolates in PBMC assays. The effect of 100% human serum was extrapolated as 75-fold based on cell culture assays.

Resistance in Cell Culture
Substitutions in INI shown to emerge in passaged resistant virus include E92Q, G118R, S153Y, T and F, G193E and R263K. Passage of mutant viruses with the Q148R or H substitutions selected for additional substitutions in INI including L74M, E92Q, T97A, E138K, G140S, M154I, and N155H.

Treatment-emergent Resistance in Clinical Trials

Treatment naïve phase 3 trials
FDA resistance analysis was performed for subjects with HIV RNA > 400 copies/mL at the virologic failure time point or at Week 24 if resistance data was available; these subjects are defined as virologic failures. In phase 3 treatment-naïve subjects, at time of virologic failure no DTG subjects had a decrease in DTG susceptibility or decreases in susceptibility to background NRTIs in the FDA resistance analysis. One subject in Study ING114467 had a treatment emergent INSTI substitution E157E/Q detected at Week 24 but no change in DTG susceptibility. In the comparator arms, 5 subjects on the RAL treatment regimen in Study ING113086 had emergent INSTI resistance substitutions and 2 of these subjects also had emergent NRTI substitutions associated with the background NRTIs; and 6 subjects in the ATRIPLA arm of Study 114467 had emergent EFV resistance substitutions with one of these subjects also having emergent NRTI resistance substitutions.

Treatment experienced, INI naïve trials
For the FDA resistance analysis, virologic failure was defined as HIV RNA >400 copies/mL at the failure time point or Week 24 or for subjects having resistance data at failure. By these criteria, there were 9% of subjects (33/357) in the DTG arm compared to 14% (49/362) of subjects in the RAL arm. Thirty-one percent (n=5) of subject isolates with post-baseline INSTI resistance data in the DTG arm had emergent INSTI substitutions (L74M and I, Q95Q/L, T97A, V151V/I, and R263K). None of the subject isolates in the DTG arm with emergent INSTI substitutions had phenotypic changes in susceptibility to either DTG or RAL. Four subjects (31%) in the DTG arm taking a background NNRTI had emergent NNRTI resistance substitutions [2 subjects were taking EFV] compared to 4 (12% subjects with emergent NNRTI substitutions in the RAL arm). No subject isolates on a PI-containing regimen had emergent PI substitutions in the DTG arm of this study.

Treatment experienced, INI experienced trial
On functional DTG monotherapy, 6 subjects had treatment-emergent INSTI substitutions (L74M, T97T/A G140A and G148R, M154I and E157E/Q) at Day 8. Five of these subject isolates had Q148R or H substitutions or mixtures plus at least one other INSTI substitution (e.g., G140S or A) at baseline. The baseline DTG phenotype of these 5 subject isolates ranged from 0.7- to 34-fold and the fold change in DTG susceptibility from baseline at Day 8 ranged from 1.1- to 32-fold.

In the FDA resistance analysis at Week 24, 18 subjects had treatment-emergent INSTI substitutions post-Day 8 on the DTG BID regimen. The most common substitution was T97A, which emerged in 45% of subject isolates. Other frequently emergent substitutions, which emerged in 10-20% of subject isolates, included E138K or A, G140S or A, Y143H or C, Q148H or R or K and M154I. The baseline mean DTG fold-change from reference was 6-fold for subject isolates with emergent INSTI substitutions

(n=18). Four subjects with emergent Q148 substitutions had a mean 49-fold change from baseline in DTG susceptibility, which highlights the significant impact on DTG susceptibility of emergent substitutions at this position. The emergence of T97A and E138 substitutions in the presence of G140S and Q148H (either present at baseline or emergent) resulted in >25-fold decreases in DTG susceptibility from baseline change. Treatment-emergent resistance to background ARV agents was observed in subjects identified as virologic failures by FDA resistance analysis. Refer to Dr. Lisa Naeger's clinical virology review for details.

Cross-resistance
In the treatment-naïve trials, none of the DTG FDA resistant analysis subjects with post-baseline resistance data were resistant to RAL. In the treatment-experienced INSTI-naïve trial, none (n=18) of the DTG FDA resistant analysis subjects with post-baseline resistance data were resistant to RAL. Additionally, none of the subject isolates in the DTG arm with emergent INSTI substitutions (n=5) had phenotypic changes in susceptibility to either DTG or RAL. The 11 subject isolates in the RAL arm with emergent INSTI substitutions all had RAL phenotypic resistance and of these 4 isolates (36%) had DTG phenotypic resistance (≥4-fold change from reference in DTG susceptibility). In Viking-3, all the subject isolates of Week 24 FDA resistance subset with INSTI substitution emergence were cross-resistant to RAL, as expected based in study inclusion criteria.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the review by Dr. Mark Seaton for details of nonclinical toxicology findings. Key nonclinical findings are summarized below.

General Toxicology
The chief toxicity finding in nonclinical studies was gastrointestinal (GI) toxicity observed in mice, rats, and cynolgomus monkeys. Gastric mucosal effects, including hemorrhage from gastric tissue in rat species, were considered secondary to local drug intolerance and not related to DTG systemic exposures. Gastric hemorrhage was noted microscopically in rats at exposure margins approximately 24-fold the anticipated human exposures and in monkeys at exposures approximately 3-fold the anticipated human exposures. For toxicity due to local GI effects, safety margins calculated using dose (mg/kg) or body surface area (BSA) were considered appropriate for comparison instead of systemic exposure based comparisons. The NOAEL for the nine month monkey study was 15-fold and 8-fold the human mg/kg equivalent dose (based on 50 kg human), and 5-fold and 3-fold the human mg/m^2 equivalent dose for a 50 mg QD and BID dose, respectively. Gastric-related adverse events observed in clinical trials are discussed in section 7.3.4 of this review.

Other findings in animal studies include effects on the liver, kidney, thymus and mesenteric lymph nodes. Liver toxicities observed in a two-week monkey study included hepatocellular single cell necrosis and diffuse hepatocellular hypertrophy and vacuolation in male monkeys given the high dose. Corresponding systemic exposures in high dose animals were approximately seven-fold and five-fold the expected human exposures for the recommended clinical doses 50 mg QD or BID, respectively. The NOAEL for the two week study in monkeys was 100 mg/kg/day, corresponding to systemic exposures four-fold and three-fold the expected human exposures for the 50 mg QD or BID dose, respectively. There were no toxicologically-significant hepatotoxicity in subchronic or chronic (i.e., one month or longer) nonclinical toxicology studies. Hepatic events observed in clinical trials are discussed in section 7.3.4 of this review.

Carcinogenesis and Mutagenesis
The carcinogenic potential of DTG was assessed in 2-year studies in rats and mice. Dolutegravir was not carcinogenic in these studies. Dolutegravir was not mutagenic or clastogenic using in vitro tests in bacteria and cultured mammalian cells and an in vivo rodent micronucleus assay.

Reproductive Toxicology
Effects on male or female fertility, parturition, or maternal behavior were not observed in animal reproductive and developmental toxicity studies. No teratogenicity was observed in animal studies. In juvenile toxicity studies, decreased food consumption and decreased body weights were observed in females at the highest dose, and two deaths in male rats were considered to be test article related. The NOAEL in juvenile rats corresponded to systemic exposures approximately 6-fold exposures at the recommended clinical dose of 50 mg QD and 4-fold exposures at the at 50 mg BID clinical dose. In clinical trials, no congenital anomalies were observed in pregnancies reported with DTG use; refer to section 7.6.2 for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Dolutegravir is an integrase strand transfer inhibitor of HIV-1 virus. Dolutegravir inhibits the HIV integrase enzyme by binding to integrase active sites and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration, which is essential for the HIV replication cycle.

4.4.2 Pharmacodynamics

Findings from analyses exploring DTG exposure-virologic response and exposure-safety are summarized here. Please refer to the clinical pharmacology and

pharmacometrics review of this NDA by Drs. Su-Young Choi, Stanley Au, and Jeffry Florian for details.

In treatment-naïve subjects dosed DTG 50 mg QD, no exposure-response relationships were observed. In the treatment-experienced, INI-naïve subjects, an apparent exposure-response relationship observed with all subject data was not reproduced following exclusion of subjects using moderate to strong metabolic inducers in the BR (such as TPV/r or EFV which reduce DTG exposures) or noncompliant subjects. Please refer to section 7.5.5 for DTG dose recommendations when co-administered with metabolic inducers.

In treatment-experienced, INI-experienced subjects, no exposure-response relationship was observed. The inhibitory quotient (IQ), however, was observed to correlate with virologic response; the relationship was driven primarily by virus susceptibility to DTG.

No correlations were observed between drug exposure and safety parameters of interest such as hypersensitivity reaction, hepatobiliary adverse events, ALT elevations, rash, renal failure adverse events, or creatinine increases. Studies evaluating pharmacodynamic effects of DTG, namely a renal function study ING114819 and a Thorough QT (TQT) study ING111856 are discussed in sections 7.4.4 and 7.4.5 of this review.

4.4.3 Pharmacokinetics

This section provides a brief summary of DTG pharmacokinetics. Please refer to the clinical pharmacology/pharmacometrics review of this NDA by Dr. Su-Young Choi for details.

Absorption
After oral administration, peak plasma DTG concentrations are achieved in 2 to 3 hours. The average terminal half-life is approximately 14 hours and steady-state is achieved after approximately 5 days with repeat dosing.

Distribution
Dolutegravir is highly protein bound. Dolutegravir distributes into cerebrospinal fluid as well as male and female genital tract tissue and secretions in clinical trials. Exposures in genital tissue and secretions ranged between 6-17% of corresponding plasma exposures at steady state.

Metabolism
Dolutegravir is metabolized primarily by the UDP-glucuronosyltransferase, UGT1A1, pathway and CYP3A4 is a minor pathway.

Elimination
Approximately 53% of DTG is excreted in feces and 31% is excreted in urine.

Food Effect
Although drug absorption is increased with co-administration with food, the effect is not considered clinically significant and DTG can be administered with or without food. Phase 3 trial data were obtained in subjects taking DTG without regard to food.

Special Populations
The effects of HIV status, hepatic function, renal function, and UGT1A1 polymorphisms on DTG pharmacokinetics are summarized here. Dolutegravir pharmacokinetic parameters are not significantly different between healthy subjects and HIV-infected subjects. No DTG dose adjustment is required for mild to moderate hepatic impairment; effects of severe hepatic impairment have not been evaluated. No dose adjustment is required for mild, moderate or severe renal impairment (also refer to section 7.4.5); and effects of hemodialysis on DTG concentrations have not been evaluated. Dolutegravir exposure was increased by 30-40% in subjects who were poor metabolizers of UGT1A1. Limited data are available on DTG pharmacokinetics in subjects older than 65 years to render conclusions about effects in elderly population. Dolutegravir pharmacokinetics in the adolescent pediatric population is discussed in section 8 Pediatric Review, along with pediatric antiviral activity findings.

5 Sources of Clinical Data

5.1 Tables of Clinical Trials

The principal source of data for the proposed indication comes from four phase 3 clinical trials conducted in HIV-infected adults, namely, Spring-2, Single, Sailing, and Viking-3 trials. The trials were conducted across three distinct HIV-infected populations: treatment-naïve, treatment-experienced and INI-naïve; and treatment-experienced and INI-experienced populations. As shown in Table 2, data for the treatment-naïve adult indication comes from Spring-2 and Single trials. Data for the treatment-experienced adult indication comes from Sailing and Viking-3 trials. Additionally, data for the adolescent indication for pediatric ages 12 to 18 years comes from study P1093.

Two phase 2b trials, one in treatment-naïve subjects Spring-1, and the other in treatment-experienced, INI-experienced subjects Viking-pilot provide supportive data in adults. Additionally, phase 1 clinical pharmacology studies and pharmacodynamic studies including a TQT study submitted in this NDA package, are discussed in the clinical pharmacology and pharmacometrics review by Dr. Su-Young Choi.

Table 2: Summary of pivotal Phase 3 studies and other supporting clinical studies

Study	Population	Design	DTG dose	Control Arm	Background Drugs	# Subjects Randomized/ treated
Phase 3						
ING113086 Spring-2	Treatment naïve	Randomized, double-blind, active control, non-inferiority	50 mg QD	RAL 400 mg BID	ABC/3TC or TDF/FTC	DTG 413/411 RAL 414/411
ING114467 Single	Treatment naïve	Randomized, double-blind, active control, non-inferiority	50 mg QD	EFV (as part of FDC Atripla)	EFV arm: TDF/FTC; DTG arm: ABC/3TC	DTG 422/414 EFV 422/419
ING111762 Sailing	Treatment experienced, INI-naïve	Randomized, double-blind, active control, non-inferiority	50 mg QD	RAL 400 mg BID	Investigator-selected	DTG 360/357 RAL 364/362
ING112574 Viking-3	Treatment experienced, INI-experienced	Open-label, single arm	50 mg BID	None	Investigator-selected	183
Phase 2b						
ING112276 Spring-1	Treatment naïve	Randomized, Parallel-group, dose-ranging	10, 25, or 50 mg QD	EFV 600 mg QD	ABC/3TC; TDF/FTC	DTG 10 mg: 53/47 25 mg: 41/45 50 mg: 51/46 EFV 50/39
ING112961 Viking	Treatment experienced, INI-experienced	Open-label, single-arm, 2 sequential dose cohorts	50 mg QD or 50 mg BID	None	Investigator-selected	Cohort 1 (50 QD): 27 Cohort 2 (50 BID): 24
Pediatric						
ING112578 P1093	Treatment experienced, INI-naïve	Phase 1/2, open-label, intensive PK and safety study, Ages 6 weeks to < 18 years	50 mg QD (cohort 1)	None	Investigator-selected	Cohort 1 ages ≥12 to <18 yrs: 24; Cohort 2 ages ≥6 to <12 yrs: enrolling

5.2 Review Strategy

Overall Review Strategy

Pooled efficacy analyses were not performed because individual phase 3 studies were distinct with respect to either the population evaluated or comparator arm.

For safety analysis, data were integrated from the treatment-naïve phase 3 trials, Spring-2 and Single. Safety data were also pooled for subjects receiving 50 mg BID dose in Viking-3 and Viking-pilot trials as both trials were conducted in populations with similar baseline disease characteristics and receiving the same DTG dose. Data from Viking-pilot, however, were not included in the Adverse Reaction section of the label. This pooling provided an integrated safety profile for DTG dosed twice daily. In addition, data from phase 2b trial, Spring-1 or ING112276 in treatment-naïve subjects was reviewed for key safety issues. Data from Spring-1 were not included in the overall pooled safety analyses and were not included in the Adverse Reaction section of the label.

As discussed in section 3.1, phase 3 data obtained from one site in Volvograd, Russia were excluded from all analyses performed for this review. Briefly, GCP violations identified in a non-DTG trial at this site led to closure of the site by the Applicant. The findings raised questions about the integrity of DTG data collected at this site. The FDA review team in conjunction with input from DSI determined that data from the Volvograd (site ID 083523 in Sailing and site ID 083505 in Spring-2) should be excluded from all analyses.

Three FDA medical officers completed review of data submitted to this NDA. Dr. Yodit Belew completed review of data from adolescent pediatric trial. Dr. Wendy Carter completed review of data from treatment naïve adult trials. Dr. Charu Mullick completed review of data from treatment-experienced adult trials and the remaining sections of this review.

5.3 Discussion of Individual Studies/Clinical Trials

This section summarizes adult phase 3 trials and the phase 2b trial Viking-pilot. Please refer to section 8 for details regarding pediatric trial P1093.

Spring-2 (ING113086)
This is an ongoing, randomized, double-blind, double-dummy, active-controlled, international, non-inferiority trial being conducted in treatment-naïve HIV-1 infected adults. Subjects were randomized 1:1 to receive DTG 50 mg QD or RAL 400 mg twice

daily, both in combination with an investigator-chosen fixed-dose dual NRTI therapy (either abacavir and lamivudine: ABC/3TC or tenofovir and emtricitabine: TDF/FTC) for 96 weeks. The backbone NRTI therapy was open-label.

To achieve balance in the treatment arms, randomization was stratified by screening HIV-1 RNA (≤100,000 copies/mL or >100,000 copies/mL) and by background NRTI (ABC/3TC or TDF/FTC). Key inclusion criteria included age ≥ 18 years, plasma HIV-1 RNA ≥ 1000 c/mL at screening, and ≤ 10 days of prior therapy with any antiretroviral agent. Additionally, any subject initiating ABC as part of the background therapy must have screened negative for the HLA-B*5701 allele. The primary efficacy objective was to demonstrate non-inferiority of treatment with DTG 50 mg QD compared to the control, RAL 400 mg twice daily in regards to the proportion of virologic responders (HIV-1 RNA < 50 copies/mL) at Week 48, with an NI margin of 10%.

The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA < 50 copies/mL through Week 48 using the FDA 'snapshot' algorithm (Missing, Switch or Discontinuation=Failure). HIV viral load is an established endpoint for assessment of treatment effect, as cited in the FDA Guidance, "Antiretroviral Drugs Using Plasma HIV RNA Measurements-Clinical Considerations for Accelerated and Traditional Approval".

Evaluations for subject safety (history, physical exam, laboratory testing, and adverse event assessments) were performed at scheduled visits: Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, every 12 weeks after Week 48, and Week 96. ECGs were performed at Day 1 and again at Week 96 or discontinuation visit (or if clinically warranted). Laboratory samples were analyzed using a central laboratory and sites were notified of subjects with abnormal results. An independent data monitoring committee (IDMC) was established to review ongoing safety of the subjects and evaluate the efficacy of the study drug. Key stopping criteria included lack of virologic response, pregnancy, switch of background therapy for any reason other than toxicity or tolerability one time (date must be recorded in case report form), QTc interval >550 msec and considered causally related, liver toxicity meeting pre-specified protocol criteria, renal toxicity meeting pre-specified protocol criteria and grade 4 clinical AEs considered causally related.

A total of 827 subjects were randomized; and 822 subjects received at least 1 dose of study medication. Additional details regarding subject disposition are in Section 6.1.3.

Single (ING114467)
This is an ongoing phase 3, randomized, double-blind, double-dummy, active-controlled, international, non-inferiority trial being conducted in HIV-1 treatment-naïve adults. This trial was designed to demonstrate the non-inferior antiviral activity of DTG 50 mg plus ABC/3TC FDC compared to FDC Atripla consisting of EFV, TDF, FTC; both administered QD over 144 weeks. The primary analysis was at Week 48; additional analyses will be conducted after the last subject completes Week 96 and Week 144 on study. The open-label phase of the study is from Week 96-144, or beyond, in countries

where DTG is not yet commercially available. Key inclusion criteria included HIV-1 infected treatment-naïve adults ≥18 years of age with plasma HIV-1 RNA ≥1000 copies/milliliter (copies/mL) at Screening who had a negative HLA-B*5701 allele assessment. The main exclusion criteria were women who were pregnant or breastfeeding, subjects with any degree of hepatic impairment, subjects with any evidence of primary viral resistance in the screening result or, subjects having an estimated creatinine clearance <50 mL/min via Cockcroft-Gault method.

Subjects were stratified by Screening plasma HIV-1 RNA ≤100,000 c/mL or > 100,000 c/mL and CD4 cell count ≤ or > 200 cells/mm^3. The primary efficacy objective was to demonstrate non-inferiority of treatment with DTG 50 mg plus ABC/3TC QD compared to the control, Atripla in regards to the proportion of virologic responders (HIV-1 RNA < 50 c/mL) at Week 48, with an NI margin of 10%. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA < 50 c/mL through Week 48 using the FDA 'snapshot' algorithm (Missing, Switch or Discontinuation=Failure).

Evaluations for subject safety (history, physical exam, laboratory testing, and adverse event assessments) were performed at scheduled visits: Week 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48, every 12 weeks after Week 48, Week 96, every 12 weeks after Week 96, and Week 144. ECGs were performed at Day 1 and again at Week 96 or discontinuation visit (or if clinically warranted). Laboratory samples were analyzed using a central laboratory and sites were notified of subjects with abnormal results. An independent data monitoring committee (IDMC) was established to review ongoing safety of the subjects and evaluate the efficacy of the study drug, and specifically ensure that subjects with high baseline viral HIV-1 RNA were not being sub-optimally treated. Key stopping criteria included lack of virologic response, pregnancy, requires switch of background therapy or dose reduction of study drugs, QTc interval >550 msec and considered causally related, liver toxicity meeting pre-specified protocol criteria, renal toxicity meeting pre-specified protocol criteria and grade 4 clinical AEs considered causally related.

A total of 788 subjects were planned for enrollment; 844 subjects were randomized, and 833 subjects received at least one dose of study medication. Additional details regarding subject disposition are in Section 6.1.3.

Sailing (ING111762)
This is an ongoing randomized, multicenter, double-blind trial evaluating safety and efficacy of DTG 50 mg QD to RAL 400 mg BID, each administered with an optimized background regimen over 48 Weeks in HIV-infected, INI-naïve treatment-experienced adults.

The primary study objective was to assess NI of the DTG-containing regimen to a RAL-containing regimen at Week 48 (pre-specified NI margin 12%). Interim analyses were

performed when the last enrolled subject completed Week 24 visit in order to support the pursued indication for this population.

Subjects with evidence of resistance to at least one agent in at least two ARV classes were enrolled. Stratification factors were screening HIV RNA (> or ≤ 50,000 copies/ml), use of DRV/r as an active agent i.e., without primary PI mutations (capped to a total of 170 subjects), and 2 or < 2 full active agents in the OBR. Limiting DRV use was intended to allow for demonstration of DTG effect in the trial, and to mimic the patient population enrolled in the RAL phase 3 pivotal trials. Subjects were randomized 1:1 to receive DTG or RAL plus a BR consisting of one fully active agent plus a second agent which may or may not be active. After completion of 48 weeks treatment, DTG subjects had the option of continuing in an open label phase. Subjects randomized to RAL were discontinued from study after 48 weeks.

HIV RNA assessments, safety evaluations and IDMC adjudications were similar to those outlined for Spring-2 trial above. Key stopping criteria include liver toxicity stopping criteria and virologic stopping criteria. Protocol-defined virologic failure was defined as plasma HIV-1 RNA decline of < 1 $\log_{10}$ from baseline by Week 16 unless HIV RNA is < 400 copies/ml, or HIV RNA ≥ 400 copies/ml on or after Week 24, or evidence of virologic rebound.

Viking-3 (ING112574)
This is an ongoing single-arm, open-label, multicenter trial evaluating safety and antiviral activity of DTG 50 mg BID in HIV-infected, treatment-experienced adults who have experienced virologic failure on an INI containing regimen.

The primary study objective is to assess efficacy and safety of DTG 50 mg BID administered for at least 24 weeks in combination with an OBR to subjects with INI resistance. Subjects received DTG in addition to their failing regimen for the initial 7 day study period, followed by DTG plus an investigator selected OBR from Day 8 onwards. The primary efficacy endpoint for this study is a composite of both Day 8 antiviral activity representing effects of DTG functional monotherapy, and Week 24 efficacy of DTG containing regimen.

Key inclusion criteria include screening or documented resistance to RAL and/or EVG, and screening or documented historical resistance to at least two ARV classes other than INI class. Protocol defined virologic failure in the functional monotherapy phase was < 0.5 $\log_{10}$ decline in HIV RNA at Day 8 unless RNA was < 400 copies/ml. Virologic failure criteria in the optimized phase were decrease in HIV RNA less than 1 $\log_{10}$ by Week 16, or confirmed HIV RNA ≥ 400 copies/ml on or after Week 24. Safety and HIV RNA assessments in this study were similar to those outlined for Spring-2 trial above.

A total of 183 subjects were enrolled in the trial. Among these, 114 subjects had completed their week 24 visit at the time of data cut-off for submission to this NDA.

ING112961 (Viking-Pilot)
This was a phase 2b, open-label, single-arm, sequential cohort pilot trial designed to assess the antiviral activity of DTG in HIV-infected, treatment-experienced subjects with RAL resistance. Key inclusion criteria were similar to Viking-3 trial presented above. Study design was also similar to Viking-3 with two exceptions: regimen optimization occurred at study day 11 (unlike day 8 in Viking-3), and the study design comprised of two sequentially dosed cohorts.

Subjects were initially enrolled to cohort 1 and received DTG 50 mg QD. As suboptimal response was observed at study day 11 in some subjects in cohort 1, recruitment into this cohort was stopped. The protocol was then amended to enroll a second cohort (cohort 2) where subjects received DTG 50 mg BID initially in addition to their failing regimen and in combination with an OBR after day 11. The total trial duration was 96 weeks. Subjects successfully continuing in cohort 1 had the option of switching to 50 mg BID dose after Week 96. HIV RNA and safety assessments were similar to those outlined for Spring-2 trial previously.

6 Review of Efficacy

Efficacy Summary

Dolutegravir was shown to be efficacious for the treatment of HIV infection in a broad population including treatment-naïve and treatment-experienced patients ages 12 years and older. Dolutegravir, dosed 50 mg QD, resulted in robust efficacy in both treatment naïve as well as treatment experienced, INI naïve adults. Dolutegravir, dosed 50 mg BID, resulted in substantial efficacy in treatment-experienced subjects who had failed an INI regimen; a population with advanced HIV disease and multiple prior antiretroviral exposures. The 50 mg QD dose in INI-naïve adolescents achieved drug exposures comparable to adult target exposures in similar population, and was associated with an acceptable antiviral efficacy at week 24. This section summarizes findings in adult phase 3 trials; please refer to Section 8 for summary findings for adolescents.

In the treatment-naïve subjects, week 48 data from two large randomized, double blind, controlled trials support the efficacy of DTG. Noninferiority to RAL was demonstrated in Spring-2 trial with 88% and 85% subjects achieving HIV RNA < 50 copies/ml in the DTG and RAL arms, respectively (treatment difference 2.5%, 95% CI: -2.2, 7.1). Superiority to the EFV-based regimen Atripla was demonstrated in the Single trial with 88% and 81% subjects achieving HIV RNA < 50 copies/ml in the DTG and EFV arms, respectively (treatment difference 7.4%, 95%; CI: 2.5, 12.3) . Treatment responses favoring DTG over EFV containing regimens in Single were primarily driven by subjects

who discontinued due for adverse events (2% DTG vs. 10% EFV); subjects discontinuing for lack of efficacy were 5% and 6% in the DTG and EFV arms, respectively. Efficacy was observed consistently across key subgroups. In DTG subjects with HIV RNA > 400 copies/ml who had available resistance data, no treatment emergent INI resistance substitutions with decreased DTG susceptibility or background NRTI resistance substitutions were observed.

In the treatment-experienced, INI-naïve trial population, week 24 data from the randomized, double-blind, controlled trial, Sailing, support efficacy of DTG. Superiority to RAL was demonstrated in this trial with 79% and 70% subjects achieving HIV RNA < 50 copies/ml in the DTG and RAL arms, respectively (treatment difference 9.7%, 95% CI 3.4, 15.9). Fewer subjects in the DTG arm (14%) had HIV RNA > 50 copies/ml at week 24 compared to RAL (24%). Efficacy of DTG was observed across key subgroups.

In the treatment-experienced, INI-experienced population with advanced HIV disease and relatively limited treatment options, week 24 data from the Viking-3 trial support efficacy of DTG. A comparator trial design was not ethically appropriate in this population with advanced HIV disease and few viable treatment options. The Viking-3 design allowed demonstration of effects of DTG monotherapy at day 8 when DTG was added to a failing regimen, as well as Week 24 response to DTG-containing regimens optimized with other ARVs. At day 8, decline in mean HIV RNA by 1.4 $\log_{10}$ (-1.5, -1.3; 95% CI) from baseline was observed providing proof-of-concept for DTG activity. At week 24, 63% subjects achieved HIV RNA < 50 copies/ml supporting efficacy. The week 24 response rate in this trial was comparable to efficacy reported for other ARVs, such as etravirine and darunavir, evaluated in a similar HIV-infected population.

Response in Viking-3 trial was influenced primarily by the baseline INI resistance profile and susceptibility to DTG at baseline. Presence of INI substitution at Q148 position resulted in reduced response; furthermore, the presence of Q148 substitution with at least 2 other INI substitutions resulted in poor virologic outcomes. This was evident for responses both at Day 8 and at Week 24. In subjects with Q148 substitutions, response was 35% at Week 24 compared to 63% overall response. In subjects with Q148 plus 2 INI substitution pattern, response was 7%; only 1 of 14 subjects achieved HIV RNA < 50 copies/ml at Week 24. The substitution pattern associated with poor outcome, Q148 plus at least 2 INI substitutions, is an uncommon resistance pathway reported in 10-13% of INI-experienced subjects; and DTG 50 mg BID is expected to be beneficial in the overall INI-experienced population as demonstrated in Viking-3 trial. As response was strongly influenced by the Q148 resistance profile, the review team recommends inclusion of pertinent language in Section 1 Indications and Usage Points to Consider to appropriately inform users and prescribers.

As expected, response was influenced by fold change susceptibility to DTG, with lower efficacy observed with DTG susceptibility > 2-fold. Although DTG exposures were not

predictive of antiviral activity, a relationship was identified between IQ and virologic response was driven by baseline susceptibility to DTG. Other variables such as baseline HIV RNA or baseline OSS did not appear to impact overall response. Although findings are from limited subjects in a non-comparative trial; day 8 and week 24 results provide substantial evidence of antiviral activity and efficacy at Week 24, respectively, of DTG containing regimen in this highly treatment experienced population; and Week 24 response is comparable to responses observed in other ARV trials in the same population type.

In all adult phase 3 trials, responses were generally comparable by race and gender. Dolutegravir treatment resulted in immunologic benefit with mean increases in CD4 cell counts from baseline observed in all adult phase 3 trials. In adolescent subjects, exposures for DTG dosed 50 mg QD was comparable to exposures in adult phase 3 subjects. Additionally, the 24 week antiviral activity data with the 50 mg QD dose in 23 treatment-experienced, INI naïve subjects showed a 65% response rate (HIV RNA < 50 copies/mL).

In conclusion, clinical trial data supports the efficacy of DTG for the treatment of HIV infection in a broad population including treatment-naïve and treatment-experienced patients ages 12 years and older.

6.1 Indication

Dolutegravir is indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV) infection in adults and children aged 12 years and older.

6.1.1 Methods

The treatment-naïve trials were independently evaluated due to the different comparator regimens (RAL and Atripla). Additionally, the phase 2b trial SPRING-1 provides supportive evidence of durable response of the DTG 50 mg QD regimen compared to Efavirenz at Week 48. Please see the statistical review by Dr. Thomas Hammerstrom for detailed efficacy analyses of the phase 2b trial. The clinical review focuses on the phase 3 treatment naïve data from SPRING-2 and SINGLE.

Data for the treatment experienced INI naïve trial were analyzed independently. As mentioned previously, the primary data supporting efficacy in the INI-experienced population comes from Viking-3 trial. This review section focuses on results from Viking-3 trial, both at Day 8 (reflecting DTG monotherapy) and Week 24 (reflecting DTG effects in combination with an OBR). Findings from cohort 2 of Viking-pilot trial provide supportive activity from an additional 27 INI-experienced subjects who received 50 mg DTG BID; antiviral activity results from this study are discussed in-depth in the statistical

review by Dr. Tom Hammerstrom. Please refer to section 8 for details regarding the pediatric review, including efficacy and safety analyses.

6.1.2 Demographics

Treatment Naïve

In SPRING-2 the demographic and baseline characteristics were generally well balanced across the treatment arms (Table 3). The majority of subjects were white (83%) and male (87%); and the median age of the mITT population was 36 years. In the DTG arm, there was 1 subject age ≥ 65 years compared to 5 subjects in this age range in the RAL arm. Most subjects had baseline plasma HIV-1 RNA ≤ 100,000 (72%) and the majority of subjects (88%) had baseline CD4 cell counts above 200 cells/mm^3. Approximately 11% of subjects were coinfected with hepatitis B and/or C virus at baseline. Most subjects were CDC Class A (86%) and identified homosexual activity as an HIV acquisition risk factor (64%).

Table 3: Demographic and Baseline Characteristics, Spring-2

	DTG 50mg QD N=403 n (%)	**Raltegravir 400mg twice daily N=405 n (%)**	**Total N=808 n (%)**
Age in Years, median (range)	37 (18,68)	35 (18,75)	36 (18,75)
Sex			
Male	347 (86)	352 (87)	699 (87)
Female	56 (14)	53 (13)	109 (13)
Ethnicity			
Hispanic or Latino	43 (11)	52 (13)	95 (12)
Not Hispanic or Latino	360 (89)	353 (87)	713 (88)
Race			
White - White/Caucasian/European Heritage	334 (83)	336 (83)	670 (83)
African American/African Heritage	49 (12)	39 (10)	88 (11)
American Indian or Alaskan Native	7 (2)	9 (2)	16 (2)
White - Arabic/North African Heritage	4 (1)	10 (2)	14 (2)
Asian	5 (1)	10 (2)	15 (2)
Japanese/East/South East Asian Heritage	3(1)	10 (2)	13 (2)
Central/South Asian Heritage	2 (<1)	0 (0)	2 (<1)
Mixed race	1 (<1)	1 (<1)	2 (<1)
Native Hawaiian or Other Pacific Islander	2 (<1)	0 (0)	2 (<1)

	DTG 50mg QD N=403 n (%)	Raltegravir 400mg twice daily N=405 n (%)	Total N=808 n (%)
Median Baseline HIV-1 viral load log10	4.5	4.6	4.6
Baseline viral load group			
≤100,000 c/mL	290 (72)	289 (71)	579 (72)
>100,000 c/mL	113 (28)	116 (29)	229 (28)
Median Baseline CD4 (cells/mm^3)			
<50	8 (2)	6 (1)	14 (2)
50 to <200	46 (11)	44 (11)	90 (11)
200 to <350	142 (35)	139 (34)	281 (35)
350 to <500	123 (31)	132 (33)	256 (32)
≥500	84 (21)	83 (21)	167 (21)
Hepatitis B & C test results*			
Neither	349 (87)	355 (88)	704 (87)
C only	40 (10)	34 (8)	74 (9)
B only	7 (2)	8 (2)	15 (2)
B and C	1 (<1)	0	1 (<1)
CDC Category			
Category A	351 (87)	340 (84)	692 (86)
Category B	43 (11)	55 (14)	98 (12)
Category C	9 (2)	9 (2)	18 (2)
HIV-1 Risk Factors			
Homosexual contact and not injectable drug user	268 (67)	251 (62)	519 (64)
No homosexual contact and not injectable drug user	115 (29)	134 (33)	249 (31)
Injectable drug user	20 (5)	20 (5)	40 (5)

*Denominator is subjects with available test result for HBV or HCV; for RAL N=404 instead of N=405
Source: demography, population flags, viral HIV-1 analysis datasets SPRING-2
mITT population

In Spring-2, the background FDC NRTI was Investigator assigned and open label. The following table 4 provides the proportion of subjects taking either ABC/3TC or TDF/FTC as background NRTI therapy at baseline. The treatment arms are balanced with a total of 39% (319/808) of subjects taking ABC/3TC and 61% (489/808) of subjects taking TDF/FTC. Additionally, a lower proportion of subjects with Baseline HIV RNA > 100,000 c/mL were assigned ABC/3TC as background therapy in DTG (9%) and RAL (10%) treatment arms. Any analyses conducted in these subgroups must be interpreted with caution due to the lower numbers of subjects enrolled.

Table 4: SPRING-2 population by stratification factors

	DTG N=403 n (%)	RAL N=405 n (%)
HIV-1 RNA ≤ 100 000 c/mL	290 (72)	289 (71)
HIV-1 RNA >100 000 c/mL	113 (28)	116 (29)
ABC/3TC	161 (40)	158 (39)
TDF/FTC	242 (60)	247 (61)
<=100,000 c/mL; ABC/3TC	125 (31)	119 (29)
<=100,000 c/mL; TDF/FTC	165 (41)	170 (42)
>100,000 c/mL; ABC/3TC	36 (9)	39 (10)
>100,000 c/mL; TDF/FTC	77 (19)	77 (19)

Source: snapshot and population flags analysis datasets – SPRING-2 (mITT)

The demographic and baseline characteristics of the trial population of SINGLE were generally similar to that of SPRING-2. As shown in Table 5, the majority of subjects in SINGLE were white (68%) and male (84%); however, a larger proportion of non-white subjects (32%) were treated in SINGLE compared to SPING-2 (17%). The median age of the population was 35 years. In the DTG/ABC/3TC arm, there was 1 subject age ≥ 65 years compared to 6 subjects in this age range in the Atripla arm, including one 85 year old subject. Overall, 68% of subjects had a baseline viral load of ≤ 100,000 c/mL and 86% had CD4 cell counts above 200 cells/mm^3. Subjects with baseline hepatitis B infection were excluded from enrollment in SINGLE. Overall, 7% of subjects were co-infected with hepatitis C. The majority of subjects (83%) were CDC class A at baseline and identified homosexual activity as an HIV acquisition risk factor (66%).

Table 5: Demographic and Baseline Characteristics, Single

	DTG 50mg QD N=414 n (%)	Atripla N=419 n (%)	Total N=833 n (%)
Age in Years, median (range)	35 (18,68)	36 (18,85)	35 (18,85)
Sex			
Male	347 (84)	356 (85)	703 (84)
Female	67 (16)	63 (15)	130 (16)
Race Group*			
White	284 (69)	285 (68)	569 (68)
Non-White	130 (31)	133 (32)	263 (32)
Race*			
White - White/Caucasian/European Heritage	279 (67)	278 (66)	557(67)
African American/African Heritage	98 (24)	99 (24)	197 (24)
American Indian or Alaskan Native	13 (3)	17 (4)	30 (4)
Mixed race	10 (2)	9 (2)	12 (1)
White - Arabic/North African Heritage	5 (1)	6 (1)	11 (1)
Asian	9 (2)	9 (2)	18 (2)
Japanese/East/South East Asian Heritage	7(2)	6 (1)	13 (2)
Central/South Asian Heritage	2 (<1)	3 (1)	5 (<1)
Median baseline HIV-1 viral load log10	4.7	4.7	4.7
Baseline viral load group			
≤100,000 c/mL	280 (68)	288 (69)	568 (68)
>100,000 c/mL	134 (32)	131 (31)	265 (32)
Median Baseline CD4 (cells/mm^3)			
<50	13 (3)	14 (3)	27 (3)
50 to <200	44 (11)	48 (11)	92 (11)
200 to <350	163 (39)	159 (38)	322 (39)
350 to <500	131 (32)	128 (31)	259 (31)
≥500	63 (15)	70 (17)	133 (16)
Hepatitis C positive†	27 (7)	29 (7)	56 (7)
CDC Category			
Category A: Asymptomatic, Lymphadenopathy or acute HIV	343 (83)	350 (84)	693 (83)
Category B: Symptomatic, not AIDS	53 (13)	52 (12)	105 (13)
Category C: AIDS	18 (4)	17 (4)	35 (4)
HIV-1 Risk Factors			
Homosexual contact and not injectable drug user	263 (64)	287 (68)	550 (66)
No homosexual contact and not injectable drug user	131 (32)	123 (29)	254 (30)
Injectable drug user	20 (5)	9 (2)	29 (3)

*One subject with missing data from Atripla arm
† Subjects with hepatitis B were excluded from enrollment in SINGLE
Source: demography population flags, viral HIV-1 analysis dataset- SINGLE

Overall, the demographic and baseline characteristics were generally well balanced across the trial treatment arms in both SPRING-2 and SINGLE. The baseline characteristics from the DTG treatment- naïve trials are consistent with baseline characteristics observed in other treatment-naïve clinical trial populations from various antiretroviral development programs.

Treatment Experienced INI naïve

In Sailing, the mITT population consisted of 715 subjects, 32% of subjects were female and remaining 68% were male (Table 6). The median age of the trial population was 43 years; with 42 subjects over age 60 years and 12 subjects over age 65 years. Subjects of Caucasian or European descent comprised 49% of the population. African or African-American subjects comprised 42% of the study population; 43% of these subjects were enrolled in the US. In general, the two study arms were balanced with respect to gender, age, and race.

Table 6: Demographic Characteristics, Sailing

	DTG N=354	RAL N=361	Total N=715
Gender			
Male	247 (70%)	238 (66%)	485 (68%)
Female	107 (30%)	123 (34%)	230 (32%)
Age (years, median)	42 (21-69)	43 (18-73)	43 (18-73)
Race			
White/Caucasian/European	175 (50%)	172 (48%)	347 (49%)
African American/African	143 (41%)	160 (44%)	303 (42%)
American Indian/Alaskan Native	10 (3%)	17 (5%)	27 (4%)
Asian	9 (3%)	6 (2%)	15 (2%)
Mixed race	12 (3%)	2 (1%)	14 (2%)
Native Hawaiian/Pacific Islander	1 (1%)	0	1 (1%)
Arabic/North African Heritage	3 (1%)	3 (1%)	6 (1%)

Source: mITT-E_demo.xpt, pop.xpt

As shown in Table 7, approximately 46% of subjects had CDC type C HIV disease category at study entry. The median CD4 count was 200 cells/mm^3 and about 50% of subjects had CD4 count <200 cells/mm^3 at baseline. The median plasma HIV RNA was 4.18 log_{10}. About 16% of the population had Hepatitis B/C coinfection. Importantly, the treatment arms were generally balanced with respect to these characteristics.

Table 7: Baseline Disease Characteristics, Sailing

	DTG N=354	RAL N=361	Total N=715
Plasma HIV RNA (median log_{10})	4.2 (1.6-6.8)	4.2 (1.2-6.5)	4.2 (1.6-6.8)
CD4 cell count (median cells/mm^3)	204 (19-1017)	193 (19-1219)	200 (19-1219)
HIV RNA category			
≤50,000 copies/mL	249 (70%)	254 (70%)	503 (70%)
>50,000 copies/mL	105 (30%)	107 (30%)	212 (30%)
≥100,000 copies/mL	52 (15%)	56 (16%)	108 (15%)
CD4 count category			
<50 cells/mm^3	62 (18%)	59 (16%)	121 (17%)
50 to <200 cells/mm^3	111 (31%)	125 (35%)	236 (33%)
200 to <350 cells/mm^3	82 (23%)	79 (22%)	161 (23%)
350 to <500 cells/mm^3	56 (16%)	59 (16%)	115 (16%)
≥500 cells/mm^3	43 (12%)	39 (11%)	82 (11%)
CDC Category			
A	111 (31%)	114 (32%)	225 (31%)
B	70 (20%)	89 (25%)	159 (22%)
C	173 (49%)	158 (44%)	331 (46%)
Hepatitis B/C coinfection			
B and C	1 (<1%)	1 (<1%)	2 (<1%)
B only	17 (5%)	16 (4%)	33 (5%)
C only	31 (9%)	48 (13%)	79 (11%)
Neither	288 (81%)	270 (75%)	558 (78%)
Missing	19 (5%)	22 (6%)	41 (6%)

Source: demo.xpt and Pop.xpt, Heptst.xpt

Virtually all subjects were exposed to at least one NRTI. As shown in Table 8, approximately 84% and 60% had received at least one NNRTI or PI agent, respectively. In line with trial enrollment criteria, no subjects had resistance to only one ARV class. Approximately 51% subjects had evidence of two-class resistance. Approximately 38% of subjects had three-class resistance, and 51% had evidence of resistance to three or more classes.

Table 8: Baseline ARV experience and resistance, Sailing

	DTG N=354	RAL N=361	Total N=715
Prior ARV exposure			
Any NRTI	354 (100%)	360 (99%)	714 (99%)
Any NNRTI	295 (83%)	309 (86%)	604 (84%)
Any PI	204 (58%)	222 (61%)	426 (60%)
CCR5 antagonist	4 (1%)	10 (3%)	14 (2%)
Fusion inhibitor	17 (5%)	12 (3%)	29 (4%)
Baseline Class Resistance			
Three or more class resistance	169 (48%)	182 (50%)	351 (49%)
Two class resistance	185 (52%)	179 (50%)	364 (51%)

Source: Pop.xpt

Background regimen and baseline GSS/PSS are presented in Table 9. A protease inhibitor-containing regimen was the most frequent background regimen. Overall, 41% of subjects received a DRV/r-containing regimen. This includes 39% of subjects in the DTG arm and 42% of subjects in the RAL arm. In the DTG arm, 20% subjects received DRV/r without a primary PI mutation compared to 22% subjects in the RAL arm. Approximately 72% of subjects had phenotypic susceptibility score (PSS) 2, and 26% had PSS of 1. By genotype-based susceptibility (GSS), 52% had GSS of 1 to < 2 and 42% subjects had GSS of 2. The two treatment arms were similar with respect to baseline GSS and PSS.

Table 9: Background regimen and susceptibility at baseline

	DTG N=354	RAL N=361	Total N=715
DRV/r background			
No DRV/r use	214 (60%)	209 (58%)	423 (59%)
DRV/r used with Primary PI mutation	69 (19%)	74 (20%)	143 (20%)
DRV/r without Primary PI mutation	71 (20%)	78 (22%)	149 (21%)
Baseline GSS			
0 to <1	26 (7%)	17 (5%)	43 (6%)
1 to <2	190 (54%)	179 (50%)	369 (52%)
2	137 (39%)	165 (46%)	302 (42%)
>2	1 (<1%)	0	1 (<1%)
Baseline PSS			
0	8 (2%)	3 (<1%)	11 (2%)
1	97 (27%)	91 (25%)	188 (26%)
2	247 (70%)	267 (74%)	514 (72%)
>2	2 (<1%)	0	2 (<1%)

Source: Pop.xpt

Treatment Experienced, INI-experienced

Demographic and baseline characteristics of Viking-3 subjects were analyzed for 2 populations: the ITT-E group includes all enrolled subjects and the week 24 ITT-E includes only subjects who completed week 24 visit. Please note the trial is currently ongoing. For the most part, these 2 populations were similar at baseline. As displayed in Table 10, women were well-represented and accounted for 23% of enrolled subjects. Approximately 27% subjects were African or African/American. The median age was 48 years. Nearly 59% of subjects had CDC category C HIV disease, and about 25% subjects had baseline HIV RNA greater than 100,000 copies/ml. The median CD4 count was 120-140 cells/mm^3, and about one-third the population had CD4 count less than 50 cells/mm^3 at baseline. Overall, these characteristics reflect a population with advanced HIV disease.

Table 10: Demographics and baseline disease characteristics, Viking-3

	ITT-E N=183	**Week 24 ITT-E N=114**
Gender		
Female	42 (23%)	25 (22%)
Male	141 (77%)	89 (78%)
Age years (median, range)	48 (19-67)	48 (19-66)
Race		
White	130 (71%)	85 (75%)
African American/African	49 (27%)	28 (25%)
Native Hawaiian/Pacific Islander	1 (<1%)	0
Asian	1 (<1%)	0
Mixed race	2 (1%)	1 (<1%)
	N=183	N=114
CDC Classification		
C (AIDS)	102 (56%)	67 (59%)
B (symptomatic, not AIDS)	37 (20%)	26 (23%)
A (asymptomatic or acute HIV)	44 (24%)	21 (18%)
Baseline HIV RNA (median, log_{10} copies/ml)	4.4 (1.6-7.4)	4.4 (2.2-7.4)
HIV RNA category		
≥100,000	41 (22%)	30 (26%)
50,000-100,000	20 (11%)	13 (11%)
10,000-<50,000	52 (28%)	29 (25%)
1000-<10,000	49 (27%)	30 (26%)
<1000	21 (11%)	12 (11%)

	ITT-E N=183	Week 24 ITT-E N=114
CD4 count (median, cell/mm^3)	140 (19-1100)	120 (19-720)
CD4 category		
<50	50 (27%)	36 (32%)
50 to <200	60 (33%)	34 (30%)
200 to <350	34 (19%)	20 (18%)
350 to <500	24 (13%)	15 (13%)
>500	15 (8%)	9 (8%)

Source: demo.xpt and Pop.xpt

Based on trial inclusion criteria, Viking-3 subjects had at least 2 or 3 class resistance not including INSTI resistance. Approximately, 82% of subjects were resistant to at least one NRTI, 73% resistant to at least one NNRTI, and 72% resistant to at least one PI. As shown in Table 11 below, 50% subjects in the optimized treatment phase had no or 1 active agent in the background regimen (not counting DTG). About 58% subjects received functional DTG monotherapy (OSS=0) through day 8. Approximately 50% subjects were failing a RAL or EVG containing regimen at time of study entry. Approximately 68% subjects had INSTI resistance detected at screening, and 67% had primary INSTI resistance at baseline as shown in Table 11.

Table 11: Summary of INI experience, INI resistance, and baseline OSS

	ITT-E N=183	Week 24 ITT-E N=114
Ralt or EVG treatment status at screening		
Ongoing at screening	101 (55%)	58 (51%)
Discontinued prior to screening	82 (45%)	56 (49%)
INI resistance at screening		
Detected at screening	124 (68%)	76 (67%)
Historic resistance documented	59 (32%)	38 (33%)
Evidence of genotypic primary IN resistance at baseline		
Primary IN resistance detected	123 (67%)	74 (65%)
Primary IN resistance not detected	60 (33%)	40 (35%)
Baseline OSS		
0	107 (58%)	7 (6%)
1	59 (32%)	48 (42%)
2	11 (6%)	43 (38%)
>2	6 (3%)	16 (14%)

Source: demo.xpt and Pop.xpt

The INI resistance profile of subjects with baseline data is summarized here; please refer to the clinical virology review by Dr. Lisa Naeger for details. Of the 182 subjects with baseline data, 30% had virus with a substitution at Q148 position. Among these subjects, 18% had Q148 substitutions with 1 INI resistance substitutions and 12% had Q148 substitutions with 2 or more INI resistance substitutions. Almost all of the Q148 +1 group had the Q148+G140 substitution combination and most of the Q148+≥2 group had the combination of Q148+G140+E138 substitutions. Approximately 33% of the study population had no primary INI substitutions at baseline, but these subjects had historical genotypic evidence of INI substitutions, phenotypic evidence of RAL or EVG resistance, or genotypic evidence of INI substitutions at screening.

6.1.3 Subject Disposition

Treatment Naïve

The numbers of subjects continuing treatment at the time of the 48 week analysis is similar between the treatment arms in both SPRING-2 and SINGLE (Tables 12 and 13). The largest difference is observed in SINGLE where 10% of subjects exposed to Atripla discontinued due to Adverse Events compared to 2% of DTG subjects. Otherwise, in both treatment naïve trials, the reasons for disposition were generally balanced between treatment arms.

Table 12: Reasons for subject disposition, SPRING-2

Reason for disposition event	**DT 50mg QD N=403 n (%)**	**Raltegravir 400mg twice daily N=405 n (%)**
Lack of efficacy	16 (4)	22 (5)
Protocol deviation	12 (3)	11 (3)
Adverse event	8 (2)	6 (1)
Withdrew consent	4 (1)	7 (2)
Lost to follow-up	4 (1)	7 (2)
Subject reached protocol-defined stopping criteria*	1 (<1)	1 (<1)

*Both cases due to ALT>8 x ULN on treatment as defined in protocol (Section 6.4.3.1)
Source: subject disposition analysis dataset- SPRING-2

Table 13: Reasons for subject disposition, SINGLE

Reason for disposition event	DTG 50mg + ABC/3TC QD N=414 n (%)	Atripla daily N=419 n (%)
Adverse event	10 (2)	42 (10)
Lack of efficacy	14 (3)	13 (3)
Lost to follow-up	14 (3)	9 (2)
Withdrew consent	5 (1)	11 (3)
Protocol deviation	7 (2)	7 (2)
Investigator discretion	1 (<1)	2 (<1)

Source: subject disposition dataset-SINGLE

Treatment Experienced INI Naïve

At the time of NDA cut-off date for 24 week analysis, 86% and 52% subjects in Sailing were continuing treatment in the DTG and RAL arms, respectively. About 1% and 31% subjects had completed treatment in the DTG and RAL arms, respectively. The difference in DTG and RAL arms is because enrollment in the trial occurred over a 15-month period due to difficulties in finding the patient population, and because DTG subjects include those in the 48-week double blind phase as well as post-48 week open label phase. In contrast, RAL subjects reaching Week 48 visit were discontinued from the study. Please refer to section 5.3 for study details. As shown in Table 14, the reasons for disposition were generally balanced between treatment arms with the exception of more withdrawals in the RAL arm (7%) compared to DTG arm (4%) for lack of efficacy.

Table 14: Reasons for Disposition for Sailing

Reason for disposition event	DTG N=354	RAL N=361
Adverse event	3 (<1)	12 (<1)
Lack of efficacy	15 (4)	26 (7)
Protocol deviation	10 (3)	6 (2)
Withdrew consent	9 (3)	4 (1)
Lost to follow-up	5 (1)	10 (3)
Subject reached protocol-defined stopping criteria	5 (1)	1 (<1)
Investigator discretion	1 (<1)	2 (<1)

Source: subject disposition dataset - Sailing

Treatment Experienced INI Experienced

In Viking-3, 155/183 or 85% subjects were continuing treatment at time of NDA data cut off. The most frequent reason for withdrawal was lack of efficacy in 13% subjects in the week 24 cohort. Other reasons for withdrawal are presented in Table 15.

Table 15: Reasons for subject disposition, Viking-3

Reason for disposition event	Day 1-7 ITT-E N=183	Day 8 OBR Week 24 ITT-E N=114
Adverse event	4 (2)	4 (4)
Lack of efficacy	19 (10)	15 (13)
Protocol deviation	2 (1)	2 (2)
Lost to follow-up	2 (1)	2 (2)
Subject reached protocol-defined stopping criteria	1 (<1)	1 (<1)

Source: subject disposition dataset – Viking-3

6.1.4 Analysis of Primary Endpoint

The proposed indication for treatment-naïve population is based on Week 48 efficacy findings. The indication for treatment-experienced population is based on Week 24 efficacy. Efficacy or virologic response is defined as proportion of subjects with HIV RNA < 50 copies/ml by Snapshot analysis.

Treatment Naïve

In SPRING 2 the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 for DTG and RAL groups was 88% and 86%, respectively (Table 16). The difference in virologic response between the groups was 2.6% (95% CI: -1.9%, 7.2%). The lower limit of the 95% CI of the difference between the treatment groups was above -10%, therefore establishing the non-inferiority of DTG to RAL at the pre-specified non-inferiority margin.

HIV RNA >50 copies/mL occurred in 5% of DTG subjects and was comparable to the observed rate of 7% of RAL subjects. A similar proportion of subjects had no virologic outcome data in the Week 48 window due to AEs or Death or discontinuation for other reasons. The “other” reasons for discontinuation among the subjects with no virologic data at Week 48 included protocol deviation, lost to follow up and withdrew consent.

Table 16: Virologic Outcomes at Week 48, SPRING-2

Outcome	DTG N=403 n (%)	RAL N=405 n (%)
HIV RNA < 50 copies/mL*	**356 (88)**	**347 (86)**
HIV RNA ≥ 50 copies/mL	**19 (5)**	**29 (7)**
Data in window not below threshold	8 (2)	5 (1)
Change in ART	4 (<1)	2 (<1)
Discontinued for lack of efficacy	5 (1)	11 (3)
Discontinued for other reason while not below threshold	2 (<1)	11 (3)
No Virologic Data	**28 (7)**	**29 (7)**
Discontinued for Other Reasons	20 (5)	23 (6)
Discontinued due to AE or Death	8 (2)	6 (1)

*Treatment difference is 2.6% (95% CI: -1.9%, 7.2%)
Source: Snapshot analysis dataset- SPRING-2; (mITT)

In SINGLE, the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 for DTG and Atripla groups was 88% and 81%, respectively (Table 17), with a treatment difference of 7.4% (95% CI: 2.5%, 12.3%). The lower bound of the 95% CI for the treatment difference of +2.5% is above 0, therefore superiority of DTG 50 mg QD + ABC/3TC is concluded. Additional analyses conducted by FDA statistician, Dr. Hammerstrom, were consistent and supportive of this result.

A similar proportion of DTG (5%) and Atripla (6%) subjects experienced HIV RNA ≥ 50 copies/mL. However, a larger proportion of subjects from the Atripla arm (13%) compared to DTG arm (7%) did not have virologic data in the Week 48 window. Primarily these results were driven by discontinuation due to AE or death. The "other" reasons for discontinuation among the subjects with no virologic data at Week 48 included protocol deviation, lost to follow up and withdrew consent.

Table 17: Virologic Outcomes at Week 48, SINGLE

Outcome	DTG 50 mg QD N=414 n (%)	Atripla QD N=419 n (%)
HIV RNA <50 copies/mL*	**364 (88)**	**338 (81)**
HIV RNA ≥50 copies/mL	**21 (5)**	**26 (6)**
Data in window not below threshold (50 copies/ml)	6 (1)	5 (1)
Discontinued for lack of efficacy	7 (2)	9 (2)
Discontinued for other reason while not below threshold	8 (2)	12 (3)
No Virologic Data	**29 (7)**	**55 (13)**
Discontinued for Other Reasons	20 (5)	14 (3)
Discontinued due to AE or Death	9 (2)	40 (10)
Missing data during window but on study	0	1 (<1)

*Treatment difference: 7.4% (95%CI: 2.5% 12.3%); Source: Snapshot dataset for SINGLE

Treatment Experienced INI Naive

Week 24 outcomes in the Sailing trial are presented in Table 18. At week 24, 79% of subjects receiving DTG and 70% of subjects receiving RAL had achieved HIV RNA < 50 copies/ml. The treatment difference of 9.7 was associated with 95% confidence interval ranging 3.4 to 15.9; p value 0.003; meeting criteria for superiority over RAL. At week 24, HIV RNA was > 50 copies/mL in 14% and 24% of subjects receiving DTG and RAL, respectively. The most frequent reason for subjects in this category was because HIV RNA was > 50 copies/ml at the Week 24 visit window, observed in 11% and 18% of subjects receiving DTG and RAL, respectively. DTG and RAL groups were balanced with respect to subjects without data at Week 24, either as a result of discontinuation or missing data for subjects still on study. Analyses conducted by FDA statistician, Dr. Hammerstrom, were consistent and supportive of this result.

Table 18: Virologic Outcomes at Week 24, Sailing

	DTG N=354	**RAL N=361**
HIV-1 RNA < 50 copies/ml	**281 (79)**	**252 (70)**
HIV RNA ≥50 copies/mL	**53 (15)**	**86 (24)**
Data in window not below threshold (50 copies/ml)	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 Window	**20 (6)**	**23 (6)**
Discontinued Study Drug due to AE or Death	6 (2)	9 (2)
Discontinued for Other Reasons and last available HIV-1 RNA > 50 copies/ml	12 (3)	11 (3)
Missing data during window but on study drug	2 (<1)	3 (<1)

Source: Snapshot.xpt, Pop.xpt - Sailing

Treatment Experienced INI Experienced

At Day 8, the mean change in HIV RNA was -1.41 $\log_{10}$, which was statistically significant to no change in RNA from baseline. This result provides proof-of-concept for antiviral activity of monotherapy of DTG dosed 50 mg BID in treatment-experienced subjects with evidence of INI resistance.

Week 24 virologic response, measured as plasma HIV RNA < 50 copies/ml by snapshot analysis, was observed in 63% of subjects (Table 19). This result demonstrates efficacy over 24 weeks of a DTG containing regimen in the treatment experienced, INI-experienced population. Overall, 20% of subjects had HIV RNA ≥ 50 copies/ml at the

Week 24 visit (n=23), and 5% subjects had discontinued for lack of efficacy i.e., met protocol defined criteria for virologic failure (n=6). Analyses conducted by FDA statistician, Dr. Hammerstrom, were consistent with these results.

Table 19: Virologic outcomes at Week 24, Viking-3

	Wk 24 ITT-E (N=114)
HIV RNA < 50 copies/ml	72 (63)
HIV RNA ≥ 50 copies/mL	37 (32)
Data in window not below threshold (50 copies/ml)	23 (20)
Discontinued for lack of efficacy	6 (5)
Discontinued for other reason while not below threshold	2 (2)
Change in ART	6 (5)
No virologic data in window at week 24	5 (4)
Discontinued Study Drug due to AE or Death	5 (4)

Source: Snapshot.xpt, Pop.xpt – Viking-3

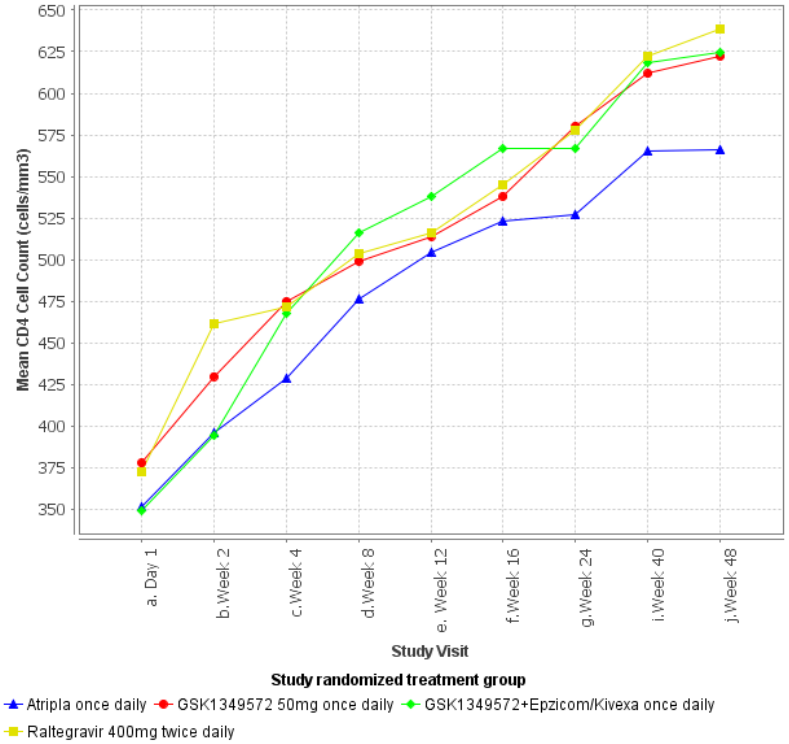
6.1.5 Analysis of Secondary Endpoints

The clinical reviewers performed analysis for mean change in CD4 count from baseline because this endpoint represents immunologic improvements from treatment. Other secondary endpoints including proportion subjects achieving HIV RNA < 400 copies/mL were analyzed by Dr. Hammerstrom. Please refer to his statistical review of this NDA for details.

Treatment Naive

In Spring-2, the median increase from baseline in CD4 cell counts were +230 cells/mm^3 in each treatment arm at Week 48. In Single, the median increase from baseline for CD4 cell counts was + 246 cells/mm^3 for DTG/3TC/ABC and + 187 cells/mm^3 for the Atripla arm. The following figure 1 shows the mean CD4 cell count over time through Week 48 for each of the treatment arms from the treatment-naïve trials. The mean CD4 cell counts increases were similar from Baseline and throughout the trial in SPRING-2 (DTG in red, RAL in yellow); however, in SINGLE the DTG arm (shown in green) mean CD4 cell count increase is above that observed in the Atripla arm (shown in blue).

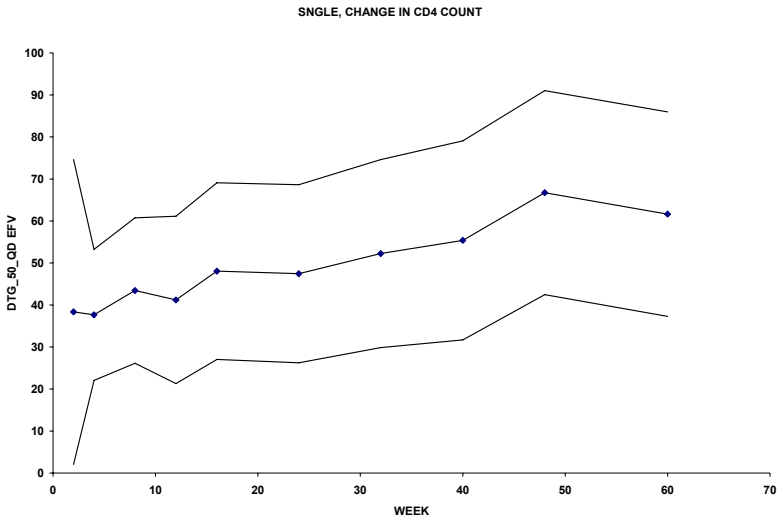
Figure 1: Mean change in CD4 count (cells/mm^3) through Week 48, treatment-naïve trials



Source: Laboratory Analysis ISS dataset

Additional analysis was completed by Dr. Hammerstrom. The following graph provides the point estimate and the 95% confidence interval for the difference of DTG/ABC/3TC-Atripla for mean change in CD4 cell count in the SINGLE trial. The DTG arm is statistically significantly superior to Atripla throughout the trial (lower bound of the 95% CI is above 0). These results support and confirm the virologic outcome results from SINGLE.

Figure 2: Difference in CD4 cell count in the treatment arms in Single



Source: Statistical Review by Dr. Thomas Hammerstrom

Treatment Experienced INI Naive
CD4 count increases from baseline to Week 24 were observed in each treatment arm, DTG and RAL. The median increase in DTG and RAL arms were 114 and 106 cells/mm^3, respectively.

Treatment Experienced INI Experienced
In Viking-3, the median increase in CD4 count from baseline to week 24 was 79 cells/mm^3.

6.1.6 Other Endpoints

Additional endpoint analyses were not performed by the clinical reviewers. Analyses of interest such change in log HIV RNA were completed by the statistical reviewer, Dr. Tom Hammerstrom. Please refer to his statistical review of the NDA for details.

6.1.7 Subpopulations

Treatment Naïve

The following table 20 summarizes Spring-2 virologic outcome by Screening viral load and the Day 1 assigned background NRTI regimen using the snapshot analysis.

Generally, the results are consistent with the overall Week 48 virologic outcome for SPRING-2. As expected, subjects with a lower Screening viral load had the highest proportion of HIV-1 RNA <50 copies/mL, regardless of background NRTI regimen (DTG: 90-92%; RAL: 91-94%). Conversely, subjects with higher Screening viral loads had a lower proportion of subjects with HIV-1 RNA <50 copies/mL (DTG: 75-84%; RAL: 70%). The subjects with HIV-1 RNA > 100,000 c/mL and assigned to ABC/3TC had the lowest proportion of subjects with HIV-1 RNA <50 copies/mL overall (DTG 75% and RAL 70%); however, these results should be interpreted with caution because these subgroups are too small for meaningful comparisons. Additionally, 14% of the subjects with high viral load and ABC/3TC background had no available virologic data in the Week 48 window.

Table 20: Subgroup analysis of virologic outcome by screening HIV RNA and Day 1 Assigned Background NRTI Regimen, SPRING-2

Initial Stratification by Screening HIV RNA and Background NRTI Regimen	**DTG N=403 n (%)**	**RAL N=405 n (%)**
HIV-1 RNA < 50 copies/ml		
HIV-1 RNA ≤ 100 000 c/mL; NRTI = TDF/FTC	152/165 (92)	154/170 (91)
HIV-1 RNA ≤ 100 000 c/mL; NRTI = ABC/3TC	112/125 (90)	112/119 (94)
HIV-1 RNA >100 000 c/mL; NRTI = TDF/FTC	65/77 (84)	54/77 (70)
HIV-1 RNA >100 000 c/mL; NRTI = ABC/3TC	27/36 (75)	27/39 (70)
HIV-1 > 50 copies/mL		
HIV-1 RNA ≤ 100 000 c/mL; NRTI = TDF/FTC	8/165 (5)	5/170 (3)
HIV-1 RNA >100 000 c/mL; NRTI = TDF/FTC	5/77 (6)	16/77 (2)
HIV-1 RNA ≤100 000 c/mL; NRTI = ABC/3TC	3/125 (2)	4/119 (3)
HIV-1 RNA >100 000 c/mL; NRTI = ABC/3TC	3/36 (8)	4/39 (10)
No Virologic Data		
HIV-1 RNA ≤ 100 000 c/mL; NRTI = ABC/3TC	10/125 (8)	10/119 (8)
HIV-1 RNA ≤ 100 000 c/mL; NRTI = TDF/FTC	7/165 (4)	10/170 (6)
HIV-1 RNA >100 000 c/mL; NRTI = TDF/FTC	6/77 (8)	7/77 (9)
HIV-1 RNA >100 000 c/mL; NRTI = ABC/3TC	5/36 (14)	2/39 (5)

Source: Snapshot and population flags analysis datasets- SPRING-2

Analysis of outcome by Screening viral load was also completed for SINGLE. All DTG subjects in SINGLE were on a fixed dose combination (FDC) background regimen of ABC/3TC (Epzicom) compared to the FDC Atripla so there was no open label investigator background regimen selection like in SPRING-2. As shown in the following table, outcome results by Screening viral load were comparable to the overall Week 48 outcome results for SINGLE. There was no significant decline in activity or durability based on whether a subject's Screening viral load was below or above 100,000 copies/mL.

Table 21: Summary of Week 48 Virologic Outcome by screening HIV RNA, SINGLE

Initial Stratification by Screening	DTG 50 mg QD N=414 n (%)	Atripla QD N=419 n (%)
HIV-1 RNA < 50 copies/mL		
HIV-1 RNA ≤ 100 000 c/mL	253/280 (90)	238/288 (83)
HIV-1 RNA >100 000 c/mL	111/134 (83)	100/131 (76)
HIV-1 >50 copies/mL		
HIV-1 RNA ≤ 100 000 c/mL	9/280 (3)	13/288 (5)
HIV-1 RNA >100 000 c/mL	12/134 (9)	13/131 (10)
No Virologic Data		
HIV-1 RNA ≤ 100 000 c/mL	18/280 (6)	37/288 (13)
HIV-1 RNA >100 000 c/mL	11/134 (8)	18/134 (13)

Source: Snapshot and population flags analysis datasets – SINGLE

Subgroup analysis for subjects achieving HIV RNA < 50 copies/mL was completed by gender, race and age for both phase 3 treatment-naïve trials. Overall, results were consistent and no subgroup was found to have a significant difference in the proportion of virologic responders (Table 22). There are some minor differences in my results compared to the proposed labeling from the Applicant, in particular for the proportion of female subjects in SPRING-2 who met HIV-1 RNA <50 copies/mL at Week 48 (females: FDA result 88% versus 84% by Applicant). However, it is not clear whether the subgroup analysis in the proposed labeling represents a snapshot analysis or another similar analysis algorithm (Missing or Discontinued = Failure) which could account for this small difference. Please see the statistical review by Dr. Hammerstrom for additional details and analyses by various subpopulations.

Table 22: Subjects with HIV-1 RNA < 50 c/mL at Week 48, subgroup analysis by Baseline Category for Gender, Race and Age, SPRING-2 and SINGLE

	SPRING-2		SINGLE	
Outcome	DTG N=403 n (%)	RAL N=405 n (%)	DTG 50 mg QD N=414 n (%)	Atripla QD N=419 n (%)
Gender				
Male	307/347 (88)	304/352 (86)	307/347 (88)	291/356 (82)
Female	49/56 (88)	43/53 (81)	57/67 (85)	47/63 (75)
Race				
White	301/338 (89)	297/346 (86)	255/284 (90)	238/285 (84)
Non-White	55/65 (85)	50/59 (85)	109/130 (84)	99/133 (74)
Age				
< 50 years	319/362 (88)	308/359 (86)	319/361 (88)	302/375 (81)
≥ 50 years	37/41 (90)	39/46 (85)	45/53 (85)	36/44 (82)

Source: Snapshot and population flags analysis datasets- SPRING-2 and SINGLE

Treatment Experienced INI Naïve

For treatment experienced trial Sailing, subgroup analysis for subjects achieving HIV RNA < 50 copies/ml at Week 24 was performed by randomization strata, key demographic features, background regimen, and baseline resistance. Response rates in the DTG arm were higher than rates observed in the RAL arm in majority of these subgroups; the exceptions and other subgroup analysis of interest are presented in Table 23. Susceptibility to background regimen, baseline HIV RNA, presence or absence of fully active PI in the background, race, age, or gender did not affect response in the DTG arm.

DRV/r used without primary PI mutations, in other words, DRV used as a fully active agent resulted in 80% and 81% response in DTG and RAL arms respectively. As this finding is from small subgroups, limited inferences can be drawn from the observation.

Table 23: Subjects with HIV-1 RNA < 50 c/mL at Week 48, subgroup analysis, Sailing

	DTG N=354	**RAL N=361**
Overall Response HIV-1 RNA < 50 copies/ml	281 (79%)	252 (70%)
DRV/r in background		
No DRV/r	164/214 (77%)	131/209 (63%)
DRV/r with primary PI mutation	60/69 (87%)	58/74 (78%)
DRV/r without primary PI mutation	57/71 (80%)	63/78 (81%)
Fully active PI in background		
None	49/65 (75%)	43/66 (65%)
At least 1 fully active PI	232/289 (80%)	209/295 (71%)
Baseline HIV RNA		
≤50,000 copies/ml	207/249 (83%)	195/254 (77%)
>50,000 copies/ml	74/105 (70%)	57/107 (53%)
Susceptibility to OBR		
PSS 2	198/249 (80%)	185/267 (69%)
PSS <2	83/105 (79%)	67/94 (71%)
Gender		
Female	89/107 (83%)	85/123 (69%)
Male	192/247 (78%)	167/238 (70%)
Age		
<50 years	215/269 (80%)	185/277 (67%)
≥50 years	66/85 (78%)	67/84 (80%)

	DTG N=354	RAL N=361
Race		
White	140/178 (79%)	121/175 (69%)
Non-white	140/175 (80%)	131/185 (71%)
African American/African	117/143 (82%)	114/160 (71%)
Non-African American/non-African	163/210 (78%)	138/200 (69%)

Source: Snapshot.xpt, Pop.xpt, demo.xpt- Sailing

Treatment Experienced INI Experienced

Only the key subgroup analysis are presented and discussed in this review. Please refer to other subgroup analyses in Dr. Tom Hammerstrom's statistical review. Breifly, day 8 and week 24 response in the Viking-3 trial was primarily influenced by baseline INI genotype and baseline DTG phenotype, and are summarized and discussed below. Please refer to Clinical Virology review by Dr. Lisa Naeger for details. Viking-3 outcomes by baseline HIV RNA and baseline OSS are also presented in this section.

Response by baseline genotype
Presence of the Q148 substitution resulted in lower response compared to the overall response, both at Day 8 and Week 24 (Table 24). At Day 8, response was 60% with Q148 substitution compared to 82% overall response. At week 24, response was 35% with Q148 substitution compared to 63% overall response. The specific resistance pattern of Q148 plus at least 2 INI substitutions was associated with even lower response (50% at day 8, and 7% at week 24). As discussed further in Dr. Naeger's virology review, the additional INI baseline substitutions contributing to decreased Week 24 response were L74M/I/Q, E138A/K/T, G140S, Y143R, S147G, Q148H or R, E157Q, G163E/K/R/Q/S/T/N and G193E/R. Lastly, relatively higher response was observed in subjects with no primary INI substitution detected at baseline, both at Day 8 (95%) and at Week 24 (75%).

Table 24: Summary of INI substitutions and response at Day 8 and Week 24, Viking-3

Baseline Genotype	Response at Day 8 (≥1 Log Change from Baseline or <50 copies/mL) (N=182)	Response at Week 24 (<50 copies/mL) Subset N=125
Overall Response	82% (150/182)	63% (79/125)
Primary INSTI Substitutions Not Detected	95% (57/60)	75% (33/44)
No Q148 Substitution	89% (115/128)	75% (66/88)
Q148H or R	60% (32/53)	35% (13/37)
Q148H+G140S	60% (27/45)	34% (11/32)
Q148+≥2 INSTI substitutions*	50% (10/20)	7% (1/14)
Q148+G140+E138	47% (7/15)	15% (2/13)

*These INSTI substitutions included L74M/I/Q, E138A/K/T, G140S, Y143R, S147G, E157Q, G163E/K/R/Q/S/T/N, or G193E/R
Source: Clinical virology review by Dr. Lisa Naeger

Above findings demonstrate response in the INI-experienced population was influenced by presence of Q148 substitutions and poor responses were observed with Q148 plus at least 2 other INI substitutions. It is important to note the majority of trial subjects did not harbor the specific resistance pattern of Q148 plus 2 at least 2 INI substitutions; the pattern was observed in only 10% of subjects. In another analysis provided by the Applicant, this specific resistance pattern was observed in 13% of INI-experienced subjects (please refer to Dr. Naeger's review for analysis details). The relatively low prevalence of this resistance pattern indicates DTG is expected to be beneficial to the overall INI-experienced population. Nevertheless, users and prescribers should be aware of lower DTG response associated with Q148 substitution and Q148 plus 2 INI substitution pattern in order to make an appropriate risk/benefit decision for individual patients. The review team therefore recommends this information is conveyed in the label section 1 Indications and Usage, under Points to Consider when starting DTG treatment. As the specific INI substitution accompanying Q148 is of relevance in clinical decision-making, this information should also be presented in section 1. Below is language recommended by the review team:

(b) (4)

Response by baseline DTG phenotype
The following analysis performed by Dr. Lisa Naeger demonstrates response to DTG was related to phenotypic susceptibility to DTG at baseline. As shown in Table 25, response at Day 8 was 92% in subjects with baseline DTG phenotype < 2-fold from reference and was 33% in subjects with baseline phenotype ≥10-fold. A similar trend of decreasing response with increasing DTG fold-change was observed at Week 24: 71% response was observed in subjects with baseline phenotype < 2-fold and 18% response in subjects with baseline susceptibility ≥10-fold.

Table 25: Response by Baseline DTG Phenotype (Fold-Change in DTG Susceptibility)

Baseline DTG Phenotype	Response ≥1 Log Change from Baseline or <50 copies/mL at Day 8 (N=182*)	Response at Week 24 (<50 copies/mL) Subset N=125
Overall Response	82% (150/182)	63% (79/125)
<2	92% (104/113)	71% (55/77)
2 - <10	76% (31/41)	48% (14/29)
≥10	33% (5/15)	18% (2/11)

Source: FDA clinical virology review by Dr. Lisa Naeger

Response by baseline HIV RNA and OSS
Also shown in Table 26, the baseline HIV RNA category did not affect Day 8 response, measured as mean change in HIV RNA from baseline. Of note, lower Day 8 HIV RNA reductions in the category of baseline RNA < 1000 copies/ml reflects this group's inability to demonstrate 1 $\log_{10}$ reduction given the low plasma RNA levels at baseline. Similarly, a clear correlation between response and baseline HIV RNA category was not observed at Week 24. Lastly, day 8 or Week 24 response did not appear to be influenced by baseline OSS. Mean HIV RNA reduction of 1.4 $\log_{10}$ at Day 8 in the OSS zero category provides an assessment of response attributed to DTG alone. At Week 24, OSS to the OBR did not appear to correlate with response suggesting outcomes were driven chiefly by DTG and not background agents.

Table 26: Subgroup analysis of Day 8 and Week 24 outcomes by baseline HIV RNA category, and OSS

	Day 8 Response (N=183)	Week 24 Response (N=114)
	Mean change in HIV-1 RNA log_{10} copies/ml (n)	Proportion of subjects with HIV RNA < 50 copies/ml
Baseline HIV RNA		
< 1000	-0.9 (n=21)	11/12 (92%)
1000 to 10,000	-1.5 (n=49)	23/30 (77%)
10,000 to < 50,000	-1.4 (n=52)	21/29 (72%)
50,000 to < 100,000	-1.4 (n=20)	8/13 (62%)
100,000 to 500,000	-1.6 (n=34)	8/24 (33%)
≥ 500,000	-1.2 (n=6)	1/6 (17%)
OSS of failing regimen (for Day 8 activity) or OBR (for week 24 activity)		
0	-1.4 (n=105)	5/6 (83%)
1	-1.5 (n=60)	30/48 (63%)
2	-1.1 (n=11)	26/44 (59%)
>2	-1.2 (n=6)	11/16 (69%)

Source: Snapshot.xpt, Pop.xpt, demo.xpt- V king-3

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

N/A

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The FDA Guidance, "Antiretroviral Drugs Using Plasma HIV RNA Measurements-Clinical Considerations for Accelerated and Traditional Approval" states that 48-Week data can be used for traditional approval. The Division considers Week 48 efficacy data sufficient for demonstration of persistence of efficacy in HIV-1 infected, treatment naïve subjects. The Division also considers Week 24 efficacy data sufficient for demonstration of persistence of efficacy in HIV-infected, treatment-experienced subjects.

6.1.10 Additional Efficacy Issues/Analyses

Please refer to section 8 for assessment of antiviral activity in the pediatric adolescent age group.

7 Review of Safety

Safety Summary

Severe hypersensitivity reactions and liver chemistry abnormalities in hepatitis B and/or C coinfected subjects were the primary safety concerns identified with DTG in adult clinical trials. Other safety issues include renal and psychiatric events. Overall, the adverse event and laboratory abnormality profiles for DTG 50 mg QD or twice daily were comparable. Additionally, no exposure-response or dose-response correlations were observed to suggest greater safety risk with twice daily dosing.

Hypersensitivity events including severe reactions with liver involvement were observed in 1% or fewer subjects in clinical trials. Although several cases were confounded by use of another co-suspect agent, one compelling case of severe HSR was observed in the absence of confounding factors and was attributed to DTG. Another case of worsening hypersensitivity with DTG rechallenge provides corroborative evidence of this risk. Overall, clinical trial data supports the Applicant's proposal for a warning for severe hypersensitivity reactions in the label. (b) (4) Rash events, regardless of causality and of all grades, were observed in 5-7% subjects in Phase 3 trial. Majority of rash events were of mild to moderate severity and did not result in drug discontinuation. No cases of serious skin reactions, other than those presenting as part of HSR, were observed in the clinical development program.

Overall, the hepatic AE profile of DTG 50 mg QD was similar to comparator drugs, RAL and Atripla. ALT or AST increases with DTG were more frequently observed in HBV/HCV coinfected subgroup compared to non-coinfected subgroups. Cases of significant ALT increases were confounded by HBV/HCV, or with evidence of pre-existing liver disease, or confounded by concurrent use of known hepatotoxic medications. No definitive case of hepatoxicity was identified, however, a disproportionate number of HBV/HCV reactivation or IRIS cases were observed in DTG treated subjects compared to controls (7 DTG vs. 1 RAL vs. none Atripla). Although viral reactivation and/or IRIS were plausible diagnoses in these cases, hepatotoxicity could not be conclusively excluded. Based on severity of liver chemistry elevations in these cases, a warning for liver biochemistry elevations and recommend monitoring of liver enzymes for hepatotoxicity in HBV/HCV patients is recommended by the clinical review team.

Renal failure events were observed in 1% or fewer subjects. All renal failure events were confounded by pre-existing and ongoing renal disease, another medical condition known to cause compromise in renal function, or use of nephrotoxic agents. Creatinine elevations with a mean increase of 0.2 mg/dl occurred within the first weeks of DTG dosing, and were observed to plateau through the dosing period in all phase 3 trials.

These non-progressive creatinine elevations and corresponding decline in creatinine clearance is attributed to DTG effects on renal tubular creatinine secretion mediated by drug inhibition of the OCT2 renal transporter. This effect has been described with other medications such as cimetidine. Dolutegravir does not have significant effects on either glomerular filtration rate or on renal plasma flow. The mean creatinine elevations were similar between the QD and BID dose; the overall magnitude of elevations (mean 0.2 mg/dl) is not likely to clinically significant.

Among psychiatric events, insomnia was the most frequently observed in 3-11% DTG subjects in phase 3 trials. These event rates were similar to RAL, and higher than observed with Atripla. Insomnia was mild to moderate in severity and did not result in discontinuations. One completed suicide in the development program was in subject receiving DTG. The case is confounded by pre-existing depression, recent social stressors including unemployment, and a protracted time to onset of 7 months since DTG initiation. Other suicidal behavior events in DTG subjects were also confounded; none resulted in drug discontinuation or were assessed as drug-related.

Lastly, no unexpected trends in CK elevations were observed with DTG compared to RAL or EFV. No compelling case of rhabdomyolysis was reported; and only one case of symptomatic myositis appears causally associated with DTG exposure.

7.1 Methods

The safety data from phase 3 trials form the principal data source for FDA safety analysis. Data from treatment-naïve trials, Spring-2 and Single, as well as the treatment-experienced trial Sailing were reviewed to support safety for DTG dose 50 mg QD. Data from the Viking-3 trial was the primary source of safety for the 50 mg BID dose. Additional data from phase 2b trial Viking-pilot, specifically data from cohort 2, were also reviewed to form an integrated assessment of safety for the BID dose.

This original NDA included 48-week data for Spring-2 and Single trials, and 24-week data for Sailing trial and Viking-3 trials. The integrated summary of clinical safety and datasets in the NDA submission provide results and data up to the following cut-off dates: 18 June 2012 for Spring-2, 4 June 2012 for Single, 4 September 2012 for Sailing, 18 June 2012 for Viking-3, and 8 June 2012 for Viking-pilot trial. An additional cut-off date for SAEs and pregnancies observed in the ongoing trials was 26 October 2012. The 60-day safety update report including SAEs, pregnancies, and AEs leading to discontinuation from 27 October 2012 to 14 January 2013 was also reviewed.

The phase 3 trials differed by either the study population, the DTG dose evaluated, or study design; factors which prohibited pooling of data across trials. In some instances, for example with treatment-naïve trials Spring-2 and Single, safety data were pooled from the DTG arms. Please refer to section 7.1.3 for other details.

All fatalities occurring in the treatment and follow-up period were reviewed. All treatment-emergent SAEs and AEs occurring within 30 days and 7 days of treatment end, respectively, were reviewed. Causality assigned by the investigator was reviewed. For select events, additional causality assessments (by Applicant and/or an independent adjudication committee) were taken into consideration during FDA review.

Strategy for assessing safety of DTG 50 mg BID
Because data for DTG 50 mg BID dose was obtained in a single-arm trial, in-trial comparative safety assessments could not be performed. The review strategy for the BID dose was to compare safety between BID dosed subjects and findings from DTG QD arm in the Sailing trial. The Sailing trial, conducted in treatment-experienced INI-naïve subjects, offered a relatively similar population for safety comparison. However, it should be noted subjects in Sailing were only moderately advanced in terms of HIV disease (based on CDC category for trial population at baseline) and treatment experience. Therefore, although not identical, the Sailing subjects provide a reasonable trial population for comparing safety of the QD and BID dose of DTG. Comparison to cohort 1 in the Viking-pilot trial, also dosed DTG QD, is considered less ideal because of the few subjects (n=24) in this cohort, and because data from this cohort represents longer duration safety exceeding 24 weeks.

7.1.1 Clinical Trials Used to Evaluate Safety

As mentioned above, safety data from phase 3 trials form the principal data source for FDA safety analysis. Safety for DTG 50 mg BID dose was evaluated by pooling data from the phase 3 trial Viking-3 and cohort 2 in the phase 2b trial Viking-pilot. For select safety evaluations including deaths, data from the treatment-naïve phase 2b trial, findings from DTG expanded access trials, and safety summaries for phase 1 trials were also reviewed. Please refer to sections 5.1 and 5.2 for phase 2b and 3 trial details.

7.1.2 Categorization of Adverse Events

Adverse events were appropriately categorized by the Applicant using MedDRA standardized criteria.

7.1.3 Pooling of Data Across Clinical Trials to Estimate and Compare Incidence

Overall, data across the phase 3 trials were not pooled because the trials were either not identically designed or evaluated different DTG dose, or were conducted in distinct populations.

Treatment-naïve phase 3 trials were evaluated independently as well as by pooling data from the DTG arms for select analyses. Pooling data from the DTG arms in these trials is appropriate because the two study populations were similar in regards to baseline

characteristics. The pooled DTG naïve safety data (N=817) are clearly displayed as 'total DTG naive' throughout the safety review.

Safety data for subjects receiving DTG 50 mg BID in Viking-3 and cohort 2 of Viking-pilot trials were also evaluated independently as well as pooled to provide aggregate safety for this dose. The pooled DTG data (N=207) are displayed as 'total DTG 50 BID' throughout the review.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 2026 HIV-infected subjects were exposed to at least one DTG dose in clinical trials at the time of NDA data cut-off.

- A total of 856 treatment-naive subjects were exposed to 50 mg QD dose for at least 48 weeks.
- A total of 311 treatment-experienced INI-naïve subjects were exposed to 50 mg QD for at least 24 weeks.
- A total of 207 subjects were exposed to 50 mg BID dose including 127 subjects exposed for at least 24 weeks in phase 2b/3 trials.
-

Please refer to section 6.1.2 for study demographics.

7.2.2 Explorations for Dose Response

Dose and exposure response relationships were evaluated by the Applicant and FDA reviewers. Specifically, exposure response correlations were evaluated for hypersensitivity reactions, rash, hepatobiliary adverse events, renal adverse events, ALT elevations, and serum creatinine elevations. Please refer to clinical pharmacology and pharmacometrics review by Drs. Su-young Choi, Stanley Au, and Jeffry Florian for details. Analysis was also performed to compare safety of the 50 mg QD and 50 mg BID doses using data from trials Sailing and Viking-3 enrolling generally similar patient populations.

7.2.3 Special Animal and/or In Vitro Testing

The nonclinical toxicity program was consistent with acceptable scientific practices and international guidelines. The pivotal studies were conducted according to good laboratory practices (GLP) standards as per Organization for Economic Cooperation and Development (OECD) Principles of GLP, which concur with FDA GLP regulations.

The primary nonclinical toxicity observed was gastrointestinal findings, presented in detail in section 4.3. Dolutegravir demonstrated in vitro activity against wild-type HIV-1 virus.

7.2.4 Routine Clinical Testing

Routine clinical evaluations for safety included medical history taking for assessment of symptoms of adverse events, vital sign measurements and physical examinations for assessment of signs of adverse events, laboratory evaluations and ECG. In phase 3 trials, key evaluations were performed at baseline, Weeks 2, 4, 8, 12, 16, 24, 32, 40, 48 and every 12 week thereafter (depending on the trial duration). Follow-up visits were scheduled for subjects who discontinued treatment prematurely due to adverse events.

7.2.5 Metabolic, Clearance, and Interaction Workup

Several drug-drug interaction studies were conducted to evaluate effects of DTG coadministration with other agents. Dolutegravir exposure can be affected by inhibitors or inducers of UGT1A1 and by drugs containing polyvalent cations. Although drug interaction studies with two drugs, dofetilide and metformin were not performed; DTG is expected to affect the exposures of these two drugs as a result of DTG inhibition of the renal OCT2 transporter. For details, please refer to section 7.5.5 of this review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Two approved drugs in the INI class are RAL and EVG. As mentioned previously in sections 2.2 and 2.3, EVG is marketed as a FDC Stribild comprising of other ARVs TDF, FTC, and cobicistat. Adverse events associated with either RAL or Stribild including serious skin reactions, gastrointestinal events, suicidal behavior events, rhabdomyolysis and serum CK elevations are presented in section 2.3. Potential adverse events were evaluated in DTG clinical trials as discussed in section 7.3.

7.3 Major Safety Results

7.3.1 Deaths

Overall, 11 deaths were observed in DTG exposed subjects in phase 2b/3 trials or the compassionate use program up to the original NDA data cut-off. This includes 7 deaths observed in DTG exposed subjects in phase 2b/3 clinical trials. All deaths were in adult trials; no deaths were observed in pediatric data submitted to the NDA. All deaths were assessed as not related to DTG by the clinical reviewers.

Adverse events leading to demise included opportunistic infection (4 cases, progressive multifocal leukoencephalopathy, lymphoma, Kaposi's sarcoma, non-Hodgkin's

lymphoma), cardiovascular events (3 cases, myocardial infarction, cardiac death, myocardial infarction with cardiorespiratory arrest); and suicide, homicide, motor vehicle accident, and brain mass in one subject each. Three additional deaths were reported in the 60-day safety update report were also not related to DTG.

Treatment Naïve

Four deaths were observed in phase 3 treatment naïve trials including 1 death in subject receiving DTG 50 mg QD, 1 death in a subject receiving RAL, and 2 deaths in subjects receiving Atripla. None of the deaths were considered by the investigators to be related to study drug. A brief clinical summary of the fatality in the subject receiving DTG is provided below.

> A 42 year old male (Subject 3264) was randomized to receive DTG 50 mg QD in combination with TDF/FTC. The subject initiated study drug on (b) (6) After 12 days on study, the subject was found deceased at home. The subject was determined to be a victim of homicide; however, the cause of death was unknown and it was unknown whether an autopsy was performed.

There were 2 additional deaths in subjects exposed to DTG from the phase 2b study SPRING-1 (ING112276):

One subject 0055 died of a presumptive myocardial infarction (MI) after receiving DTG 50 mg QD in combination with Truvada (TDF/FTC) over 935 days. The subject was a 49 year old male chronic smoker, with a known history of coronary artery disease (mid-RCA stenosis 100% and distal left main stenosis 30%) and dyslipidemia and a previous MI at Week 93 while on study. He was found dead at home and was presumed to have died of an MI as no autopsy was performed. The subject's partner reported that the subject was in his usual state of health and had no symptoms or complaints the week of the event. The study coordinator had spoken with the subject earlier in the week, and he reported being fine. The subject did have a history of alcohol use/abuse and symptoms consistent with anxiety in the past, but there was no prior history of suicidal ideation or attempts and no evidence for suicidal intent around the time of his death. The police were involved and stated that there was no foul play and no suspicion of suicide.

The second subject from SPRING-1 was a 35 year old male who was randomized to DTG 10 mg QD in combination with Epzicom. After 636 days on study, the subject died after sustaining multiple trauma and internal bleeding for a car accident. The subject's car was hit by another driver. According to the subject's wife, he was having no symptoms or health problems prior to the accident.

After clinical review of the narratives, the primary reviewer concurs with the investigators' causality assessments that these deaths were not related to DTG

exposure and believes there is no indication that DTG led to the demise of the study subjects.

Treatment Experienced, INI Naïve

No deaths were observed in subjects receiving DTG in the Sailing trial. Two fatalities were observed in this trial; both were in subjects randomized to RAL, and both were considered by the investigators as unrelated to study drug. Cause of death was assessed by the investigators to be metastatic adenocarcinoma in one RAL subject, and end-stage AIDS in the second RAL subject.

Treatment Experienced, INI Experienced

Two deaths were observed in subjects receiving DTG 50 mg BID. One fatality was a subject in Viking-3 with PML, an opportunistic infection occurring in patients with advanced AIDS, and one subject in cohort 2 Viking-pilot died from completed suicide. Both events were considered by investigators as unrelated to study drug. Brief narratives for these two cases are provided below.

Subject 1203, a 47-year-old female died due to complications from PML. The subject had a history of multiple opportunistic infections and baseline was CD4 count 19 cells/mm^3. Her ARV regimen consisting of DTG, MVC, TDF/FTC and ENF was stopped for rash and pruritis. Subsequently, 33 days after discontinuing ARVs, this subject was diagnosed with PML based on findings on MRI of the brain. The patient succumbed due to complications from PML about 10 weeks after discontinuing DTG.

Subject 2463, a 45-year-old male, committed suicide 7 months after initiating treatment with DTG, DRV/r, and ETR. The subject had a history of depression for which he was taking escitalopram. There was no prior history of suicidal ideation or attempts. The event was associated with recent loss of his apartment and job.
The cause of death was ethylene glycol and drug intoxication. An autopsy was not performed. The subject did not express any anxiety or suicidal thoughts to the study staff, and use of drugs or alcohol was not reported. There was no known family history of psychiatric disorders and/or suicide attempts. The subject was concerned about housing and job but he was reported as working on his PhD, and making plans to return to South Beach to get another job. He was working part-time as a teacher of English. He had also just bought a new car. The narrative reports no activities to suggest the subject was planning on committing suicide. There were the psychosocial stressors of losing his job and apartment. The investigator assessed the event as unrelated to study drug.

Based on the information provided, the primary reviewer concurs with the investigators' assessments that these deaths were not related to DTG. In subject 1203 with low CD4 count and history of multiple opportunistic infections, the diagnosis of PML is not

unexpected. With progressive brain involvement, PML can eventually result in death; therefore, I agree with the investigators assessment. In subject 2463 with history of depression, the recent social stressors (homeless, loss of full-time employment) may have contributed to the suicide event. The event is less likely to be related to DTG based on the protracted timing of suicide relative to DTG initiation and lack of symptoms suggestive of worsening depression and/or suicidal ideation in the intervening 7 months while on DTG. Based on the available information, I agree with the investigators causality assessment that death was not related to DTG.

An additional two deaths were observed in subjects receiving DTG 50 mg QD in cohort 1 in Viking-pilot. One death was due to brain mass and the other death was due to immunoblastic lymphoma with bone marrow aplasia. Both events were considered by the investigators unrelated to DTG. Brief summaries are provided below.

Subject 1111, a 48-year-old male died due to brain lesion that was suspected to be a meningioma. The subject was diagnosed with a frontal brain mass 44 days after initiating treatment with regimen containing DTG. Following this diagnosis and with deterioration in the subject's general health, all ARVs were discontinued. The subject was transferred to a nursing facility for supportive and palliative care. He died approximately 3 months later after DTG treatment was stopped.

Subject 1680, a 55-year-old male developed immunoblastic lymphoma with bone marrow involvement. This was diagnosed approximately 3 months after initiating a DTG-containing regimen. Chemotherapy was initiated with cyclophosphamide, doxorubicin, vincristine and prednisone. ARVs were continued. Two months later the subject died due to complications from lymphoma, chemotherapy and bone marrow disease.

The primary reviewer concurs with the investigators' assessments that these deaths were not related to DTG.

Other fatalities in DTG exposed subjects
Three deaths were observed in the compassionate use program. All three subjects had advanced HIV disease with opportunistic infections, and were receiving DTG dosed 50 mg BID. In all cases, the investigators assessed the death was not related to DTG.

One subject died due to pulmonary hemorrhage 12 days after initiating ARVs including DTG 50 mg BID. This subject had a history of CMV retinitis for which he was receiving ganciclovir infusions. He also had a history of Kaposi's sarcoma for which he was receiving periodic paclitaxel infusions. The subject died due to pulmonary hemorrhage shortly after a paclitaxel infusion. Previously, Kaposi exacerbation including bleeding from cutaneous Kaposi's lesions was reported following paclitaxel infusion. Although pulmonary Kaposi's was not diagnosed pulmonary hemorrhage due to Kaposi's sarcoma with pulmonary involvement was considered by the investigator. The event

was also considered to be possibly secondary to thrombocytopenia developing as a result of ganciclovir therapy. The event was considered by the investigator unrelated to DTG.

One subject died due to non-Hodgkin's lymphoma (NHL). NHL with brain involvement and adrenal insufficiency were diagnosed about 4.5 months after initiating DTG containing regimen. Hypotension due to adrenal insufficiency was managed with steroid and mineralocorticoid supplementation. Due to the overall poor condition of the subject, chemotherapy for NHL was not initiated. He died due to worsening brain lymphoma about 6 months after starting DTG. The event was assessed unrelated to DTG by the investigator.

The third subject died due to septic shock with MI and cardiorespiratory arrest; concurrent medical conditions reported were encephalitis, pancytopenia and meningioma. Limited information is available for this subject enrolled in the expanded access program. Based on available information, the case appears unrelated to DTG.

One additional subject enrolled in study ING116529 died from 'cardiac death' 34 days after starting DTG 50 mg BID; this subject was a 66-year-old male with hypertension, left ventricular hypertrophy and history of stroke. The subject was evaluated in the podiatry clinic on day prior to death and expressed no complaints. No autopsy was performed. The cause of death is presumed to be vascular in nature, given the subject's past history of stroke.

Limited information was provided for case 3 (septic shock with MI) to form a reasonable causality assessment, although the available information does not suggest a DTG-related adverse event resulted in subject demise. For rest of the cases, the primary reviewer agrees with the investigators' assessments that the deaths were not related to DTG.

Fatalities reported in the 60-day Safety Update Report

No additional deaths were reported in the SUR for the treatment-naïve population. Four fatalities were reported in treatment-experienced subjects, two subjects in the Viking trial and two subjects enrolled in the compassionate use program. All events were considered by investigators as unrelated to DTG. Brief summaries for these cases are provided below:

Subject 1633, a 57-year-old female died of cardiac arrest approximately 40 months after initiating a regimen containing DTG 50 mg QD. Risk factors for cardiovascular disease included hypercholesterolemia. The subject was diagnosed with coronary stenosis, underwent angioplasty procedure with coronary stent placement. Post-procedure the subject developed complications of pulmonary edema, torsades de pointes, and succumbed to cardiac arrest the following day.

Subject 2310, a 49-year-old female died of hemochromatosis and fibrosis secondary to hepatitis C. This subject with pre-existing hepatitis C infection was diagnosed with grade 3 secondary hemochromatosis 35 weeks after initiating DTG 50 mg BID, DRV/r, ETR, MVC, TDF, FTC, ABC. Hemochromatosis was treated with deferasirox, an iron chelating agent. Three weeks later, grade 4 hepatic fibrosis secondary to Hepatitis C was diagnosed. Anemia, hypoalbuminemia and hypokalemia were diagnosed 48 to 50 weeks after DTG initiation. DTG and other ARVs were discontinued at this time. The subject died 46 weeks after DTG discontinuation due to hemochromatosis and fibrosis secondary to Hepatitis C. The events were not considered related to DTG by the investigator.

Two deaths reported in the compassionate use program were considered related to Kaposi's sarcoma or a fungal pneumonia; both events were assessed by the investigator as not related to DTG. The primary reviewer concurs with this assessment.

7.3.2 Nonfatal Serious Adverse Events

Treatment Naïve

The incidence of subjects reporting an SAE was similar across the treatment groups for the phase 3 treatment-naïve trials (8-9%). Due to the low incidence of SAEs, the data were pooled for the treatment naïve trials to evaluate for any emerging safety trends. A summary of the nonfatal SAE that occurred in 2 or more subjects from any treatment arm is provided in the following table. Please note that clinically similar and relevant Preferred Terms (PT) were pooled to provide a more clinically relevant analysis of the safety data. The pooling for this analysis is detailed in the footnotes of the table.

Table 27: Summary of Nonfatal SAEs in 2 or more subjects from any treatment arm, treatment naive

Preferred Term	SPRING – 2		SINGLE		Total DTG N=817 n (%)
	DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)	
# of subjects with any SAE	**31 (8)**	**36 (9)**	**37 (9)**	**35 (8)**	**68 (8)**
Drug Hypersensitivity[a]	3 (1)	0	1 (<1)	2 (<1)	4 (<1)
Suicide Attempt*	2 (<1)	3 (1)	2 (<1)	2 (<1)	4 (<1)
Intentional overdose	0	0	2 (<1)	0	2 (<1)
Depression	0	0	0	2 (<1)	0
Pneumonia**	2 (<1)	4 (1)	2 (<1)	2 (<1)	4 (<1)
Convulsion‡	0	2 (<1)	1 (<1)	0	1 (<1)
Syphilis†	2 (<1)	0	2 (<1)	0	4 (<1)
Appendicitis	1 (<1)	0	1 (<1)	3 (1)	2 (<1)
Laceration	0	2 (<1)	0	0	0
Abdominal Pain/lower	2 (<1)	0	0	0	2 (<1)

[a]Includes PT hypersensitivity
*Includes PT suicidal behavior
**Includes PTs pneumonia, lung infection, pneumonia cytomegalovirus, pneumonia bacteria, pneumonia aspiration
‡ Includes PT grand mal convulsion
† Includes PTs secondary syphilis, neurosyphilis
Source: AE-ISS analysis dataset

Overall, 15 treatment-naïve subjects experienced 19 nonfatal SAEs that were considered related to study drug treatment of which, 3 DTG subjects had drug-related nonfatal SAEs. The nonfatal SAEs that occurred in the pooled treatment-naïve trials that were considered related to drug and occurred in 2 or more subjects are summarized in the table below.

Table 28: Non-fatal SAEs considered related to study drugs by the Investigator and Observed in ≥2 subjects- Pooled Tx naïve data

Preferred Term	Total DTG N=817 n (%)	Comparator Regimen	
		Atripla N=419 n (%)	Raltegravir N=405 n (%)
# of subjects with any related SAE	***3 (<1)***	***7 (2)***	***5 (1)***
Hypersensitivity Reactions*	2 (<1)	2 (<1)	1 (<1)
Suicidal Ideation	0	2 (<1)	0
Convulsion	0	0	2 (<1)

*Pooled PT terms of hypersensitivity and drug hypersensitivity
Source: AE-ISS analysis dataset

The nonfatal SAEs considered related to DTG were: 2 subjects with hypersensitivity and 1 subject with cardiac arrhythmia. The cases are detailed below.

Subject 4529 SPRING-2 (SAE-hypersensitivity): This subject is a 42 year old male who was randomized to DTG 50 mg plus ABC/3TC background therapy. After 10 days of study drug, the subject experienced flu-like symptoms of fever and body aches which progressed over the next 4 days, despite discontinuation of study drug, to include a profuse, purpuric and coalescing rash, joint swelling and pain, palpable liver, jaundice and new onset atrial fibrillation. At the time of presentation, the subject's ALT was 1081 U/L (NR 0-45), AST 906 U/L (NR 0-34) and Total Bilirubin 104 µmol/L (NR 0-21) and GGT 253 µmol/L (NR 0-64). The subject's ALT peaked at >20xULN and his total bilirubin at > 4xULN. However, he did not show other evidence of liver dysfunction (PT/PTT were not prolonged, no encephalopathy). The subject was hospitalized and study drugs were all stopped. The subject was treated with prednisone which led to clinical and laboratory improvement. The subject was also treated with oseltamivir phosphate for suspected influenza, sotalol and aspirin for atrial fibrillation, and omeprazole. He was investigated extensively for non-drug causes of his hypersensitivity reaction, including testing for hepatitis A/B/C/D/E, cytomegalovirus, Epstein-Barr virus (EBV), syphilis and autoimmune disease and repeat HLA-B*5701 testing (negative), but an alternative cause could not be identified. The subject underwent skin patch test evaluation for abacavir hypersensitivity which was negative at 24 and 48 hours. A skin biopsy obtained during hospitalization revealed leukocytoclastic vasculitis. A transthoracic echocardiogram showed normal left ventricular function and no atrial dilation. The subject was taking several over-the-counter supplements, but they had been taken by the subject on a regular daily basis and had not been changed in quantity or brand. The patient denied use of anabolic steroids. The subject continued to clinically improve to include resolution of his elevated ALT and Total Bilirubin. The subject was not re-challenged with DTG or ABC/3TC.

The Investigator and Sponsor both believed that a drug-induced HSR related to DTG was possible in this case; however, only the Sponsor believed that an abacavir HSR reaction remained co-suspect in this case.

Based on review of this case, the reviewer concurs with the assessment of the Investigator that this case is represents hypersensitivity most likely related to DTG and not to ABC. The most convincing evidence against ABC being attributed to this hypersensitivity reaction is the combination of 2 negative HLA-B*5701 tests and negative skin patch testing. The PREDICT-1 study was a randomized, double-blind prospective trial designed to determine whether pre-screening for HLA-B*5701 could significantly reduced the incidence of hypersensitivity (HSR) reaction to abacavir. Screening eliminated immunologically confirmed (skin patch test positive) HSR with a negative predictive value of 100% and a positive predictive value of 47.9%. Additionally, the odds ratio of having a skin patch test positive (or immunologically confirmed case) of abacavir HSR was 0.03 (95% confidence interval [CI], 0.00 to 0.18; p<0.001). No case of clinically diagnosed abacavir HSR in subjects pre-screened for HLA-B*5701 was immunologically confirmed with skin patch testing. Skin patch testing was found to have a specificity of 100% (95% CI, 96.4 to 100). Of 61 evaluable subjects from the control group who had clinically diagnosed HSR and skin patch testing, all 23 who had positive skin patch test results were also HLA-B*5701 positive, in contrast to 32 of 38 with negative skin patch test who were HLA-B*5701 negative (with the remaining 6 being HLA-B*5701 positive) (Mallal, 2008).

Subject 6929 SINGLE (SAE- Drug Hypersensitivity): This 25 year-old female subject was randomized to DTG/ABC/3TC. On June 4, 2011 she took her first dose of study drugs and developed a sore and swollen throat. She took another dose of study drugs on June 5, 2011 and then self-stopped all study drugs from June 6-13th. On June 14, 2011 the study took another dose of study drugs and experienced swollen and scratchy throat, diarrhea, nausea, fatigue, cough and fever. The subject was discontinued for study drugs and study on June 14, 2011. The investigator attributed the events to be related to ABC and not to DTG. The subject was HLA-B*5701 negative at screening. No skin patch testing was recorded for this subject. She was not re-challenged with any study drugs. After review of this case, DTG remains co-suspect as related to this HSR reaction by my clinical judgment due to the fact that this subject was HLA-B*5701 negative; however, although exceedingly rare, ABC HSR can occur in HLA-B*5701 negative subjects.

Subject 3884 SPRING-2 (SAE-Arrhythmia): This is a 36 year old male who was randomized to DTG plus TDF/FTC. The subject had a history significant for tobacco smoking (24 pack year) and COPD. At Baseline, the subject was HBV and HCV screen negative. After 196 days on study therapy, the subject developed Grade 3 cardiac arrhythmia and was clinically symptomatic with dizziness and weakness. The subject was seen at an unscheduled visit approximately 1 mo after the Week 24 visit (which had been unremarkable) for evaluation. At that time, an ECG showed short runs of non-

sustained ventricular tachycardia (NSVT). Vital signs including blood pressure were normal. The subject was sent to the ER and was admitted for observation and treatment. Study drugs were withdrawn pending further evaluation.

Admission labs revealed new elevation of ALT to 122 U/L (Calcium, Mg, K, LDH, CK, Na, CRP, CBC and TSH and other labs were normal). His cardiac work up was normal (no ischemic disease and trans-esophageal echo normal). Cardiac monitoring revealed NSVT, premature ventricular contractions (PVC) and bigeminy with evidence of ischemia. There was no evidence of prolonged QT or electrolyte abnormalities. He was discharged after 3 days admission.

Two weeks after discharge he was followed up in clinic. His ECG showed premature atrial contractions (PACs) and occasional premature ventricular contractions (PVCs) without NSVT. His Hepatitis C HCV RNA PCR was positive at 25,500 IU/mL. The site considered the patient to have acute hepatitis C (no details for risk factors were given). Full cardiology evaluation was completed (including holter monitoring) and the sponsor had 3 independent cardiologists review the EKGs. All believed that the dysrhythmia was consistent with Right Ventricular Outflow Tract Ventricular Tachycardia (RVOT VT). While the investigator attributed this SAE as drug related, the cardiologists believed that RVOT VT was unlikely to be a drug induced event. The subject was withdrawn from study. AST and ALT results trended down (ALT 96 and AST 40 at final visit) and the subject was being considered for initiation of HCV therapy.

Based on review of this case, I concur with the cardiologist evaluation that it is unlikely that DTG was causally associated to the cardiac arrhythmia. There is no preclinical signal for cardiac toxicity and this represents the only cardiac nonfatal SAE considered related to DTG across the 1167 subjects exposed to DTG 50 mg QD during phase 2b/3 trials.

The nonfatal SAEs considered related to Atripla or RAL were observed in single subjects, respectively, and are provided below.

> Atripla: Bipolar disorder, Cerebrovascular accident, Depression, Hallucination visual, Homicidal ideation, and Paranoia.
> RAL: Aphasia, Blood CPK increased, Diarrhea, and Hypersensitivity.

Treatment Experienced INI Naïve

A total of 87 nonfatal SAEs were observed in 66 subjects in Sailing. This includes SAEs in 27 (8%) and 39 (11%) subjects in the DTG and RAL arms, respectively.

Events observed in at least 2 subjects in either arm were: suicidal ideation (3 DTG, 1 RAL), pancreatitis (2 DTG, 1 RAL), pneumonia (2 DTG, 4 RAL), alcohol withdrawal syndrome (2 DTG, none RAL), depression (2 DTG, none RAL), anemia (none DTG, 2 RAL), cerebrovascular accident (none DTG, 2 RAL), dehydration (none DTG, 2 RAL), postoperative wound infection (none DTG, 2 RAL). Suicidal behavior events are discussed in detail in section 7.3.5 under Psychiatric Events of Interest. Pancreatitis AEs are also discussed in detail in section 7.3.5.

Drug-related nonfatal SAEs are displayed in Table 29. The drug-related SAEs in the DTG arm were: hepatoxicity in one subject and myositis with acute renal failure in one subject. These two cases are summarized below, and also discussed in section 7.3.5 under Hepatobiliary Analysis and Renal Analysis respectively. The drug-related SAEs in the RAL arm were pancreatitis, hepatitis, rash plus oral blisters, and suicidal ideation; these events were observed in one subject each.

Table 29: All drug-related nonfatal SAEs, Sailing

Preferred Term	DTG N=354	RAL N=361
Subjects experiencing ≥ 1 SAE	27 (8)	41 (11)
Subjects experiencing ≥ 1 drug-related SAE	2 (<1)	4 (1)
Hepatotoxicity	1 (<1)	0
Renal failure acute	1 (<1)	0
Myositis	1 (<1)	0
Oral mucosal blistering	0	1 (<1)
Pancreatitis	0	1 (<1)
Rash pruritic	0	1 (<1)
Suicidal ideation	0	1 (<1)
Hepatitis	0	1 (<1)

Source: AE-ISS analysis dataset

Subject 9098 (Hepatoxicity SAE/DTG) is a 42-year-old male with previously diagnosed hepatitis B infection. The subject was HBsAg positive at screening, and had HBV DNA 250 copies/ml on day 1. Baseline ALT, AST and total bilirubin were within normal range. The treatment regimen discontinued at the time of study entry included lamivudine. On day 1, the subject was started on DTG and LPV/r. At week 8, ALT was 1011 U/L (normal 0-48), AST was 909 U/L (normal 0-42), total bilirubin was 34 umol/L (normal 0-22), and direct bilirubin 16 umol/L (normal 0-6). The subject denied use of concomitant medications, herbal products, or alcohol intake. Viral hepatitis work-up was negative; abdominal ultrasound was reported as unremarkable. Five days later, ALT was 1290

U/L, AST was 1030 U/L, and total bilirubin was 78 umol/L. The investigator assessed the event as hepatotoxicity SAE reasonably related to DTG. The ARVs including DTG were discontinued. HBV DNA was 3,030,000 copies/ml at the time of liver chemistry elevation. At follow-up, 23 days after the initial evaluation ALT was 51 U/L, AST was 29 U/L, and total bilirubin was 20 umol/L. At baseline, the subject's HIV RNA was 2959 copies/ml and CD4 count was 266 cells/mm^3. At week 8, when peak ALT and AST were reported, the HIV RNA was 166 copies/ml and CD4 count was 358 cells/mm^3. The Applicant considered this case as hepatitis B flare after removal of HBV therapy (lamivudine) and possible IRIS. The IDMC considered this case as hepatitis B flare after discontinuation of lamivudine. Liver chemistry elevations occurring in the setting of recent cessation of an HBV active agent, and the corresponding marked increase in HBV RNA from baseline together support HBV reactivation. The CD4 count increase by 92 cells/mm^3 over 8 weeks makes HBV IRIS a plausible diagnosis.

Subject 2809 (Acute renal failure/DTG) developed acute renal failure in conjunction with symptomatic myositis in one subject. The subject had normal renal function at baseline with creatinine clearance 133 ml/min and serum creatinine 0.75 mg/dL. During an episode of symptomatic myositis, he developed serum creatinine elevation to 1.5 mg/dL and reduced creatinine clearance 58.1 ml/min. The subject was hospitalized; the AEs resulted in drug discontinuation and were considered related to DTG. The renal abnormalities resolved with resolution of myositis. The subject was subsequently rechallenged with the same DTG-containing regimen, and experienced muscle pain with mild increase in CK after two DTG doses. Due to positive rechallenge, myositis and ARF events were considered by the investigator as related to DTG. This case is also discussed under Myositis/CK evaluation. By my assessment, the renal laboratory abnormalities were secondary to myositis and are less likely to represent drug-induced direct renal toxicity.

Treatment Experienced INI Experienced

Nonfatal SAEs were observed in 17% of subjects dosed with 50 mg BID ('total 50 BID group'). Nonfatal SAEs observed in at least two subjects are displayed in Table 30. Among these, SAEs considered related to DTG were observed in 1 subject only. This was a case of drug eruption with increased ALT and hyperbilirubinemia.

Table 30: Nonfatal SAEs observed in INI-experienced trials

Preferred AE term	Total 50 BID N=207	Viking-3 50 BID N=183	Viking-Pilot 50 BID N=24	Viking-Pilot 50 QD N=27
Subjects with ≥ 1 SAE	35 (17)	27 (15)	8 (33)	6 (22)
SAE observed in ≥ 2 subjects				
Pneumonia	4 (2)	4 (2)	0	0
Pleural effusion	2 (1)	2 (1)	0	0
Pyrexia	2 (1)	2 (1)	0	0
Dehydration	2 (1)	2 (1)	0	0
Viral gastroenteritis	2 (1)	1 (<1)	1 (4)	0
Coronary artery disease	2 (1)	0	2 (8)	0

Source: AE-ISS analysis dataset

The case details for the single drug-related SAE are summarized here.

Subject 568, (SAE-drug eruption with increased ALT) is a 54-year-old male with features consistent with severe HSR after initiating DTG, ETR, and DRV/r. A full body rash, fever, nausea, and vomiting were accompanied by ALT elevation (4.6 x ULN) and direct hyperbilirubinemia (6 x ULN). Elevations in AST, creatinine, and alkaline phosphatase were also noted. The onset was 15 days after initiating DTG and 7 days after initiating ETR and DRV/r. The subject was diagnosed with HSR. All ARVs were discontinued; he was treated with steroids followed by complete resolution within 2 weeks. No use of food supplements, herbal or complementary medicines, or illicit drugs was reported. The subject had no liver disease and no relevant medical history. The investigator assessed the events collectively indicated a hypersensitivity reaction and there was reasonable possibility that HSR was caused by DTG. In this case, symptoms and signs taken together are representative of severe hypersensitivity reaction. The case is confounded by concurrent use of etravirine and DRV, both of which can cause HSR.

One other subject in Viking-3 trial was originally considered to develop DTG-related SAE of rash and pruritis. Upon further evaluation, the investigator amended causality to implicate ETR and not DTG. The case details are provided below:

Subject 1219 (SAE-rash and pruritis), a 44-year-old male, developed grade 2 rash and grade 3 pruritis after initiating DTG, ETR, and LPV/r. Both events began 16 days after initiating DTG. The subject was hospitalized, all ARVs were discontinued, and supportive care including steroids provided. The subject had tolerated LPV/r in the past without developing rash. After symptom resolution, DTG was reintroduced without recurrence. Although initial causality attribution was to both DTG and ETR, the investigator subsequently concluded this SAE was not attributable to DTG. Based on

lack of symptom recurrence with DTG rechallenge and because ETR is known to cause cutaneous toxicity, the primary reviewer concurs with investigator's final assessment.

Additional cases in 60-day Safety Update Report

Two additional nonfatal SAEs considered related to DTG were reported in the SUR. These include one case of suicide attempt and one case of eosinophilia, summarized below.

Subject B0844953A in ING115502 (SAE-eosinophilia), a 54-year-old female was diagnosed with eosinophilia associated with itchy skin lesions. The subject was on DTG 50 mg BID, DRV/r, ENF; other concomitant medications included cefixime, levoceterizine, and racecadotril. Itchy lesions developed 11 days after starting DTG and 38 days after starting ENF. About 3 weeks later, hypereosinophilia was observed with total eosinophil count 2.18 G/L. The previous eosinophil count was within the normal range in the previous month. The subject had no history of allergies and no recent travel where she may have acquired a parasitic infestation. In the first week after starting DTG, she had taken cefuroxime for 5 days for bronchitis. Only ENF was discontinued following which the events resolved; DTG was continued. The investigator considered the AE related to ENF, DTG and cefixime. In my assessment, resolution of events despite continued DTG use and following cessation of ENF indicate these events are related to ENF and not DTG.

Subject 476801 (SAE- suicide attempt) is a 21 year old male with a significant history of past suicide attempt and mental illness (bipolar disorder, ADHD, anxiety, anger-management and depression), who attempted suicide by taking an overdose of acetaminophen (with elective hospitalization) after 342 days of DTG 50 mg QD therapy. The subject called 911 after taking the overdose and was treated with oral charcoal. This subject had transferred from another study site and the reporting Investigator had never seen this subject because he was lost to follow-up after his hospitalization discharge (he did not report for his Week 48 visit). Therefore, the investigator did not believe that he/she could definitively state that the event was not related to study drug. In my assessment, I do not believe that DTG is causally related in this case. This assessment is based on the subject's extensive history of mental illness and prior suicide attempt, along with the fact that the subject was taking DTG for over 1 year prior to the currently reported suicide attempt event.

7.3.3 Dropouts and/or Discontinuations

Treatment Naïve

In the treatment-naïve trials, 70 subjects (70/1641; 4%) discontinued investigational product (IP) due to an adverse event. Generally, the discontinuation rate was low and

did not reveal a DTG-related safety pattern. The highest proportion of discontinuation due to AE was observed in subjects on the efavirenz (EFV) based, Atripla regimen where 42 subjects (42/419; 10%) experienced AEs that led to IP discontinuation. The following table summarizes the SOC categorization for AEs leading to discontinuation for the treatment-naïve trials.

Table 31: Adverse events leading to discontinuation by SOC, treatment-naïve trials

SOC	SPRING – 2		SINGLE		Total DTG N=817
	DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)	
Any AE leading to discontinuation	**9 (2)**	**9 (2)**	**10 (2)**	**42 (10)**	**19 (2)**
Psychiatric disorders	1 (<1)	2(<1)	2 (<1)	15 (4)	3 (<1)
Skin and subcutaneous tissue disorders	1 (<1)	1(<1)	2 (<1)	8 (2)	3 (<1)
Infections and infestations	2(<1)	3 (1)	1 (<1)	2 (<1)	3 (<1)
Immune system disorders	1(<1)	1(<1)	2 (<1)	3 (1)	3 (<1)
Investigations	2(<1)	2 (<1)	0	1 (<1)	2 (<1)
Injury, poisoning and procedural complications	0	1(<1)	2 (<1)	0	2 (<1)
Nervous system disorders	1(<1)	1 (<1)	0	13 (3)	1 (<1)
Gastrointestinal disorders	1 (<1)	2 (<1)	0	8 (2)	1 (<1)
General disorders and administration site conditions	1(<1)	0	0	7 (2)	1 (<1)
Renal and urinary disorders	0	0	1(<1)	1 (<1)	1 (<1)
Cardiac disorders	1 (<1)	0	0	0	1 (<1)
Social circumstances	1 (<1)	0	0	0	1 (<1)
Ear and labyrinth disorders	0	0	0	3 (1)	0
Metabolism and nutrition disorders	0	0	0	2 (<1)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	2 (<1)	0
Musculoskeletal and connective tissue disorders	0	1(<1)	0	1 (<1)	0
Blood and lymphatic system disorders	0	1 (<1)	0	1 (<1)	0
Hepatobiliary disorders	0	1 (<1)	0	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	1 (<1)	0

Source: AE-ISS analysis dataset

In SPRING-2, the discontinuation rate due to AE was low at 2% (9 subjects per arm) in both the DTG and RAL treatment arms. Overall, for DTG, the most frequent AEs leading to discontinuation were due to acute hepatitis C (subjects 4389 and 3950) and increased alanine aminotransferase (subjects 3170 : HBV flare possible IRIS and 4529: drug hypersensitivity), each reported in 2 subjects (additional information regarding these cases is presented in the hepatobiliary AE section and hypersensitivity section, respectively). When clinically similar MedDRA preferred terms (PTs) for rash are pooled, only 1 subject from the DTG arm and no subjects from the RAL arm discontinued due to rash. All other AEs leading to discontinuation occurred in a single patient for both the DTG and RAL treatment arms.

In contrast, in SINGLE, the incidence of AE leading to discontinuation was 10% (N=42) for Atripla but remained low at 2% (N=10) for DTG. The AEs leading to discontinuation for the DTG treatment arm in 2 subjects each were: rash and hypersensitivity/drug hypersensitivity. All other AEs that led to discontinuation were in single subjects and did not reveal an emergent safety issue. Overall, subjects randomized to Atripla discontinued due to AE at a higher rate (10%). The most frequent reasons for discontinuation due to AE for Atripla were related to the labeled psychiatric, nervous system disorders, skin (rash) and gastrointestinal (nausea/vomiting) side effects known to be associated with use of efavirenz.

Treatment Experienced, INI Naïve

In the Sailing trial, a total of 19 subjects (3%) discontinued treatment due to an AE. As shown in Table 32, fewer discontinuations were observed in the DTG arm (2%) compared to the RAL arm (4%). The most frequent reasons for discontinuations in the DTG subjects were a hepatic event (four subjects) or a renal event (two subjects), followed by drug hypersensitivity or myositis in one subject each. Additional information for these cases is presented in section 7.3.5 under Hepatic Analysis, Renal Analysis and Myositis/CK analysis.

Table 32: Adverse events leading to discontinuation, Sailing

Preferred Term	DTG N=354	RAL N=361
Discontinuations due to ≥ 1 AE	**6 (2)**	**13 (4)**
Renal failure acute	2 (<1)	1 (<1)
Hepatotoxicity	1 (<1)	1 (<1)
Drug hypersensitivity	1 (<1)	0
Liver disorder	1 (<1)	0
Myositis	1 (<1)	0
Transaminases increased	1 (<1)	0
Tuberculosis liver	1 (<1)	0
Acute hepatic failure	0	1 (<1)
Adenocarcinoma	0	1 (<1)
Blood alkaline phosphatase increased	0	1 (<1)
Cervix carcinoma	0	1 (<1)
Coagulation factor deficiency	0	1 (<1)
Epistaxis	0	1 (<1)
Extrapulmonary tuberculosis	0	1 (<1)
Gastrooesophageal reflux disease	0	1 (<1)
Helicobacter gastritis	0	1 (<1)
Hepatitis	0	1 (<1)
Immunoblastic lymphoma	0	1 (<1)
Infection	0	1 (<1)
Lactic acidosis	0	1 (<1)
Nausea	0	1 (<1)
Oral mucosal blistering	0	1 (<1)
Pancreatitis	0	1 (<1)
Progressive multifocal leukoencephalopathy	0	1 (<1)
Rash pruritic	0	1 (<1)
Suicidal ideation	0	1 (<1)

Source: AE-ISS analysis dataset

Treatment Experienced, INI Experienced

In subjects treated with DTG 50 mg BID, 3% (6/207) discontinued due to an AE. These subjects and AEs are listed in table 33. Two additional subjects receiving 50 mg QD also discontinued treatment in cohort 1 of Viking. Four of these AEs had fatal outcomes; these are subject IDs 1111, 2463, 1680, and 2310 (see table below for AE for these cases) were presented previously under section 7.3.1. Subject 568 with drug eruption and hyperbilirubinemia with ALT elevation, a nonfatal SAE, was presented in under section 7.3.2. Remaining cases are discussed in the relevant analysis in section 7.3.5.

Table 33: Discontinuations due to adverse events, treatment-experienced, INI-experienced

Subject ID	Dose 50 mg	Event leading to Discontinuation
1203	BID	Rash, Pruritus, Paraesthesia
1242	BID	Cholelithiasis
2310	BID	Anemia, Hypoalbuminaemia, Hypokalaemia
2463	BID	Completed suicide
0041	BID	Blood creatine phosphokinase increased, ALT increased, AST increase
1111	QD	Brain mass
1680	QD	Febrile bone marrow aplasia

Source: AE-ISS analysis dataset

One case of cholelithiasis is summarized (subject 1242) is briefly summarized below and the remaining cases are discussed in the respective sections under section 7.3.5 (Hepatic Analysis, HSR). Subject 1242, a 57-year-old male developed exacerbation of pre-existing cholelithiasis 6 months after initiating DTG, DRV/r, MVC, TDF/FTC. Following cholelithiasis resolution, the subject was expected to re-start ARVs, but was withdrawn from study for meeting criteria for virologic failure.

Overall, the frequency of discontinuations with DTG 50 mg BID (3%) was similar to observations with the 50 mg QD dose in treatment-naïve populations (discontinuation rate 2%) and treatment-experienced population (also 2% discontinuation rate). No obvious similarities were observed in pattern of AEs resulting in discontinuation with QD and BID dosing; although it is notable that similar to QD observations, discontinuations related to liver abnormalities and hypersensitivity/rash were also observed with BID dosing. Unlike the QD findings, some discontinuations with BID dosing were associated with fatal outcomes, which is not entirely unexpected because of relatively advanced HIV disease and other co-morbidities in the INI-experienced population.

7.3.4 Significant Adverse Events

Other Medically Serious Events

Evaluation of reported AEs according to CDER's list of Designated Medical Events (DME) was performed to identify subjects in Phase 3 trials who experienced one of the following: acute pancreatitis, acute respiratory failure, agranulocytosis, anaphylaxis or anaphylactoid reaction, aplastic anemia, blindness, bone marrow depression, deafness, disseminated intravascular coagulation, hemolytic anemia, liver failure, liver necrosis, liver transplant, pancytopenia, renal failure, seizure, Stevens-Johnson syndrome, torsades de pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation.

The majority of AEs qualifying as a DME are discussed as part of safety events of interest in section 7.3.5 Submission Specific Primary Safety Concerns. Few AEs not

covered elsewhere in this review are summarized below. Based on the available information, the primary reviewer agrees the investigators' assessments that the DTG events were not drug-related.

Treatment Naïve

There was 1 subject (ID 6920) from SINGLE randomized to DTG/ABC/3TC who experienced grade 3 angioedema on Day 130 of study drug. The event was attributed to newly initiated lisinopril and not to study drug which was continued without further incident. The angioedema resolved after hospitalization and medical intervention. One additional event of angioedema was observed in the DTG arm from SPRING-2. This subject reported intermittent angioedema of the left eye 233 days after starting DTG/ABC/3TC. The event was reported as grade 2 and was considered to be resolving and not related to study drug. Study drug was continued without interruption. Additionally, there was 1 subject (ID 5924) from the Atripla arm that also experienced angioedema considered not related to study drug. The grade 1 angioedema event occurred 82 days after initiation of Atripla, lasted for 3 days and did not result in discontinuation of Atripla. No RAL subjects reported angioedema.

Loss of hearing, coded as deafness, was reported in on DTG treatment-naïve subject (ID 5590). This subject reported grade 1, mild, bilateral loss of hearing and tinnitus on Day 59 of study. Neither event was considered related to study drug; both events were recorded as not resolved. The subject continued on study drug without dose interruption. The root preferred term 'deafness' was also reported in 2 Atripla subjects and 1 RAL subject in the treatment-naïve phase 3 trials.

Treatment Experienced INI Naïve

Disseminated intravascular coagulation in one subject (ID 2528) in the DTG arm occurred in the context of disseminated histoplasmosis infection and was not considered related to DTG. Deafness was observed in one subject in the RAL arm (ID 2774); deafness and dizziness observed on study day 138 were assessed as secondary to labrynthitis, were considered unrelated to RAL, and did not result in drug discontinuation. Acute pancreatitis AE was observed in one subject in the RAL arm (ID 9972) was diagnosed as gall stone pancreatitis and assessed as unrelated RAL. Additionally, pancreatitis AEs were observed in two subjects each in DTG and RAL treatment arms. Both events in DTG subjects were assessed by investigators as not related to study treatment. In one case, the subject was diagnosed with biliary sludge and DTG treatment was continued without recurrence. The second case was in a subject with history of pancreatitis; again, events resolved with continued use of DTG. Based on the narratives submitted, I agree with the investigators causality assessment. Two pancreatitis events in the RAL arm were confounded by bile duct injury following cholecystectomy in one subject, and use of steroids and trimethoprim/sulfamethoxazole, agents associated with pancreatitis, in the second subject.

Treatment Experience INI Experienced

In subjects dosed DTG 50 mg BID, no seizure events were observed; however, two AEs of convulsion were reported. Both events occurred in the setting of an existing organic brain lesion (such as PML, central nervous system toxoplasmosis) which could have triggered convulsions. Both events were assessed by investigators unrelated to DTG.

7.3.5 Submission Specific Primary Safety Concerns

The following adverse events of interest were reviewed either because of nonclinical toxicity findings or because these were associated with use of other approved INI agents (i.e., events associated with RAL or with use of Stribild, the FDC including EVG):

- Hypersensitivity reactions and rash
- Hepatobiliary analysis (hepatobiliary AEs and hepatic laboratory analysis)
- Gastrointestinal AEs of interest
- Renal analysis (renal AEs and renal laboratory analysis)
- Psychiatric AEs of interest
- Musculoskeletal analysis (select musculoskeletal AEs and serum CK analysis)

Each safety concern is reviewed from the perspective of trial population as well as the DTG dose (QD or twice daily) studied. Review of trial data are followed by an overall summary and the reviewer's labeling recommendation.

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Hypersensitivity Reactions and Rash

Compared to the general population, HIV-1 infected subjects have a higher incidence of drug hypersensitivity and skin rash and these events are associated with many antiretroviral drugs. The Atripla and Isentress labels both include a Warnings and Precautions for rash events, including more severe rash such as erythema multiforme and Stevens-Johnson syndrome.

The ABC/3TC once FDC tablet was used in the phase 3 clinical trials in treatment-naïve subjects either as an investigator selected dual NRTI background therapy in combination with either DTG or RAL in SPRING-2 or in combination with DTG vs. Atripla (EFV/TDF/FTC) in the Single trial. A serious safety risk associated with use of ABC is a well characterized drug-related hypersensitivity reaction (ABC HSR), which is generally manageable by stopping drug and avoiding rechallenge. The genetic version of HLA-B, known as HLA-B*5701 has been highly associated with a high risk of developing ABC HSR. (b) (4) all subjects in the DTG clinical development

program who used ABC in their treatment regimen were required to have screened negative for HLA-B*5701 prior to starting therapy. Compared to skin patch testing, HLA-B*5701 screening has a negative predictive value of 100% and a positive predictive value of 47.9%, as demonstrated in the PREDICT-1 trial. Further, no case of clinically diagnosed abacavir HSR in subjects pre-screened for HLA-B*5701 was immunologically confirmed with skin patch testing.

In the following analyses, evaluation for rash was completed by exploring events that had any of the following preferred terms: rash, exfoliative rash, rash erythematous, rash follicular, rash generalized, rash macular, rash papular, rash maculo-papular, rash pruritic, rash vesicular, drug eruption. Hypersensitivity was evaluated by including any terms with the root preferred term 'hypersensitivity' (e.g. hypersensitivity, drug hypersensitivity). For treatment-experienced analyses, additional AE terms of 'drug eruption', 'angioedema' were included. Lastly, events of suspected ABC hypersensitivity were included in analysis for treatment-naïve trials. All rash or hypersensitivity AEs of interest were reviewed, regardless of the time to onset.

Treatment Naïve

The following table provides the summary of rash AE characteristics for the phase 3 trials. Rash AEs were more frequently reported for Atripla exposed subjects compared to total DTG or RAL treated subjects. In SPRING-2, reporting rates for DTG were comparable to RAL. In the phase 3 treatment-naïve trials, there were no serious or fatal rash related events. The majority of rash events were mild or moderate, were single episodes, and resolved with treatment interruption or discontinuation. No DTG subjects were reported to have a grade 3 or 4 rash AE. Most rash events in DTG subjects were not considered drug related, however, of the subjects reporting rash events (without regard to causality) 25% of DTG events overall and 36% of RAL events were considered to be drug-related. In contrast, 68% of the reported Atripla rash events (all cause) were considered related.

Table 34: Summary of rash adverse events characteristics, Treatment-naïve

	SPRING-2		SINGLE		
	DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)	DTG total N=817 n (%)
Total Subjects with Rash AE*	***23 (6)***	***25 (6)***	***21 (5)***	***73 (17)***	***44 (5)***
Number of Events (all cause)	29	28	23	80	52
Event Characteristics (per subject)					
Drug – related	6 (26)	9 (36)	5 (24)	50 (68)	11 (25)
Serious	0	0	0	0	0
Fatal	0	0	0	0	0
Grade 3/4	0	1 (4)	0	1 (1)	0
Grade 2	3 (13)	6 (24)	4 (19)	29 (40)	7 (16)
Grade 1	20 (87)	18 (72)	17 (81)	43 (59)	37 (84)
Outcome*					
Resolved	20 (87)	20 (83)	17 (81)	63 (86)	37 (84)
Resolving	3 (13)	2 (8)	0	0	3 (7)
Not Resolved	1 (4)	1 (4)	3 (14)	3 (4)	4 (9)
Resolved with Sequelae	1 (4)	1 (4)	1 (5)	7 (10)	2 (5)
Action Taken					
Study Drug Discontinued	1 (4)	1 (4)	2 (10)	6 (8)	3 (7)
Dose Not Changed	22 (96)	24 (96)	19 (90)	65 (89)	41 (93)
Dose Interrupted/Delayed	0	0	0	2 (3)	0
Mean Time to Onset, days	157	162	110	97	135

*per event, some data missing
Source: AE-ISS analysis dataset

A summary of rash and hypersensitivity events reported by preferred term for the phase 3 treatment naïve trials is presented in the following table. Overall for DTG, 5% of subjects reported a rash/hypersensitivity AE compared to 6% of RAL subjects and 17% of Atripla subjects.

Table 35: Summary of Rash and Hypersensitivity Adverse Events, Treatment Naive

	SPRING-2		SINGLE		
Preferred Term	**DTG 50 mg QD + 2NRTI N=403 n (%)**	**RAL 400 mg BID + 2 NRTI N=405 n (%)**	**DTG 50 mg + ABC/3TC QD N=414 n (%)**	**Atripla QD N=419 n (%)**	**DTG total N=817 n (%)**
Total Subjects with Rash/Hypersensitivity AE	***23 (6)***	***25 (6)***	***21 (5)***	***73 (17)***	***44 (5)***
Rash	18 (5)	16 (4)	14 (3)	58 (14)	32 (4)
Rash pruritic	1 (<1)	1 (<1)	3 (1)	1 (<1)	4 (1)
Rash papular	2 (<1)	1 (<1)	2 (<1)	0	4 (1)
Rash maculo-papular	1 (<1)	0	2 (<1)	5 (1)	3 (<1)
Rash macular	1 (<1)	2 (<1)	1 (<1)	1 (<1)	2 (<1)
Rash erythematous	1 (<1)	0	0	0	1 (<1)
Hypersensitivity	0	2 (<1)	3 (1)	3 (1)	3 (<1)
Drug eruption	0	1 (<1)	0	3 (1)	0
Drug hypersensitivity	5 (1)	0	1 (<1)	2 (<1)	6 (1)
Rash generalized	0	0	0	8 (2)	0
Genital rash	0	1 (<1)	0	0	0
Rash pustular	0	2 (<1)	0	0	0
Toxic skin eruption	0	1 (<1)	0	0	0

*per event, some data missing
Source: AE-ISS analysis dataset

Further evaluation of hypersensitivity reaction was completed by characterizing and exploring the reported events. The summary of characteristics for the HSR events in provided in the following table. Overall, few HSR events were reported for DTG and rates were comparable with RAL and Atripla. In total, 9 subjects (1%) receiving DTG reported an HSR event. All the subjects reporting HSR events in DTG and RAL were on ABC/3TC as part of their treatment regimen.

Table 36: Summary of Hypersensitivity Adverse Events, Treatment naive

	SPRING-2		SINGLE		
	DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)	DTG total N=817 n (%)
Total Subjects with Hypersensitivity AE*	***5 (1)***	***2 (<1)***	***4 (1)***	***5 (1)***	***9 (1)***
Number of Events	5	2	4	5	9
Preferred Term					
Hypersensitivity	0	2 (<1)	3 (1)	3 (1)	3 (<1)
Drug Hypersensitivity	5 (1)	0	1 (<1)	2 (<1)	6 (1)
Event Characteristics(per subject)					
Drug – related	2 (40)	2 (100)	2 (50)	3 (60)	4 (44)
Serious	3 (60)	1 (50)	1 (25)	2 (40)	4 (44)
Fatal	0	0	0	0	0
Grade 3/4	1 (20)	0	1 (25)	4 (80)	2 (22)
Grade 2	3 (60)	2 (100)	1 (25)	0	4 (44)
Grade 1	1 (20)	0	2 (50)	1 (20)	3 (33)
Outcome					
Resolved	4 (80)	2 (100)	3 (75)	3 (60)	7 (78)
Not Resolved	0	0	1 (25)	1 (20)	1 (11)
Resolved with Sequelae	1 (20)	0	0	1 (20)	1 (11)
Action Taken					
Study Drug Discontinued	1 (20)	1 (50)	2 (50)	3 (60)	3 (33)
Dose Not Changed	4 (80)	0	2 (50)	2 (40)	6 (67)
Dose Interrupted/Delayed					
Mean Time to Onset, days	42	26	143	67	84

*All DTG and RAL subjects were on ABC/3TC background
Source: Adverse Event dataset ISS

According to study protocol, all events of clinically suspected ABC HSR had to be reported as SAEs, even if the associated signs and symptoms did not meet ICH E2A criteria for seriousness. Of the 7 HSR events reported as SAEs, none resulted in a fatal outcome. The 5 SAE cases of HSR from SPRING-2 and SINGLE for DTG (n=4) and RAL (n=1) were confounded by the ABC containing background regimen and all were reported as clinically suspected ABC HSR by the investigator (despite negative HLA-B*5701 testing), or were considered to meet case definitions for ABC HSR by the Sponsor (subjects 4383 and 4529). All subjects were HLA-B*5701 negative at study baseline.

In SPRING-2, 4 SAE cases were reported: 3 subjects on DTG/ABC/3TC and 1 subject on RAL/ABC/3TC. In 2 of the 3 DTG cases (subject 3250, 4076), all symptoms resolved after subjects were removed from ABC/3TC and changed to TDF/3TC with continued DTG administration, implicating ABC as the source for the event. The third case is subject 4529, who developed severe symptomatic drug hypersensitivity with associated liver laboratory chemistry abnormalities.

This case is described in more detail in Section 7.3.2 Non Fatal Serious Adverse Events. This subject's event of drug hypersensitivity was considered to be related to DTG and not to ABC by the investigator, but the Sponsor reported ABC as co-suspect with DTG for the event. Based on the subject's negative ABC skin patch testing, my assessment is that this event more likely represents drug hypersensitivity related to DTG use.

One RAL subject (4383) with a history of hepatitis C infection at baseline was reported to have an SAE of grade 2 hypersensitivity and cytolytic hepatitis 8 days after starting RAL/ABC/3TC. The subject simultaneously had reported grade 2 moderate influenza (positive serology) and grade 2 viral cervical lymphadenitis. All study drugs were withdrawn. The subject was hospitalized and received amoxicillin for the painful enlarged lymph nodes. After 2 days on the amoxicillin, the subject developed a pruritic rash on the chest, neck and face. The subject had associated fever and watery stool. After 4 days of hospitalization laboratory results showed the following: ALT 310 U/L (NR 0-45), ALP 137 U/L (NR 53-128), AST 273 U/L (NR 0-35) , bilirubin 21.9 µmol/l (NR 0-20), erythrocyte sedimentation rate (ESR) 6 mm/h and gamma-glutamyltransferase (GGT) 514 U/L (NR 0-55). Liver laboratory chemistries improved over the next 2 weeks (ALT 91 U/L and AST 83 U/L). The rash resolved more rapidly (reportedly 1-2 days). The investigator reported that the hypersensitivity event may have been caused by study drug (RAL) and that ABC/3TC was co-suspect in the adverse event. No reporting regarding the amoxicillin was provided.

Overall in SPRING-2 there were 3 reported non-serious hypersensitivity cases, 2 in DTG and 1 in RAL subjects. Two DTG subjects (4351 and 3943) reported non-serious hypersensitivity. Subject 4351 developed grade 2 hypersensitivity 47 days after starting DTG/ABC/3TC. The event was resolved after 39 days and DTG dosing was not stopped. The investigator attributed the event to DTG despite continued therapy and resolution of the event. Subject 3943 developed grade 1 hypersensitivity 49 days after starting therapy. The event was reported as lasting 1 day and recovered without change in study drugs. The investigator reported the event as not related to study drugs.

One RAL subject (4132) reported non-serious grade 2 hypersensitivity on Day 85 of study. The verbatim term reported was 'systemic allergic reaction'. Study drug was interrupted and the subject was considered recovered after 58 days. The event was considered related to study drug, but the subject continued on study.

Three cases of serious HSR were reported in SINGLE, 1 case in DTG and 2 in Atripla. Subject 6929 received DTG/ABC/3TC and after 2 doses self-stopped study drugs for approximately 1 week because of symptoms of sore and swollen throat. The subject then took another dose of study drugs and symptoms reappeared (swollen and scratchy throat, diarrhea, nausea, fatigue, cough, fever- not quantified). She did not call the study site and informed the site at her Week 2 visit. Due to the symptoms that were consistent with possible ABC HSR, the subject was withdrawn from the study on the same day (case also presented in Section 7.3.2 Nonfatal SAEs)

Two subjects receiving Atripla experienced grade 3 serious hypersensitivity reactions. Subject 5771 developed skin rash, edema, nausea, fever and increased CPK value. The study drugs were stopped and the subject was discontinued from the study. The events resolved after 14 days. The investigator believed that the events were caused by study drug. Subject 6624 developed generalized macular-papular rash, pruritis, fever, chills, nausea, diarrhea, sore eyes, tachycardia and general malaise. Study drug was stopped and the subject was withdrawn from study. The subject was treated with prednisone and resolved after 23 days. The investigator attributed study drug to the hypersensitivity event.

Non-serious HSR events were reported in 3 subjects in both treatment arms. Subject 5080 reported a grade 1 event of 'allergic reaction right index finger' and subject 5572 reported 'allergy symptoms'. Both subjects continued all study medications and the events resolved. Subject 6393 developed grade 3 hypersensitivity 5 days after starting DTG/ABC/3TC. The subject had study drugs stopped and the event resolved in 8 days. The investigator considered the event related to study drug and originally reported the event as serious. However, for unclear reasoning the event status was changed by the investigator to non-serious following investigator unblinding for patient management. Atripla subjects 5083 and 5119, had events reported which were considered allergic reaction to vitamin D supplement and Bactrim, respectively. Both events resolved on continued study drug. Subject 6117 was reported to have a grade 3 'hypersensitivity cutaneous reaction' 9 days after starting study drugs. The study drugs were stopped and the subject recovered after 24 days. The investigator considered the event as related to study drug but did not consider the event as serious.

Summary of HSR/rash in treatment-naive
In summary, for the overall DTG treatment naïve data, the observed cases of HSR were confounded by concomitant ABC use, albeit all subjects screened negative for HLA-B*5701 prior to enrollment. Most cases were managed with withdrawal of the potentially offending drugs without additional medical intervention. Some subjects, with non-serious events, were continued on study drugs, which indicates that another reason is more likely to explain the events than a DTG related hypersensitivity reaction. However, subject 4529 from SPRING-2, who was HLA-B*5701 negative and ABC skin patch test negative, provides convincing evidence that DTG is associated with a risk for

hypersensitivity reaction. Supportive evidence in the treatment naïve population comes from subject 6929, who self-stopped medication and self re-challenged resulting in similar, but more severe hypersensitivity symptoms. Based on these hypersensitivity events we agree with the Applicant that data support DTG product labeling for drug hypersensitivity, characterized by rash, constitutional findings and sometimes organ dysfunction, including liver injury in the Warnings and Precautions section. Additionally, language indicating DTG should not be used in patients who have experienced a previous hypersensitivity reaction to DTG is warranted based on subject 6929 who worsened after re-challenge.

Treatment Experienced INI Naïve

In the Sailing trial, rash or HSR AEs (all grades and regardless of causality) were observed in 7% and 8% subjects in DTG and RAL arms, respectively. As shown in the following table, one subject discontinued treatment in each study arm. No grade 3 or 4 AEs were observed in the DTG arm; and no SAEs were reported in DTG subjects.

Rash of any type was observed in 6% and 7% of subjects in DTG and RAL arms respectively. Rash AEs were either grade 1 or 2 in severity, and did not result in DTG discontinuation. HSR events were observed in 2 subjects; one of these resulted in drug discontinuation. Overall, the median time to onset for DTG events was 28 days; and majority had resolved with continued drug use.

Table 37: Treatment-emergent hypersensitivity reaction and rash events, Sailing

	DTG QD N=354	RAL N=361
Subjects experiencing ≥ 1 AE[a]	24 (7)	29 (8)
SAE	0	1 (<1)
Discontinuations	1 (<1)	1 (<1)
Toxicity		
Grade 1	22 (6)	20 (6)
Grade 2	3 (1)	6 (2)
Grade 3 or 4	0	3 (1)
Time to onset		
Median, days (min, max)	28 (1-309)	42 (2-250)
Duration		
Median, days (min, max)	23 (2-134)	34 (1-227)
Outcome		
Resolved/resolving	22 (6)	24 (7)
Not resolved	6 (2)	5 (1)
Preferred AE Term		
Rash[a]	21 (6)	24 (7)
Drug hypersensitivity	1 (<1)	1 (<1)
Hypersensitivity	1 (<1)	1 (<1)
Angioedema	1 (<1)	0
Swelling face	0	2 (1)
Drug eruption	0	1 (<1)

[a]Note some subjects experienced more than 1 AE listed under Preferred AE Term
[b]Includes preferred AE terms rash, rash pruritic, rash erythematous, rash macular
Source: AE-ISS analysis dataset

Two cases of drug hypersensitivity or HSR observed in the DTG arm were confounded by concurrent use of other suspect medications and both were considered by the investigator as unrelated to DTG. Pertinent details are provided here. Grade 1 hypersensitivity reaction (subject 2622) was observed 10 days after initiating DTG, ETR and DRV/r. The AE resolved after discontinuation of all ARVs. The investigator assessed the AE as related to either ETR or DRV and not related to DTG. In another subject (subject 2697), hypersensitivity was observed 75 days after initiating DTG-containing regimen. The AE lasted for 2 days, resolved with continued ARV exposure including DTG use, and was assessed by the investigator as not related to DTG. An additional AE of angioedema (subject 2573) in the DTG arm resolved with continued DTG use. The event began 177 days after initiating DTG, and was assessed as unrelated to study treatment.

One SAE identified in this analysis was in a subject randomized to the RAL arm. This 47-year-old subject (0387) with history of lupus developed diffuse grade 3 rash and oral

mucosal blisters approximately 24 days after starting RAL, ETR, and DRV/r. All ARVs were discontinued. The subject was hospitalized and the event resolved completely. The investigator attributed the AE as reasonably related to RAL or ETR or DRV. As mentioned previously, HSR and severe skin reactions are labeled events for RAL.

Treatment Experienced, INI Experienced

In subjects dosed DTG 50 mg BID, rash or HSR AEs were observed in 9% of subjects. As displayed in Table 38, the vast majority of the events were either grade 1 or 2 in severity; with only 1 case of grade 3 AE (drug eruption AE). No grade 4 AEs were observed. Two subjects nonfatal SAEs and two drug discontinuations were observed. These cases are further elaborated below.
One AE of drug eruption or hypersensitivity were observed; the remaining AEs in this analysis were rash events. The median time to event onset was 18 days, median duration was 16 days, and majority of AEs were resolved or resolving.

Table 38: Treatment-emergent rash and HSR AEs, treatment-experienced, INI-experienced trials

	Total 50 BID **N=207**	**Viking-3 50 BID** N=183	**Viking-Pilot 50 BID** N=24	**Viking-Pilot 50 QD** N=27
Subjects with ≥ 1 AE	18 (9)	16 (9)	2 (8)	1 (4)
SAE	2 (1)	2 (1)	0	0
Discontinuations	2 (1)	2 (1)	0	0
Toxicity				
Grade 1	14 (7)	13 (7)	1 (4)	0
Grade 2	5 (2)	4 (2)	1 (4)	1 (4)
Grade 3 or 4	1 (<1)	1 (<1)	0	0
Time to onset (days)				
Median (min, max)	18 (2-505)	18 (3-148)	253 (2-505)	421 (421-421)
Duration (days)				
Median (min, max)	16 (2-83)	16 (2-83)	35 (10-59)	NA
Outcome				
Resolved/resolving	17 (8)	15 (8)	2 (8)	0
Not resolved	2 (1)	2 (1)	0	1 (4)
Preferred AE term				
Rash[a]	15 (7)	14 (8)	2 (8)	1 (4)
Hypersensitivity	1 (<1)	1 (<1)	0	0
Drug eruption	1 (<1)	1 (<1)	0	0

[a]Note that some subjects experienced more than 1 AE listed under Preferred AE Term
[b]Includes preferred AE terms rash, rash pruritic, rash erythematous, rash macular

Cases reported as SAE (ID 568 and ID 1219) were summarized in section 7.3.2. These AEs of drug eruption and rash with pruritis were confounded by concurrent use of ETR, an ARV known to cause serious skin reaction. Please refer to the narratives and reviewers assessments in section 7.3.2. An additional AE of rash resulted in drug discontinuation: subject 1203, a 47-year-old female subject was diagnosed with grade 2 rash. The event began 6 days after starting DTG. The AE was assessed by investigator as related to study treatment.

In summary, the frequency of HSR and/or rash AEs with DTG dosed 50 mg BID was generally comparable to findings with the 50 mg QD dose in the treatment-experienced, INI-trial (9% in 50 mg BID cohort vs. 7% in the DTG arm in Sailing trial). Similar to 50 mg QD findings, the majority of these AEs were mild to moderate in severity, and did not result in drug discontinuation. The only severe cases in subjects dosed 50 mg BID included one case presenting with features consistent with HSR, and one hospitalization for grade 2 rash; both cases were confounded by concurrent use of other agents known to cause serious skin reactions. Overall, the HSR and rash safety profile for DTG 50 mg BID appears similar to the profile for 50 mg QD dose.

HSR and rash: Summary and Labeling Recommendations

In summary,

- HSR events were observed infrequently in DTG subjects across phase 3 trials. The majority of cases were confounded by concurrent use of another agent associated with these events including ABC or ETR. However, one case of severe HSR in a subject with no known risk factors (such as genetic allele associated with ABC hypersenstitivity) and not taking other co-suspect medication provides compelling evidence of the risk for developing HSR with DTG. Another case of positive rechallenge with DTG provides additional corroborative supporting evidence.
- Rash events were reported in 5-7% of subjects across the DTG trials. The proportion of subjects (treatment-naïve and treatment-experienced) experiencing rash was similar between DTG and RAL. Numerically fewer subjects developed rash with DTG compared to Atripla. Majority of rash was mild to moderate in severity and did not result in drug discontinuation. No cases of SJS or toxic epidermal necrolysis were observed with DTG use. Cases of severe rash were observed infrequently and occurred in the context of a broader clinical syndrome of HSR.
- The HSR/rash safety profile for 50 mg BID dose appears similar to clinical trials observations with 50 mg dosed once daily.

Based on above findings, and in light of the life-threatening potential of hypersensitivity reactions, the clinical review team agrees with the Applicant's proposal for a

Warning/Precautions statement. Proposed language indicating DTG should not be used in patients who have experienced a previous hypersensitivity reaction to DTG is acceptable. The review team recommends the following revisions to specify the frequency of DTG HSR events in clinical trials (b) (4)

5.1 Hypersensitivity Reactions

(b) (4) (b) (4)

Rash will be displayed in the ADR table recommended by the review team (all-grade, treatment-emergent ADRs observed in at least 3% subjects in either arm in treatment-naïve trials). (b) (4)

Hepatobiliary Analysis

Hepatobiliary analysis was performed to explore for hepatotoxicity as liver toxicity was observed in one nonclinical study of DTG, and because ARV drugs in general are associated with hepatotoxicity.

This analysis includes the following elements:
1) Review of hepatobiliary AEs,
2) Review of hepatic laboratory abnormalities, and
3) Review of select cases of interest – HBV/HCV reactivation or IRIS.

1) Hepatobiliary Adverse Events

Clinical hepatobiliary AEs are presented by the individual trial populations. Briefly, hepatobiliary AEs regardless of causality or grade were observed in 2%, 3%, and 5% of DTG subjects in the three trial populations. In the controlled trials, the frequency of AEs in the DTG arms was similar to the comparator arm, either RAL or Atripla. No treatment-naïve subjects discontinued DTG due to AEs; and discontinuations were observed in

1% or fewer subjects in treatment-experienced trials. The majority of AEs were mild or moderate in severity; and most were assessed by investigators as not related to DTG. SAEs were observed in 1% of DTG subjects receiving the 50 mg QD and 3% subjects receiving 50 mg BID dose; most of the SAEs were assessed as not related to DTG. Of note, the protocol required subjects meeting pre-defined liver stopping criteria to discontinue treatment (refer to section 5.3 Individual Clinical Studies). Some cases which therapy was discontinued for meeting stopping criteria were not captured as an AE; and this aspect should be taken into consideration.

Treatment Naïve

The clinical hepatobiliary AEs were all reported from Spring-2 trial, and no AEs were reported for DTG subjects in Single. The following table summarizes all AEs reported in the phase 3 treatment-naïve ISS dataset. None of the AEs led to treatment discontinuation for DTG or Atripla subjects. One subject in the RAL arm who reported cytolytic hepatitis and hypersensitivity discontinued from treatment. Most of the events were grade 1 and 2 and all were not considered related to DTG exposure. Brief summaries of the events are provided after the table.

Table 39: Summary of Hepatobiliary Adverse Events (All Grades/All Causality), Treatment-Naïve

Preferred Term	SPRING – 2		SINGLE	
	DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)
# *Subjects with Event*	**6 (2)**	**6 (2)**	**0**	**3 (1)**
Autoimmune hepatitis	0	0	0	1 (<1)
Cholecystitis	0	0	0	1 (<1)
Cholelithiasis	0	0	0	1 (<1)
Cytolytic hepatitis	1 (<1)	1 (<1)	0	0
Hepatic cyst	1 (<1)	0	0	0
Hepatic steatosis	2 (<1)	2 (<1)	0	0
Hepatitis toxic	0	2 (<1)	0	0
Hepatomegaly	0	1 (<1)	0	0
Hypertransaminasaemia	0	1 (<1)	0	0
Jaundice	1 (<1)	0	0	0
Portal vein thrombosis	1 (<1)	0	0	0

Source: AE-ISS analysis dataset

One DTG subject (ID 4582) from Spring-2 experienced an SAE of 'abdominal pain' and 'jaundice' (grade 2) that resulted in hospitalization. The subject was co-infected with hepatitis C at Baseline. The event occurred 488 days from initiation of study drugs DTG/TDF/FTC and was considered not resolved. Study drugs were continued. Lab data for this same subject is only reported to Day 422. The event was not considered related to study drug by the investigator. A second SAE in the DTG arm occurred in a 38 year old female subject (ID 3337) who was on oral contraceptive pills. This subject developed grade 3 severe portal vein thrombosis 143 days after starting study therapy with DTG/ABC/3TC. The patient went to the emergency room with abdominal pain and was admitted. A diagnostic laparoscopy ruled out an internal hernia, but a CT of the abdomen and chest revealed an occlusive thrombosis in the superior mesenteric vein which extended into the main portal vein. The subject was treated with heparin and coumadin. Study drugs were continued. The investigator did not believe the event was related to study drug, but did believe that the oral contraceptive medication contributed to the thrombosis. For both these SAEs, the reviewer agrees with the investigators assessments of causality based on the provided data and the fact that the subjects remained on DTG therapy.

In the DTG arm from Spring-2, two subjects experienced non-serious Hepatic Steatosis. One subject had a grade 1 event lasting 1 day in duration after 7 days on study medication of DTG/ABC/3TC. The event was reported as resolved with sequelae. The other subject also experienced a grade 1 event which began after 281 days on DTG/TDF/FTC. No duration for this event was reported and the event was considered to be ongoing. Neither of these subjects was infected with Hepatitis B or C. Both of these cases were mild, and were not considered related to DTG by the Investigator. The reviewer agrees with this assessment based on the data provided and the fact that these subjects were on NRTIs which are also associated with hepatic steatosis.

There was 1 reported AE for Cytolytic Hepatitis from Spring-2 in the DTG arm. This event was reported as grade 1 and was not considered related to study drugs. The event began 46 days after starting study and lasted 14 days. This subject's ALT, AST and Alkaline Phosphatase increased from the patient's baseline at Week 4 (not above ULN), but only the Alkaline Phosphatase increased above upper limit of normal to 134 IU/L. This case also was reportedly mild and resolved after 14 days while remaining on DTG and therefore, in my assessment, is unlikely to be causally related to DTG.

Treatment Experienced, INI naïve

In the Sailing trial, hepatobiliary AEs were observed in 3% of subjects in each treatment arm, DTG or RAL (Table 40). Three SAEs were reported in the DTG arm; of these only one SAE was assessed as drug-related: this was SAE of hepatotoxicity in subject 9098, summarized in section 7.3.2. A similar proportion of DTG and RAL subjects (1%) discontinued treatment. The two DTG discontinuations were due to AEs of

hepatotoxicity (case ID 9098 just mentioned, and summarized in section 7.3.2) and liver disorder (ID 283 discussed in the next subsection).

Grade 3 or 4 AEs in the DTG arm were liver disorder (ID 283), cytolytic hepatitis (ID 2030), hepatotoxicity (ID 9098), and hepatitis (ID 2640). Of these cases, subject ID 9098 is discussed in section 7.3.2 and the other cases are discussed later in this analysis. Subject 2030 with grade 4 cytolytic hepatitis AE had a single grade 2 ALT elevation observed at week 24 which returned to normal with continued DTG treatment; and was assessed as not related to DTG.

Table 40: Treatment-emergent hepatobiliary adverse events, Sailing

	DTG N=354	**RAL N=361**
Subjects experiencing ≥ 1 AE	12 (3)	10 (3)
SAE	3 (1)	3 (1)
Discontinuations	2 (1)	3 (1)
Severity		
Grade 1	6 (2)	6 (2)
Grade 2	1 (<1)	1 (<1)
Grade 3	1 (<1)	1 (<1)
Grade 4	3 (1)	2 (1)
Preferred AE Term		
Jaundice	5 (2)	4 (2)
Hepatitis	1 (<1)	1 (<1)
Hepatotoxicity	1 (<1)	1 (<1)
Cytolytic hepatitis	1 (<1)	0
Hepatocellular injury	1 (<1)	0
Liver disorder	1 (<1)	0
Cholelithiasis	1 (<1)	2 (1)
Bile duct stone	1 (<1)	0
Acute hepatic failure	0	1 (<1)
Biliary colic	0	1 (<1)

Source: AE-ISS analysis dataset

Treatment Experienced, INI Experienced

In the DTG BID group, hepatobiliary AEs were observed in 5% subjects. SAEs were observed in 3% of subjects (Table 41). Only one SAE was assessed as drug-related (ID 568; drug eruption with hyperbilirubinemia) discussed in section 7.3.2. Other SAEs were assessed as unrelated to DTG therapy; these include hepatic cirrhosis, cholelithiasis, acute cholecystitis, acute hepatitis, and hepatic fibrosis in one subject each. No discontinuations due to AE were observed.

Table 41: Treatment-emergent hepatobiliary AEs in INI-experienced trials

	Total 50 BID N=207	Viking-3 50 BID N=183	Viking-Pilot 50 BID N=24	Viking-Pilot 50 QD N=27
Subjects with ≥ 1 AE	10 (5)	9 (5)	1 (4)	3 (11)
SAE	6 (3)	5 (3)	1 (4)	0
Discontinuations	0	0	0	0
Toxicity				
Grade 4	2 (1)	1 (<1)	1 (4)	0
Grade 3	6 (3)	5 (3)	1 (4)	0
Grade 2	1 (<1)	1 (<1)	0	2 (7)
Grade 1	3 (2)	2 (1)	1 (4)	1 (4)
AE term				
Hepatomegaly	2 (1)	2 (1)	0	1 (4)
Hyperbilirubinemia	2 (1)	1 (<1)	1 (4)	0
Hepatic steatosis	1 (<1)	1 (<1)	0	1 (4)
Cholecystitis acute	1 (<1)	1 (<1)	0	0
Cholelithiasis	1 (<1)	1 (<1)	0	0
Hepatic cirrhosis	1 (<1)	1 (<1)	0	0
Hepatic fibrosis	1 (<1)	0	1 (4)	0
Hepatitis acute	1 (<1)	1 (<1)	0	0
Hypertransaminasaemia	1 (<1)	1 (<1)	0	0
Jaundice	1 (<1)	0	1 (4)	0
Portal hypertension	1 (<1)	0	1 (4)	0
Cytolytic hepatitis	0	0	0	1 (4)

Source: AE-ISS analysis dataset

2) Hepatic Laboratory Abnormalities

In addition to evaluating the clinical hepatobiliary adverse events, an exploration of liver-related laboratory abnormalities was performed. The following were reviewed:

A) Frequency of key laboratory parameters in the overall trial,
B) Analysis by HBV/HCV coinfection status, and
C) Analysis for laboratory abnormalities indicating drug induced liver injury.

A) Overall hepatic laboratory analysis
Treatment-emergent graded increases in ALT, AST, and total bilirubin were evaluated for the 3 trial populations. Grade 2-4 ALT increases were observed in approximately 2-4%, 4%, and 10% of DTG subjects across the 3 respective populations. Grade 2-4 AST increases were observed in approximately 2-6%, 4%, and 10% of DTG subjects across

these trial populations. The frequency of graded abnormalities in DTG arms was generally similar to the respective controls in QD dosed trials. A trend towards higher frequency of abnormalities in the treatment-experienced trials (10%) may be explained by greater concurrent use of hepatotoxic drugs (i.e., use of PI, TPV, MVC in treatment-experienced populations compared to treatment-naïve population), more co-morbidity from advanced HIV disease and prior ARV exposure, and a higher proportion of HBV/HCV coinfected subjects.

Treatment Naïve

As shown in Table 45, graded laboratory abnormalities were similar for DTG exposed subjects as compared to the comparator regimens of RAL and Atripla.

Table 42: Summary of Subjects Meeting Laboratory Abnormality Criteria at Any Post-Baseline Visit, Treatment-naïve Studies

	SPRING-2		SINGLE	
	DTG 50 mg QD + 2NRTI N=403 n (%)	**RAL 400 mg BID + 2 NRTI N=405 n (%)**	**DTG 50 mg + ABC/3TC QD N=414 n (%)**	**Atripla QD N=419 n (%)**
ALT				
Grade 2 (≥ 2.5 - < 5xULN)	9 (2)	10 (2)	9 (2)	18 (4)
Grade 3 (≥ 5 - < 10xULN)	5 (1)	5 (1)	0	1 (<1)
Grade 4 (≥ 10xULN)	4 (1)	1 (<1)	1 (<1)	1 (<1)
AST				
Grade 2 (≥ 2.5 - < 5xULN)	12 (3)	13 (3)	7 (2)	14 (3)
Grade 3 (≥ 5 - < 10xULN)	8 (2)	7 (2)	0	6 (1)
Grade 4 (≥ 10xULN)	3 (1)	0	0	2 (<1)
Total Bilirubin				
Grade 3 (2.6-5.0 x ULN)	1 (<1)	1 (0)	0	0
Grade 4 (> 5.0 x ULN)	0	0	0	0

Source: Laboratory ISS dataset

Treatment Experienced, INI Naïve

As shown in Table 43, graded laboratory abnormalities were similar between the DTG and RAL arms.

Table 43: Summary of hepatic laboratory abnormalities in Sailing

Hepatic laboratory parameter	DTG N=354	RAL N=361
ALT		
Grade 2 (2.5-5.0 x ULN)	11 (3)	6 (2)
Grade 3 (5.1-10.0 x ULN)	3 (1)	4 (1)
Grade 4 (>10.0 x ULN)	3 (1)	1 (<1)
AST		
Grade 2 (2.5-5.0 x ULN)	7 (2)	15 (4)
Grade 3 (5.1-10.0 x ULN)	4 (1)	2 (1)
Grade 4 (>10.0 x ULN)	5 (1)	2 (1)
Total Bilirubin		
Grade 3 (2.6-5.0 x ULN)	16 (4)	10 (3)
Grade 4 (> 5.0 x ULN)	3 (1)	1 (<1)

Source: Laboratory ISS dataset

Treatment Experienced, INI Experienced

As shown in the following table, in the 50 mg BID group, grade 2-4 ALT increases were observed in 10% subjects compared to 5% subjects in the DTG arm in Sailing. Grade 2-4 AST increases were observed in 9% BID dosed compared to 4% subjects in the DTG arm in Sailing. A trend towards higher frequency of abnormalities in the treatment-experienced trials may be explained by greater concurrent use of hepatotoxic drugs (i.e., use of PI, TPV, MVC in treatment-experienced populations compared to treatment-naïve population), more co-morbidity from advanced HIV disease and prior ARV exposure, and a higher proportion of HBV/HCV coinfected subjects. However, individual cases of grade 3-4 ALT increases were reviewed to explore for potential drug induced liver injury.

Table 44: Summary of post-baseline hepatic laboratory abnormality

Hepatic laboratory parameter	Total 50 BID	Viking-3 50 BID	Viking-Pilot 50 BID	Viking-Pilot 50 QD
	N=207	N=183	N=24	N=27
ALT				
Grade 4 (>10xULN)	2 (1)	2 (1)	0	0
Grade 3 (5.1-10.0 x ULN)	4 (2)	3 (2)	1 (4)	0
Grade 2 (2.5-5.0 x ULN)	15 (7)	14 (8)	1 (4)	2 (7)
AST				
Grade 4 (>10xULN)	1 (<1)	1 (<1)	0	0
Grade 3 (5.1-10.0 x ULN)	2 (1)	2 (1)	0	0
Grade 2 (2.5-5.0 x ULN)	16 (8)	12 (7)	4 (16)	0
T bilirubin				
Grade 3 (2.6-5.0 x ULN)	4 (2)	2 (1)	2 (8)	0
Grade 4 (> 5.0 x ULN)	2 (1)	1 (<1)	1 (4)	0

Source: Laboratory ISS dataset

b) Analysis by HBV/HCV coinfection

This analysis was performed because HIV patients coinfected with HBV and/or HCV are known to be at higher risk of hepatic abnormalities. Overall in DTG treated subjects, a higher proportion of graded laboratory abnormalities were observed in HBV/HCV coinfected subjects compared to mono-infected subjects across the 3 trial populations. In the QD controlled trials, this finding was also observed for each comparator arm, RAL and Atripla. Importantly, the finding is consistent with observations in the general HIV population receiving ARV agents. Overall, the profile in the BID dose group appeared similar to the QD profile; although it should be noted that BID observations come from a relatively limited number of subjects in the HBV/HCV coinfected subgroup.

Treatment Naïve

A similar number of subjects for the DTG arm with hepatitis B and/or C coinfection (9%) experienced at least 1 event as compared to RAL (10%) and Atripla (7%). As shown in the following table, the proportion of subjects without hepatitis coinfection was the same, 9%, in all treatment groups. Likewise, for both the coinfected and mono-infected subgroups, grades 2-4 laboratory abnormalities experienced by DTG subjects were either similar or less frequent when compared to RAL or Atripla.

Table 45: Summary of Grade 2-4 Treatment Emergent On-Treatment Laboratory Abnormalities by HBV and/or HCV coinfection, Treatment Naïve Data

Laboratory Test	HBV and/or HCV coinfected			No HBV and/or HCV infection		
	Total DTG n (%)	RAL n (%)	Atripla n (%)	Total DTG n (%)	RAL n (%)	Atripla n (%)
Overall Number of Subjects with lab abnormality (any grade)	76 (9)	42 (10)	30 (7)	741 (9)	363 (9)	389 (9)
ALT (IU/L)	10 (13)	8 (19)	6 (20)	12 (2)	6 (2)	12 (3)
AST (IU/L)	9 (12)	5 (12)	6 (20)	14 (2)	12 (3)	15 (4)

Source: Laboratory ISS dataset

Treatment Experienced, INI Naïve

As shown in the following table, grades 2-4 laboratory abnormalities were more frequent in HBV/HCV coinfected subjects compared to mono-infected subjects, in each treatment arm, DTG or RAL. In the HBV/HCV infected subgroup, ALT increases were observed in more DTG subjects compared to RAL.

Table 46: ALT, AST, and Total bilirubin analysis by HBV and/or HCV coinfection, Sailing

	HBV and/or HCV infected		Neither HBV and/or HCV*	
	DTG	RAL	DTG	RAL
	N=48	N=65	N=287	N=269
ALT				
Grade 2 (≥ 2.5 - < 5xULN)	4 (8)	2 (3)	8 (3)	5 (2)
Grade 3 (≥ 5 - < 10xULN)	3 (6)	2 (3)	2 (1)	2 (1)
Grade 4 (≥ 10xULN)	3 (6)	0	0	1 (<1)
AST				
Grade 2 (≥ 2.5 < 5xULN)	3 (6)	11 (17)	4 (1)	3 (1)
Grade 3 (≥ 5 < 10xULN)	3 (6)	0	3 (1)	1 (<1)
Grade 4 (≥ 10xULN)	3 (6)	1 (2)	2 (<1)	2 (<1)

*Excludes subjects with missing or no reported status
Source: Laboratory ISS dataset

Treatment Experienced, INI Experienced

Analysis of graded laboratory abnormalities in DTG 50 mg BID group by baseline HBV/HCV status (table 47) showed a higher frequency in the coinfected group compared to non-coinfected group. In general, the frequencies are similar or lower than findings in DTG arms in Sailing, although the comparisons should be considered in light of relatively small sample size of coinfected subjects in the 50 mg BID group.

Table 47: ALT, AST, T bilirubin analysis by HBV and/or HCV coinfection in DTG 50 mg BID group

	HBV and/or HCV infected	Neither HBV and/or HCV infected
	N=46	N=157
ALT		
Grade 2 (≥ 2.5 < 5xULN)	2 (4)	7 (4)
Grade 3 (≥ 5 < 10xULN)	2 (4)	2 (1)
Grade 4 (≥ 10xULN)	0	2 (1)
AST		
Grade 2 (≥ 2.5 < 5xULN)	4 (9)	9 (6)
Grade 3 (≥ 5 < 10xULN)	0	2 (1)
Grade 4 (≥ 10xULN)	0	1 (1)

*excludes 4 subjects with missing data
Source: Laboratory ISS dataset

C) Analysis for drug induced liver injury

As part of routine safety assessment, two analyses were performed to evaluate drug induced liver injury (DILI). First, subjects experiencing grade 3 ALT elevation (at least 5 x ULN) without significant total bilirubin elevation i.e., total bilirubin < 2 x ULN were reviewed to evaluate DILI. This analysis was performed by the Applicant and narratives provided in the NDA submission were reviewed by the clinical review team. Secondly, the laboratory criteria for identifying Hy's Law (ALT or AST ≥ 3 x ULN and Total Bilirubin ≥ 2 x ULN with ALP < 2 x ULN) was evaluated.

The first analysis for grade 3 ALT elevations without significant total bilirubin elevation revealed that DTG cases were confounded by HBV/HCV coinfection, alcohol abuse or use of known hepatotoxic agents; or occurred in the context of hypersensitivity reaction. Notably, more cases of HBV reactivation/IRIS and HCV IRIS were observed in DTG subjects relative to comparator subjects (7 DTG vs. 1 RAL vs. none Atripla), which were explored further and are discussed in the next subsection.

In the second analysis, 8 DTG and 3 RAL and no Atripla subjects met the laboratory criteria for Hy's Law. All these cases were well-supported by an alternative explanation for the findings, and none fulfilled all criteria for Hy's law; as discussed in detail below.

Treatment Naïve

The only DTG subject that met laboratory criteria for Hy's Law is DTG subject 4529 who had drug hypersensitivity and was previously described. One RAL subject was considered to have hepatitis B flare due to IRIS. One additional RAL subject from

Spring-2 met laboratory criteria when using AST but not ALT. This subject had a grade 2 seizure 60 days after starting study drugs. It was believed that the AST elevation related to a muscle source due to a concomitant increase in CPK (15,266) and that the reason for the seizure related to alcohol withdrawal.

Treatment Experience, INI Naïve

Four subjects met laboratory criteria for Hy's law including 3 subjects in the DTG arm and 1 subject in the RAL arm. None of the cases fulfilled all criteria for Hy's law case because all were confounded either by hepatitis B reactivation after cessation of HBV active agents, or hepatitis C infection, or alcohol abuse.

Of these, case 2166 in the RAL arm was confounded by underlying hepatitis C infection and reported ongoing alcohol abuse with a transaminase elevation pattern suggestive of alcoholic liver disease. Case 9098 in the DTG arm was described previously in section 7.3.2. Briefly, the case was attributed to HBV reactivation and IRIS as laboratory abnormalities occurred following cessation of an HBV active agent, was supported by corresponding marked increase in HBV RNA from baseline and substantial increase in CD4 count from baseline. Two other DTG cases were attributed to HBV reactivation (ID 2640) and acute HCV infection (ID 283) are briefly summarized below.

Subject 2640 (DTG), is a 46-year-old male with previously diagnosed hepatitis B infection and HBV DNA PCR < 116 copies/ml on study day 1. ALT, AST and total bilirubin were within normal range on day 1. The treatment regimen discontinued at the time of study entry included tenofovir and lamivudine. The subject started DTG, DRV/r and ETR. At week 12, ALT was 681 U/L (normal 0-48), AST was 567 U/L (normal 0-42), and total bilirubin was 24 umol/L (normal 0-22). One week later, abdominal pain and choluria was reported. At this time, ALT was 1888 U/L, AST 1574 U/L, and total bilirubin 82 U/L (direct bilirubin 36 U/L). On this day, HBV DNA PCR was > 989,000,000 copies/ml, HBsAg and HBcIgM antibodies were positive. The ARVs were discontinued. About one week later, entecavir, an HBV active agent, was started. Liver biopsy performed at this time showed hepatitis with intense inflammatory component. About 4 months later, ALT was 31 U/L, AST 31 U/L, total bilirubin was 8 umol/L, and HBV DNA 1240 IU/ml. ARVs including DTG were restarted with no recurrence. The investigator reported the event as hepatitis SAE. The IDMC considered the event as hepatitis B flare following discontinuation of tenofovir and lamivudine. Hepatitis B reactivation after cessation of HBV active agent/s is well described. The severity of presentation with ALT/AST values exceeding 1000 U/L during hepatitis B reactivation is also well described. In this case, the timing of onset after cessation of tenofovir/lamivudine, marked rise in HBV DNA, normalization of ALT, AST, bilirubin associated with decline in HBV DNA following institution of entecavir, lack of recurrence with DTG rechallenge and while the subject was on entecavir; taken together support HBV reactivation and not DILI.

Subject 283 (DTG) had no history of either hepatitis B or C infection at baseline, HCV RNA on day 1 was negative, and baseline ALT, AST and total bilirubin were within normal limits. Around week 18, ALT was 470 U/L (normal 0-48), AST was 370 U/L (normal 0-48), and total bilirubin was 86 umol/L (normal 0-22). The ARVs were interrupted. The HCV RNA at this time was 54,300 IU/ml. The investigator reported this as an SAE of liver disorder. The Applicant considered the event as acute hepatitis C infection. Based on the information provided, I agree with the Applicant's assessment of acute hepatitis C infection.

Treatment Experienced, INI Experienced

Four subjects met the laboratory criteria for Hy's law. Again, none of the cases fulfilled all criteria for Hy's law because they were confounded by either HBV reactivation or underlying chronic hepatitis C or hypersensitivity reaction.

One subject 568 diagnosed with severe hypersensitivity reaction associated with liver chemistry abnormalities was described in section 7.3.2. The remaining 3 cases were attributed to HBV reactivation (ID 1201) and chronic HCV infection (ID 1263 and 2203), described below.

Subject 1201 is a 52-year-old male with history of prior exposure to Hepatitis A, B, and C infections. The subject was initially reported as having negative serology for these viral hepatitis infections. Prior ARV regimen included TDF/FTC and DRV/r. At baseline, HIV RNA was 154,899 copies/ml and CD4 count was 80 cells/mm^3. The subject was started on DTG, MVC, ABC/3TC, and T20. On day 153 of starting DTG, the subject developed ALT and AST > 30 x ULN and total bilirubin > 5 x ULN. At this time, HBV DNA was > 110,000,000 IU/mL. The HIV RNA was 156 copies/ml and CD4 count was 360 cells/mm^3. Stored plasma from Day 1 was found to be positive for Hepatitis B surface antibody (IgG) and HBV DNA was < 169 copies/ml, DTG was interrupted; TDF/FTC was restarted along with other supportive therapy. At this time, the hepatitis B surface antigen (HBsAg) was also reactive. Liver chemistries and HBV DNA declined after TDF/FTC was restarted. By month 7, all chemistries had improved and the subject was rechallenged with DTG (with TDF/FTC) with no recurrence. The investigator reported the case as SAE of acute hepatitis assessed as related to DTG. The Applicant assessed the case as reactivation of Hepatitis B following withdrawal of TDF/FTC and not related to DTG. Based on the information provided, this case does not fulfill all criteria for Hy's law case by my assessment. Specifically, marked rise in HBV DNA levels which coincided with peak ALT, AST and bilirubin elevation, and decline in HBV DNA and corresponding improvement in liver chemistries after TDF/FTC was started; all support HBV reactivation as the etiology for observed elevations. Dolutegravir rechallenge in the presence of TDF/FTC did not lead to recurrence further supporting HBV reactivation and not DTG-related DILI.

Subject 1263 is a 48-year-old male with chronic Hepatitis C infection. At baseline, ALT was 322 U/L (normal 0-30), AST was 238 U/L (normal 0-50), and total bilirubin was 21 umol/L (normal 0-22). The subject was started on DTG, DRV/r, D4T, and T20. The total bilirubin was 30 umol/L at week 12 and was 45 umol/L at week 19. During this period, ALT and AST had declined to below baseline values. At week 24, ALT was 162 U/L, AST was 115 U/L and bilirubin had declined to 23 umol/L. This case is confounded by hepatitis C infection and does not fulfill Hy's law criteria. Subject 2203 is a 42-year-old female with chronic hepatitis C infection. The subject was started on DTG 50 mg BID, 3TC, ETR, and DRV/r in Cohort 2 of Viking-pilot. At baseline, ALT was 56 U/L (normal 0-48), AST was 41 U/L (normal 0-42), and total bilirubin was 22 umol/L (normal 0-22). ALT and AST remained elevated above normal range, either below or above the baseline value, through the 96 week treatment period. The subject remained asymptomatic; DTG was continued to 96 weeks. This case is confounded by hepatitis C infection and does not fulfill Hy's law criteria.

3) HBV/HCV reactivation and/or IRIS

As mentioned previously, a routine review for hepatotoxicity was performed including review of AEs and key hepatic laboratory abnormalities. During review of grade 3 ALT increases, more cases of HBV/HCV reactivation/IRIS cases were observed in DTG subjects relative to comparator arms (7 DTG vs. 1 RAL vs. none Atripla).

As background, reactivation of HBV is known to occur in patients who stop HBV treatment. Approved ARVs TDF, 3TC, and FTC are also active against HBV; and discontinuation of these HBV active agents can result in HBV reactivation or flare. HBV reactivation is characterized by associated increase in plasma HBV DNA and increases in transaminases which may be markedly elevated and may be symptomatic. Because HBV reactivation is immune-mediated, some cases may not be associated increases in plasma HBV DNA. With either HBV or HCV, disease flare may occur secondary to immune restoration from potent ARV therapy. This entity of IRIS is well-described in HIV patients harboring subclinical infection which manifests clinically following initiation of ARV therapy. Immune reconstitution inflammatory syndrome has been more commonly reported with OIs such as tuberculosis and cryptococcal infection. In contrast, HBV/HCV IRIS is not well-described in literature; partly because of difficulties in distinguishing IRIS from drug induced toxicity. Further, definitively diagnosing HBV or HCV IRIS in the clinical setting is unlikely to alter patient management, as there are no specific measures/drugs (i.e., steroids) shown to be beneficial for HBV/HCV IRIS.

With respect to the DTG cases, HBV/HCV IRIS or reactivation following cessation of HBV active therapy was a plausible explanation for liver chemistry abnormalities. For the IRIS cases, direct liver toxicity could not be excluded in the absence of convincing evidence such as liver biopsy findings or documented recurrences with use of multiple different ARV regimens excluding DTG. In sum, the cases identified were plausible for viral reactivation or IRIS; however, drug toxicity could not be conclusively excluded

based on available information. Several of the reactivation/IRIS cases occurred in the Sailing trial. Similar increases in mean CD4 count from baseline were observed in the DTG and RAL arms in this trial; therefore, the disproportionate distribution of cases could not be explained by greater immune restoration from DTG treatment relative to RAL treatment.

Treatment Naïve

One DTG subject (3170) was reported to have HBV IRIS (confirmed by hepatology consultation) which led to study withdrawal due to meeting the liver stopping criteria (ALT 28 x ULN, AST 32 x ULN). This 44 year old male had a Baseline HIV-1 RNA of 60,812 c/mL, CD4 cell count of 28 cells/mm^3 and chronic active hepatitis B with HBV DNA of log 7.23 IU/mL. He was previously untreated for hepatitis B. After 4 weeks of DTG/TDF/FTC, his HIV RNA was < 50 c/mL and his CD4 cells increased to 104 cells/mL. At that same visit, his ALT and AST were grade 2. However, his ALT and AST continued to rise (ALT 450 U/L, AST 346 U/L) and study drug was stopped at Week 6. The patient was asymptomatic. By Week 7 his HBV DNA had declined from log 7.23 IU/mL to log 4.09 IU/mL. By Week 9 his ALT peaked at 1220 U/L and AST 1203 U/L. A full work-up for other etiologies for the hepatitis was negative. The subject was HBeAg positive. The subject was not re-challenged but withdrawn from the study due to the complexity of treating his active hepatitis in the context of a randomized clinical trial.

One RAL subject (4052) also was considered to have HBV IRIS as the reason for liver laboratory abnormalities. This subject had a baseline HIV RNA of 9118 c/ml and CD4 cell count 454 cells/mm^3 and by Week 4 his viral load was fully suppressed and his CD4+ cell count was 638 cells/mm^3. By Week 8, his ALT was approximately 10xULN (ALT 465; AST 176; ALP 125) with a normal bilirubin; however, due to a central lab error, the result was not flagged to the site or medical monitors. By Week 12 the ALT had fallen to 122 U/L while the subject had continued study drugs. No HBV DNA levels were reported. The laboratory abnormalities were attributed to HBV IRIS by the investigator and Sponsor. Review of the 2 narratives and data supports the possibility of HBV IRIS for these cases, and while the possibility of drug-induced liver injury is not excluded, the cases are confounded by the underlying hepatitis coinfection and the possibility of IRIS. Therefore, these cases are not compelling evidence of a direct toxicity of DTG on the liver.

Treatment Experienced, INI Naïve

In the Sailing trial, two HBV reactivation cases were described previously in the subsection for evaluation of DILI (ID 2640) and section 7.3.2 (ID 9098). Additional cases not summarized previously are presented below:

Subject 2467 is a 41-year-old male with Hepatitis C infection, and HCV RNA 3,670,000 million IU/ml at baseline. The subject was started on DTG, ATV/r, and 3TC. At baseline, ALT, AST and total bilirubin were normal. At week 8, ALT was 482 U/L (normal 0-42), AST 321 U/L (normal 0-22) and total bilirubin was 29 umol/L (normal 0-6). One week later, ARVs were discontinued. The next day, ALT was 438 U/L, AST was 259 U/L, total bilirubin was 39 umol/L, and HCV VL was 12,100,000 IU/ml. Other concomitant medications include valproic acid, aminophylline and ambroxol. Three weeks later, ALT and AST had improved to grade 1. At baseline, this subject's HIV RNA was 5.57 $\log_{10}$ copies/ml and CD4 count was 79 cells/mm^3. At week 8, the HIV RNA was 2.82 $\log_{10}$ and CD4 count was 190 cells/mm^3. The Applicant considered this a case of HCV IRIS, although participation of DTG could not be ruled out. By my assessment, this is a plausible case of HCV IRIS because of substantial increase in CD4 count and decline in HIV RNA at the time of transaminase elevation. The increase in HCV RNA from baseline suggests an active disease process, although there is no known clear-cut association between HCV DNA and IRIS development. As such the entity of HCV IRIS is not well characterized based on peer-reviewed literature search as well as other sources such as ACTG definitions for IRIS (refer to section 9.1). In comparison, IRIS is well described for other conditions such as tuberculosis or cryptococcus, and in these situations, diagnosis of IRIS carries clinical significance as it alters patient management (for example, initiating steroids). In the above-mentioned resources, there is agreement that distinguishing IRIS from hepatotoxicity is difficult. In conclusion, this is a plausible case of HCV IRIS and drug toxicity cannot be excluded.

Subject 942 is a 53-year-old male with Hepatitis B infection. At baseline, HBV DNA was 6 million copies/mL, ALT was 78 U/L (normal 0-48), AST was 110 U/L (normal 0-42), and total bilirubin was 14 umol/L (normal 0-22). The treatment regimen discontinued at the time of study entry included tenofovir and emtricitabine. On day 1, the subject was started on DTG and tenofovir. At week 8, ALT was 476 U/L, AST was 633 U/L, and total bilirubin was 30 umol/L. The subject reported drinking 3 light beers in the preceding 2 days. All ARVs were discontinued. One week later, entecavir was started. Entecavir was interrupted temporarily for one week due to fever and suspected reaction to entecavir, but restarted. HBV DNA 94,000 copies/ml after starting entecavir was reported. About 6 weeks later, ALT was normal. At baseline, the subject's HIV RNA was 373,024 copies/ml and CD4 count was 75 cells/mm^3. By week 4, the HIV RNA was 482 copies/ml and CD4 count was 189 cells/mm^3. The investigator assessed the event as drug-related 'transaminase elevated'. The Applicant considered this a case of HBV IRIS and HBV flare after withdrawal of emtricitabine, and alcoholic hepatitis. The IDMC considered the case of HBV IRIS with HBV flare after emtricitabine discontinuation. By my assessment, this is a plausible case of HBV reactivation because two-drug HBV therapy was changed to monotherapy when DTG-containing regimen was started. Additionally, HBV response to entecavir, measured as decline in HBV DNA corresponding to enzyme/bilirubin resolution, supports HBV reactivation. HBV IRIS is plausible based on substantial increase in CD4 count (by 114 cells/mm^3 from baseline of 75 cells/mm^3), and decrease in HIV RNA over a relatively short duration of 4 weeks

which taken together provides for a more convincing case for IRIS; although by no means are these definitive for IRIS. Further, information supportive of drug induced liver injury such as positive rechallenge or no recurrence when challenged with same ARVs except DTG is not available to form conclusions for DTG liver injury.

Subject 9040 is a 31-year-old male with HBV infection. At baseline, ALT was 52 U/L (normal 0-35), AST 66 U/L (normal 0-35), and total bilirubin was 9 umol/L (normal 0-22). Treatment was initiated with DTG and LPV/r. At week 32, ALT was 92 U/L, AST 97 U/L, total bilirubin was normal, and HBV DNA was > 9 million copies/ml. At week 40, ALT was 319 U/L, AST was 313 U/L, and total bilirubin 29 umol/L. ARVs were interrupted. About five weeks later, ALT was 35 U/L and AST was 42 U/L. The same ARV regimen plus TDF/FTC was started. At week 60 visit (or 12 weeks after starting DTG, LPV/r, and TDF/FTC), the ALT was increased to 241 U/L, AST 170 U/L and total bilirubin was normal. At a follow-up visit, ALT had decreased to 81 U/L and AST was 71 U/L while on ARVs. The investigator assessed the initial event as 'acute hepatitis B flare' AE term (MedRA preferred AE 'hepatitis B') and transient elevations at week 60 were likely due to alcohol intake. The Applicant considered the case of hepatitis B flare in the absence of treatment.

Treatment Experienced, INI Experienced

Only one HBV/HCV reactivation or IRIS case was observed in subjects receiving 50 mg BID dose; this subject ID 1201 in Viking-3 was summarized previously in the subsection for DILI.

Hepatic Analysis: Summary and Labeling Recommendations

In summary,

- The hepatic AE profile of DTG 50 mg QD was generally similar to comparator drugs, RAL and Atripla. The hepatic AE profile of DTG 50 mg BID was generally comparable to the QD dose profile observed in the Sailing trial.
- Treatment-emergent grades 2-4 ALT or AST increases were observed in approximately 2-4% of DTG subjects receiving DTG 50 mg QD dose. This frequency of graded abnormalities in DTG arms was generally similar to the respective controls. A trend towards higher frequency of graded ALT/AST abnormalities in the treatment-experienced trials (10%) may be explained by greater concurrent use of hepatotoxic drugs (i.e., use of PI, TPV, MVC in treatment-experienced populations compared to treatment-naïve population), more co-morbidity from advanced HIV disease and prior ARV exposure, and a higher proportion of HBV/HCV coinfected subjects.
- Graded ALT or AST increases with DTG were more frequently observed in HBV/HCV coinfected subgroup compared to non-coinfected subgroups; a finding consistent with each comparator drug and also consistent with observations in the general HIV population treated with antiretroviral agents.

- Cases of grade 3 ALT increases were confounded by HBV/HCV, or with evidence of pre-existing liver disease, or confounded by concurrent use of known hepatotoxic medications. No definitive case of hepatoxicity was identified.
- More cases of HBV/HCV reactivation or IRIS cases were observed in DTG treated subjects compared to controls (7 DTG vs. 1 RAL vs. none Atripla). Although viral reactivation and/or IRIS were plausible diagnoses, hepatotoxicity could not be conclusively excluded in these cases. Based on severity of liver chemistry elevations, a Warning for liver biochemistry elevations and recommendation for monitoring of liver enzymes for hepatotoxicity is warranted HBV/HCV coinfected patients.
- Of note, the Applicant's has proposed (b) (4) . The review team disagrees with the Applicant's proposed (b) (4)
- The following alternative language is recommended under a separate heading in Warnings/Precautions:

Effects on serum liver biochemistries
Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY. In some cases the elevations in transaminases were suggestive of immune reconstitution syndrome or HBV reactivation particularly in the setting where anti-hepatitis therapy was withdrawn.

Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY is recommended in patients with underlying hepatic disease such as hepatitis B or C.

The Applicant's proposal to include 'hepatitis' under Less Common ADRs is acceptable. The proposal to describe trial findings in HBV/HCV coinfected subjects (b) (4) is acceptable pending some revision.

Gastrointestinal Adverse Events of Interest

Gastrointestinal mucosal inflammation and hemorrhage was observed in nonclinical studies, across different animal species. Gastrointestinal adverse events in phase 2b/3 clinical trials which were suggestive of local GI intolerance or gastric mucosal damage were reviewed. This section provides FDA review of 1) AEs representing GI intolerance, 2) AEs representing gastric ulceration or inflammation, and 3) analysis of hemoglobin changes from baseline exploring potential subclinical GI bleeding.

1) Gastrointestinal Intolerance

Evaluation of GI intolerance while on-treatment was completed by exploring the preferred AE terms of diarrhea, nausea, vomiting and abdominal pain.

Treatment Naïve

Overall in the treatment-naïve studies, diarrhea and nausea (all grades and regardless of causality) were the most commonly reported GI AEs that may be associated with gastrointestinal intolerance. The reporting rates were similar across the phase 3 treatment-naïve studies (Table 48). Most subjects experienced a single episode of GI intolerance and most frequently, this occurred in the first 2 weeks of starting ART. Generally for SPRING-2, the majority of events were mild to moderate in severity and resolved without treatment interruption or discontinuation. In SINGLE, more subjects in the Atripla arm had temporary treatment interruption (n=1) or discontinuation (n=5) compared to DTG (N=1 for dose interruption only). Additionally, 2 episodes of GI events were reported as nonfatal SAEs both from SPRING-2 (1 subject each from DTG and RAL- arms; abdominal pain and diarrhea, respectively).

Table 48: Treatment-emergent events of gastrointestinal intolerance, treatment-naive

	SPRING-2		SINGLE		
Preferred Term	**DTG 50 mg QD + 2NRTI N=403 n (%)**	**RAL 400 mg BID + 2 NRTI N=405 n (%)**	**DTG 50 mg + ABC/3TC QD N=414 n (%)**	**Atripla QD N=419 n (%)**	**DTG total N=817 n (%)**
Total Subjects with GI Intolerance Event	***342 (85)***	***345 (85)***	***369 (89)***	***387 (92)***	***711 (87)***
Abdominal Pain	16 (4)	12 (3)	12 (3)	13 (3)	28 (3)
Diarrhea	49 (12)	51 (13)	72 (17)	75 (18)	121 (15)
Nausea	60 (15)	54 (13)	59 (14)	57 (14)	119 (15)
Vomiting	16 (4)	18 (4)	20 (5)	19 (5)	36 (4)

Source: AE-ISS analysis dataset

Treatment experienced, INI Naïve

As shown in Table 49, AEs representing GI intolerance (all grades and regardless of causality) were observed in 27% and 23% subjects in the DTG and RAL arm respectively. In the DTG arm, the vast majority of AEs were grade 1 or 2 in severity. No grade 4 AEs, SAEs, nor discontinuations were observed in the DTG arm. Grade 3 AEs include one case of vomiting, and two cases of diarrhea. Diarrhea, the most frequent AE, was observed in 20% and 17% subjects in the two treatment arms. The majority of episodes were single episodes, with median time to onset 26 days, and median duration

5 days. Importantly, there were no drug discontinuations or hospitalizations due to diarrhea in the DTG arm.

Table 49: Treatment-emergent Events of Gastrointestinal Intolerance, Sailing

	DTG N=354	RAL N=361
Subjects experiencing ≥ 1 AE	97 (27)	84 (23)
Diarrhea	72 (20)	62 (17)
Nausea	26 (7)	28 (8)
Vomiting	17 (5)	20 (6)
Abdominal pain	12 (3)	6 (2)

Source: AE-ISS analysis dataset

Treatment Experienced, INI Experienced

In subjects dosed DTG 50 mg BID, GI intolerance AEs (all grades and regardless of causality) were observed in 23% of subjects (Table 50). The majority of the AEs were grade 1 or 2; with only a single grade 3 AE of diarrhea. No grade 4 AEs were observed, and no discontinuations were reported in these BID dosed subjects. One nonfatal SAE of grade 2 diarrhea was reported in one subject (2432); the event was assessed as unrelated to DTG, and resolved with continued treatment. Diarrhea was the most frequent AE observed in 16% subjects receiving the 50 mg BID dose. The majority of diarrhea AEs had resolved with continued DTG treatment. The median time to onset of diarrhea AEs was 46 days, and the median duration was 9.5 days.

Table 50: Treatment-emergent GI intolerance AEs, treatment-experienced, INI-experienced trials

	Total 50 BID N=207	Viking-3 50 BID N=183	Viking-Pilot 50 BID N=24	Viking-Pilot 50 QD N=27
Subjects with ≥ 1 AE	48 (23)	38 (21)	10 (42)	9 (33)
Diarrhea	34 (16)	25 (14)	9 (38)	5 (19)
Nausea	19 (9)	17 (9)	2 (8)	2 (7)
Vomiting	9 (4)	7 (4)	2 (8)	1 (4)
Abdominal pain	7 (3)	3 (2)	0 (13)	3 (7)

Source: AE-ISS analysis dataset

Summary of GI intolerance AEs with 50 mg QD dosing
Overall, the vast majority of GI intolerance AEs observed with 50 mg QD dose of DTG were of mild or moderate in severity. Diarrhea was among the most frequently observed AEs in this analysis. In each treatment-naïve trial and the Sailing trial, the frequency of diarrhea events was comparable to the respective control, either RAL or Atripla. Majority of the AEs were single episodes which resolved with continued drug use, were not reported as SAEs, and were assessed by investigators as unrelated to DTG. In general,

the median time to onset of events ranged from 14 days to 26 days after DTG - containing regimen was started.

Summary of GI intolerance AEs with 50 mg BID dosing
An increase in GI intolerance AEs was not observed with the 50 mg BID dose compared to observations in treatment-experienced, INI-naive subjects receiving 50 mg QD of DTG (23% frequency in total 50 BID group vs. 27% frequency in DTG arm of Sailing). Similar to 50 mg QD observations, diarrhea was the most frequent AE with the BID dose. Again, diarrhea events were self-limited, did not result in drug discontinuation, and were assessed as unrelated to DTG.

2) Gastric Ulcer-related Events

Gastric ulcer AEs were evaluated by searching for the following preferred AE terms, gastritis, nausea, vomiting, upper abdominal pain, epigastric pain, dyspepsia, gastric hemorrhage, hematemesis, duodenitis, gastric mucosal lesion, hearburn, gastroesophageal reflux disease.

Treatment Naïve

Event preferred terms considered potentially clinically related to GI ulceration or bleeding were infrequently reported in the treatment-naïve subjects. Only 1 event of gastric ulcer in a DTG subject with a history of gastritis at baseline was reported in the phase 3 treatment-naïve studies. Additionally, a single case of duodenal ulcer was reported in a DTG subject enrolled in the phase 2 study Spring-1. The duodenal ulcer was associated with a grade 4 Burkitt's-like Non-Hodgkin lymphoma of the GI tract, and assessed by the clinical reviewer as unlikely to be caused by DTG. No cases of gastric/duodenal ulcer were observed in the controls arms in phase 2b or 3 trials. Evaluation for other AEs suggestive of GI mucosal erosion or breakdown was performed. Events of 'gastritis erosive' and 'erosive duodenitis' were observed in one subject each in the RAL arm in treatment-naïve trials. These events were not observed in either DTG or Atripla subjects.

Treatment Experienced, INI Naïve

No gastric, duodenal or peptic ulcer AEs were observed, with either DTG or RAL, in the Sailing trial. No hematemesis event was observed either. One AE of melena and another AE of gastric mucosal erosion observed in the DTG arm, were attributed to hemorrhoids and assessed as not drug-related. The AE of gastric mucosal lesion occurred in subjects with history of portal hypertension, and was attributed to portal hypertensive gastropathy.

Treatment Experienced, INI Experienced
In subjects dosed 50 mg BID, one gastric ulcer and one erosive gastritis AE was observed. Both AEs were assessed by the investigator as unrelated to DTG, and did not result in drug discontinuation. The gastric ulcer AE was confounded by concurrent aspirin use; the erosive gastritis AE was attributed to *Helicobacter pylori* infection. An additional AE of rectal hemorrhage reported as an SAE was attributed to angiodysplastic lesion in a subject with pre-existing diagnosis of colon angiodysplasia.

Other trials

One case of hematemesis observed in the clinical development program is summarized here: the hematemesis SAE was observed in a subject ID 476019 in the treatment-naïve trial 114915. The AE was observed 53 days after initiating regimen containing DTG 50 mg QD. The subject was taking non-steroidal anti-inflammatory drugs (NSAIDs) concurrently; the AE was considered not related to treatment and did not recur with continued DTG use.

Summary of gastric ulcer and related AEs
Overall, two AEs of gastric or duodenal ulcer were observed in subjects dosed DTG 50 mg QD compared to none in the control arms. Both events were confounded by ongoing GI pathology such as pre-existing gastritis in one case and GI malignancy in the second case. In subjects dosed DTG 50 mg BID, only one gastric ulcer AE was observed which was confounded by concurrent aspirin use. Other AEs suggestive of GI mucosal erosion or breakdown, in subjects dosed DTG either QD or BID, were attributed to medical conditions including pre-existing colon angiodysplasia, hemorrhoids, portal hypertension; and none were assessed as related to DTG.

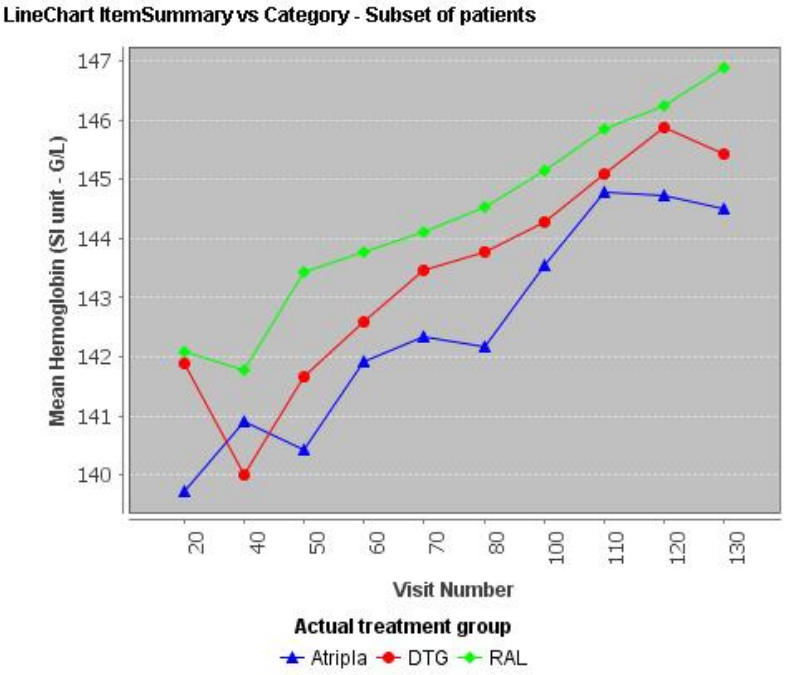
3) Subclinical GI Bleed

An analysis of mean change from baseline for hemoglobin during the treatment period in phase 3 trials was completed to assess subclinical GI bleed.

Treatment Naïve

The following graph shows the pooled treatment-naïve population as DTG to comparator to determine if there was a difference for DTG treated subjects. As shown below, all the treatment groups showed a small improvement in their mean change from baseline for hemoglobin over the 48-Week treatment period (DTG +3.5 g/L, RAL +4.8 g/L and Atripla +4.8 g/L), likely reflecting the positive overall effects of ART therapy.

Figure 3: Mean change in hemoglobin from baseline, treatment-naïve

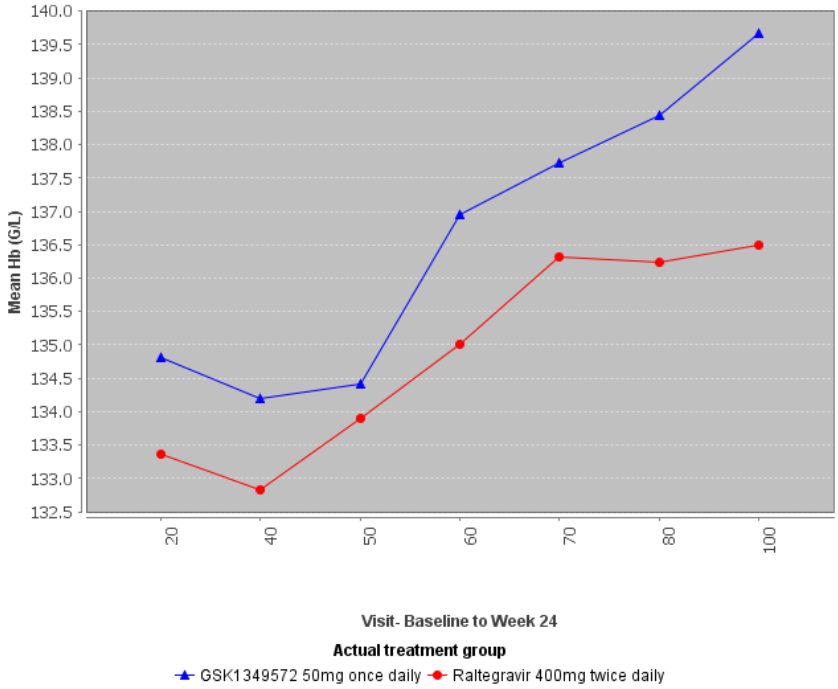


Source: lab-ISS analysis dataset

Treatment experienced, INI-naïve and Treatment experienced, INI experienced

Similar to above findings in treatment naïve trials, mean hemoglobin increased over 24 weeks in both DTG and RAL treatment arms in the Sailing trial (see figure 4). The mean increase in hemoglobin at Week 24 was 4.6 mg/dL in the DTG arm and 3.1 mg/dL in the RAL arm. In subjects receiving 50 mg BID in the INI-experienced trial Viking-3, similar findings were observed with mean a mean increase of 2.9 mg/dL from baseline observed at week 24.

Figure 4: Mean change in hemoglobin from baseline to Week 24, Sailing



Source: lab-ISS analysis dataset

Gastrointestinal Adverse Events Analysis: Summary and Labeling Recommendations

In summary,

- In subjects dosed with DTG 50 mg QD, AEs representing GI intolerance (diarrhea, nausea, vomiting, and abdominal pain) were observed in 85% of DTG subjects in treatment-naïve trials and 27% subjects in the treatment-experienced, INI-naïve Sailing trial. These differences in frequencies in the two trial populations may be explained by duration of follow up, 24 weeks for Sailing trial and 48 weeks for the treatment naïve trials. Importantly, the frequency of GI intolerance AEs in DTG arms in individual trials was comparable to the respective controls, either RAL or Atripla.
- The majority of AEs were mild to moderate in severity, and did not result in drug discontinuation.
- Diarrhea was among the most frequent AEs in this category. The majority of diarrhea events resolved with continued DTG use, were not reported as SAEs, and were assessed by the investigators as unrelated to the study drug.

- Three AEs of gastric or duodenal ulcer were observed in DTG treated subjects; none were observed in the control arms. All 3 events were confounded by pre-existing gastric pathology (gastritis or GI malignancy) or concurrent use of aspirin. Other AEs possibly representing a GI ulcerative process were observed infrequently, and these were attributed to medical conditions including pre-existing colon angiodysplasia, hemorrhoids, portal hypertension; and none were assessed as related to DTG or resulted in drug discontinuation.
- Additionally, improvements in mean hemoglobin from baseline over the 24 or 48 week trial period were observed in the DTG arms in each trial, a finding suggesting low likelihood of subclinical GI bleeding with DTG.
- Lastly, the GI safety profile of the BID dose was comparable to 50 mg once daily. An increase in GI intolerance AEs was not observed with the 50 mg BID dose compared to observations in treatment-experienced, INI-naive subjects receiving 50 mg QD of DTG. The pattern of GI intolerance AEs was also similar to 50 mg QD, with diarrhea being the most frequently observed event. Similar to the GI safety profile for the QD dose, events were mostly mild to moderate in severity, did not result in drug discontinuation, and were assessed by investigators as unrelated to DTG. Cases suggestive of GI ulceration or hemorrhage occurred in the setting of NSAID use or another predisposing medical condition.

Drug-related, all-grade nausea and diarrhea were observed in at least 3% subjects in the treatment-naïve trials, and should be displayed in the label section 6 as part of the treatment-emergent ADR table. Events of abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting are proposed by the Applicant under Less Common Adverse Reactions, which is appropriate. No additional labeling is warranted based on this review.

Renal Analysis

In the treatment-naïve phase 2b trial Spring-1, grade 1 serum creatinine elevations were observed more frequently in the DTG arm relative to EFV arm. This finding prompted further evaluation and resulted in identification of DTG effects on renal tubular transporter OCT2. By blocking OCT2, DTG affects creatinine secretion leading to elevation in serum creatinine and corresponding decline in the measured creatinine clearance. Although decline in creatinine clearance were observed, DTG did not affect GFR and renal plasma flow in a renal function trial using alternative and specific measures such as iohexol and PAH (details in section 7.4.5). Small changes in serum creatinine and creatinine clearance attributed to OCT2 inhibition are expected to be non-pathological.

The following renal analyses were performed to characterize creatinine changes and evaluate for renal toxicity in phase 3 clinical trials: 1) renal AE analysis, 2) change from

baseline in serum creatinine and creatinine clearance, and graded creatinine toxicity, and 3) proteinuria analysis.

1) Renal Adverse Events

Analysis for renal AEs was completed by evaluating all AEs, excluding infections, listed under Renal System Organ Class for phase 3 subjects. Events of renal failure (RF) or suggestive of new-onset compromise in renal function (e.g., renal insufficiency) were carefully reviewed to explore potential nephrotoxicity.

Treatment Naïve

The following table summarizes the renal events observed in 2 or more DTG exposed subjects in treatment naïve phase 3 trials. Overall, there was a low event rate for renal AEs.

Table 51: Summary of Selected Renal Adverse Events that occurred in 2 or more DTG Treatment-Naïve Subjects

	SPRING-2		SINGLE		
Preferred Term	**DTG 50 mg QD + 2NRTI N=403 n (%)**	**RAL 400 mg BID + 2 NRTI N=405 n (%)**	**DTG 50 mg + ABC/3TC QD N=414 n (%)**	**Atripla QD N=419 n (%)**	**DTG total N=817 n (%)**
Total Subjects with Renal AESI	***20 (5)***	***13 (3)***	***17 (4)***	***21 (5)***	***37 (5)***
Number of Events	25	16	18	23	43
Selected Renal AESI in ≥ 2 DTG Subjects					
Dysuria	4 (1)	3 (1)	4 (1)	4 (1)	8 (1)
Hematuria	1 (<1)	2 (<1)	2 (<1)	0	3 (<1)
Nephrolithiasis	1 (<1)	1 (<1)	2 (<1)	3 (1)	3 (<1)
Micturition urgency	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Pollakiuria	2 (<1)	0	0	0	2 (<1)
Polyuria	1 (<1)	0	1 (<1)	0	2 (<1)
Proteinuria	2 (<1)	0	0	2 (<1)	2 (<1)
Renal impairment	2 (<1)	0	0	0	2 (<1)
Urinary retention	1 (<1)	0	1 (<1)	0	2 (<1)

Source: AE ISS dataset

There were few reports of subjects who developed AEs 'renal impairment' or 'renal failure' while being treated with DTG and none of the events were considered related to DTG by the investigator or Applicant. As shown in the above table, 2 DTG subjects (3507 and 4549) in SPRING-2 reported treatment-emergent 'renal impairment' events, summarized below.

Subject 3507, who was on TDF/FTC background therapy, developed fluctuating creatinine levels that peaked at grade 1. This subject continued on study. Subject 4549, also on TDF/FTC background therapy, developed an SAE of septic hip joint and was treated with intravenous vancomycin. During his antibiotic therapy, the subject had transient grade 3, or severe renal impairment that was considered related to vancomycin therapy and not study drug, this subject also remained on study and the renal impairment resolved.

In addition, 'chronic renal failure' (CRF) AE was reported from 1 DTG subject (3200) in SPRING-2 and 'renal failure' was reported from 1 DTG subject (7802) in SINGLE. These cases are not captured in the table above because only 1 subject was reported for each of the respective preferred terms. Subject 3200 had a pre-existing renal disorder (not specified), diabetes, hypertension and proteinuria and was on TDF/FTC as background therapy. During study, his creatinine trended up from 1.02 mg/dL at baseline to 1.27 mg/dL at Week 48, with a corresponding decrease in creatinine clearance from 146 to 107 mL/min. While there were no renal labs that met graded criteria, the subject was reported as chronic renal failure by the investigator. The second subject 7802 also had pre-existing renal risks with diabetes, hypertension and proteinuria at baseline and was on ABC/3TC as background therapy. During study, his diabetes was poorly controlled with frequent grade 2 and 3 elevations. His creatinine peaked to grade 1 at Week 32, and the subject was eventually discontinued at Week 48 with his creatinine still at grade 1. His creatinine clearance declined from Baseline of 122 mL/min to 70 mL/min at Week 48.

By the reviewer's assessment, the 4 renal impairment/renal failure cases do not implicate DTG as causally related to the renal events. Generally, the subjects all had underlying risk factors for renal impairment and/or failure, concomitant medications that are labeled for renal AEs including renal failure, and, other than the vancomycin related renal-toxicity (creatinine peak of grade 3 which resolved on study drug), all had creatinine peaks at grade 1.

The characteristics of the renal events are summarized in the following table. Generally, the majority of renal events were not considered related to DTG, only 1 event of grade 1 pollakiuria (increased urinary frequency) was considered related to DTG. In SPRING-2 there was 1 event of grade 3 renal impairment (subject 4549) described above, and 1 event of grade 4 exacerbation of nephrolithiasis. In SINGLE there was 1 event of grade 3 renal cyst. The event leading to discontinuation of study drug was renal failure (grade 1) in subject 7802 from SINGLE as described above. The fatality that occurred in the Atripla arm was a subject who developed a pulmonary aspergilloma with pseudoaneurysm of a lung vessel, candidemia, septic shock, and renal failure. These events were considered unrelated to study drugs.

Table 52: Summary of Characteristics of Renal AESI in Treatment-Naïve Subjects

Preferred Term	SPRING-2		SINGLE		DTG total N=817 n (%)
	DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)	
Total Subjects with Renal AESI	***20 (5)***	***13 (3)***	***17 (4)***	***21 (5)***	***37 (5)***
Number of Events	25	16	18	23	43
Event Characteristics					
Serious	3 (15)	0	1 (6)	2 (10)	4 (11)
Drug Related	1 (5)	2 (15)	0	5 (24)	1 (3)
Leading to Withdrawal (Temporary or Permanent)	0	0	1 (6)	2 (10)	1 (3)
Severe or Grade 3 or 4	2 (10)	0	1 (6)	2 (10)	3 (8)
Fatal	0	0	0	1 (5)	0

Source: AE ISS dataset

Treatment Experienced, INI Naïve

In the Sailing trial, renal AEs were observed in 5% subjects in the DTG and RAL arms (Table 53). Two AEs of 'acute renal failure' in the DTG arm were reported as SAEs and also resulted in drug discontinuation. Grade 3-4 AEs include one subject with grade 4 hematuria which resolved with continued DTG use, and was assessed by the investigator as unrelated to study agent. The only other grade 3-4 AE was a grade 3 event of acute renal failure. All AEs in the DTG arm were assessed as not related to study agent except one AE of acute renal failure assessed as drug-related. All renal failure AEs and grade 3-4 AEs are discussed in more detail in the subsequent paragraph.

Table 53: Summary of renal adverse events, Sailing trial

	DTG N=354	RAL N=361
Subjects experiencing ≥ 1 AE	**17 (5)**	**17 (5)**
SAE	2 (<1)	1 (<1)
Discontinuations	2 (<1)	1 (<1)
Drug-related	1 (<1)	2 (<1)
Toxicity grades 3-4	2 (<1)	0
Renal AE in ≥ 2 DTG subjects		
Dysuria	5 (1)	2 (<1)
Hematuria	2 (<1)	2 (<1)
Nephrolithiasis	2 (<1)	0
Pollakiuria	2 (<1)	4 (1)
Renal failure acute	2 (<1)	1 (<1)
Renal colic	2 (<1)	0

Source: AE ISS dataset

Of the 2 acute renal failure events in the DTG arm, one case (ID 2809) was discussed previously in section 7.3.2 Nonfatal SAEs. This subject was diagnosed with acute renal failure during an episode of myositis. The events resulted in hospitalization, drug discontinuation. By the reviewer's assessment, the renal abnormalities were secondary to myositis associated with increased creatinine breakdown, and are less likely to represent drug-induced direct renal toxicity. The second case of acute renal failure was observed in a subject with baseline renal insufficiency (creatinine clearance 46 ml/min, serum creatinine 1.1 mg/dL). Increase in serum creatinine to 1.4 mg/dL was observed during hospitalization for hepatic tuberculosis following which ARVs were discontinued and the AE was considered not related to DTG.

Treatment Experienced INI Experienced

In DTG BID group, renal AEs excluding infections were observed in 5% subjects (Table 54) at a frequency similar to the DTG arm in the Sailing trial. Renal failure or acute renal failure AEs were observed in 3 subjects; the individual cases are discussed in the next paragraph. Two SAEs were one renal failure event and an event of acute renal failure discussed. No discontinuations were observed. The only AE assessed as drug-related was urinary frequency in one subject; this event resolved with continued use of DTG. Two grade 3 events in this BID group were renal failure AEs also discussed below. No grade 4 AEs were observed with 50 mg BID dose.

Table 54: Renal Adverse Events in INI-experienced trials

	Total 50 BID N=207	Viking-3 50 BID N=183	Viking-Pilot 50 BID N=24	Viking-Pilot 50 QD N=27
Subjects with ≥ 1 AE	10 (5)	7 (4)	3 (13)	1 (4)
SAE	2 (1)	2 (1)	0	1 (4)
Discontinuations	0	0	0	0
Drug-related	1 (2)	0	1 (4)	0
Toxicity grades 3-4	2 (1)	2 (1)	0	1 (4)
Preferred AE term				
Renal failure	2 (1)	2 (1)	0	0
Renal failure acute	1 (<1)	1 (<1)	0	1 (4)
Nocturia	2 (1)	1 (<1)	1(4)	0
Dysuria	1 (<1)	1 (<1)	0	0
Glomerulonephropathy	1 (<1)	1 (<1)	0	0
Renal colic	1 (<1)	1 (<1)	0	0
Strangury	1 (<1)	1 (<1)	0	0
Urinary tract obstruction	1 (<1)	1 (<1)	0	0
Pollakiuria	3 (2)	0	3 (13)	0
Urethral pain	1(<1)	0	1 (4)	0

Source: AE ISS dataset

All cases of renal failure AE in BID dosed subjects are briefly summarized in Table 55 below. Additionally, cases of grade 3 or 4 creatinine toxicity are also summarized. Of the 5 cases, 3 subjects had baseline grade 2 or 3 creatinine elevations due to pre-existing renal disease (IDs 1057, 1214, 227). Rise in creatinine during the treatment period was attributed by investigators as secondary to the underlying renal disease. Grade 1 creatinine elevation in one subject (0504) was reported by the investigator as 'renal failure'; this event occurred during viral illness associated with dehydration. These 4 cases were confounded by underlying renal disease or another ongoing condition, and in my assessment, are not related to DTG. The last case, ID 2, of new onset grade 4 creatinine elevation was assessed by the investigator as related to DTG and treatment was discontinued. Subsequently, the subject reported taking twice the dose of TDF in the preceding weeks. Improvements in renal function were observed after discontinuation of DTG and institution of the correct TDF dose. In my assessment, this case is confounded by intake of incorrect TDF dose although causality to DTG cannot be definitively excluded.

Table 55: Renal AEs and grade 3-4 creatinine toxicity in INI-experienced trials

ID/ DTG 50 mg BID	AE	S. creatinine toxicity		Pertinent case information
		Day 1	Max	
1057	RF	Grd 2	Grd 3	Pre-existing HIV nephropathy and CRF with worsening renal function and proteinuria observed on treatment. Renal biopsy findings were consistent with CRF. DTG continued.
1214	Acute RF	Grd 2	Grd 3	Pre-existing CRF, congestive heart failure (CHF) with volume overload state (ascites, pleural effusion); grade 2-3 fluctuations in serum creatinine attributed to underlying CRF and CHF.
227	-	Grd 3	Grd 4	Pre-existing HIV nephropathy and chronic kidney disease with worsening renal function at Weeks 12 and 16 attributed to pre-existing chronic kidney disease.
0504	RF	normal	Grd 1	Week 16 serum creatinine 1.5 mg/dL with creatinine clearance 80 ml/min in the context of viral syndrome and dehydration.
2	-	normal	Grd 4	Marked decline in renal function at Week 48, worsening proteinuria, 1+ glycosuria resulted in DTG discontinuation. Subsequently, subject reported taking twice the dose of TDF in the days preceding grade 4 toxicity. Renal function improved after DTG cessation and institution of the correct TDF dose.

Source: AE ISS dataset

Additional renal failure cases

Two additional DTG cases of renal failure noted in the 60-day SUR were in the context of legionella pneumonia hospitalization (subject receiving DTG 50 mg QD) and following intake of an incorrect dose (twice daily) dose of Truvada (the DTG 50 mg BID was resumed after renal function improved without a recurrence).

In summary, renal AEs were observed at a similar frequency of 4-5% in DTG arms across all Phase 3 trials. The frequency was generally comparable to event rates for the comparator arm in the controlled trials. Events related to renal failure were observed less frequently in the treatment-naïve trials compared to treatment-experienced trials. All renal failure or grade 3-4 creatinine toxicity cases were confounded by virtue of pre-existing ongoing renal disease or because they were concurrently using drugs known to cause nephrotoxicity. In one case, improvement in renal function occurred after DTG discontinuation and tenofovir dose correction; causality to DTG could not be definitively excluded in this case. As discussed in section 4.4.2, an exposure-response relationship was also not observed for renal failure AEs or for creatinine abnormalities (refer to clinical pharmacology and pharmacometrics review by Dr. Su-Young Choi).

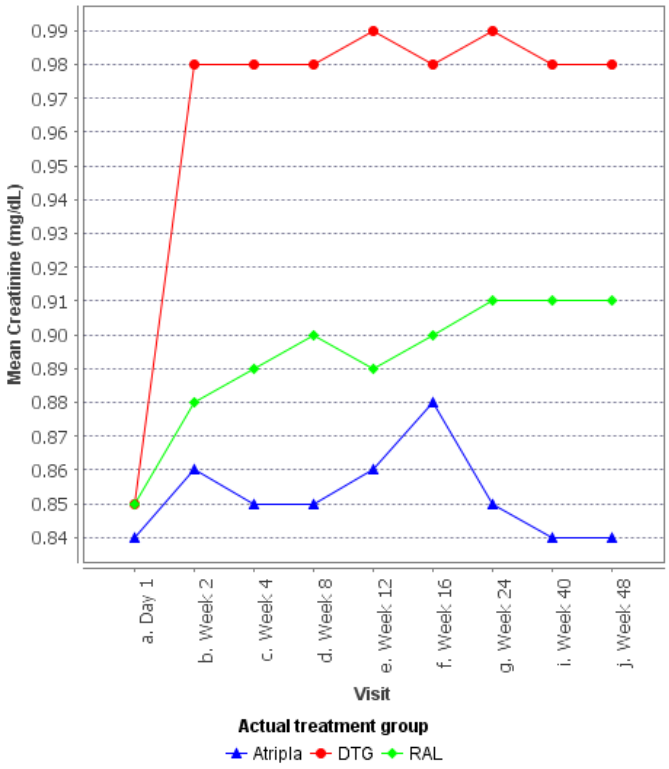
2) Creatinine and Creatinine Clearance

This subsection summarizes changes from baseline in serum creatinine and creatinine clearance in Phase 3 trials. As mentioned previously, creatinine increase with DTG use is a result of drug effects on renal tubular secretion mediated by inhibiting the OCT2 receptor. This effect is not due to DTG effects on GFR because no clinical change in GFR was observed in the clinical study using iohexol, a highly specific marker of glomerular filtration. DTG effect on this renal transporter protein and consequent effect on serum creatinine and creatinine clearance tend to occur within the first week of treatment with subsequent plateau of the effect. Importantly, changes were non-progressive, i.e., did not worsen over time, as demonstrated in 48 week data in treatment-naïve trials. This effect on OCT2 transporter has been described with other drugs such as cimetidine and another ARV drug rilpivirine.

Treatment Naïve

Analysis evaluating the mean change in creatinine (mg/dL) through Week 48 with the pooled treatment-naïve DTG population is displayed below. The mean creatinine rises quickly in the first week of treatment with a mean increase of approximately 0.13 mg/dL. This increase then plateaus through Week 48. Interestingly, for RAL there is a more gradual, small increase in creatinine which also plateaus by Week 24.

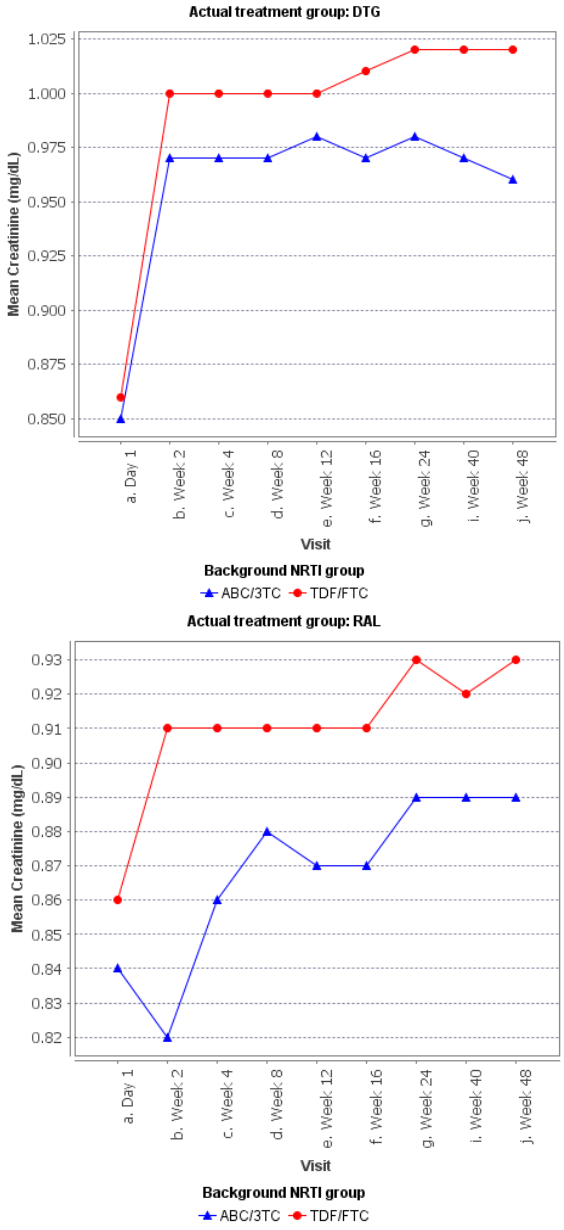
Figure 5: Mean change in creatinine (mg/dL) through Week 48, pooled treatment-naïve



Source: Laboratory ISS dataset

Evaluation of the mean increase in creatinine through Week 48 was completed by background NRTI regimen, ABC/3TC or TDF/FTC, for the DTG and RAL treatment-naïve subjects (Atripla is not included as all subjects received TDF/FTC as background therapy). TDF/FTC has been associated with new onset or worsening of renal function. As shown in the following figure, both for the DTG and RAL treatment arms, the subjects exposed to TDF/FTC as compared to ABC/3TC as background therapy observed a higher increase in mean creatinine over time (difference of mean change of 0.05 mg/dL at Week 48 for DTG/TDF/FTC compared to DTG/ABC/3TC, and 0.02 mg/dL at Week 48 for RAL/TDF/FTC compared to RAL/ABC/3TC). Albeit, these observed changes were small and the clinical significance of these differences from this Week 48 data can not be determined.

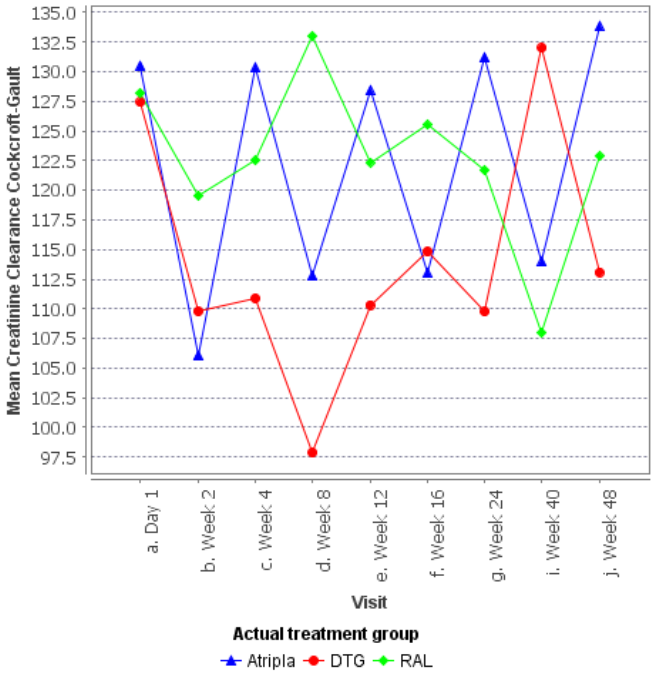
Figures 6 and 7: Mean change in creatinine (mg/dL) by background NRTI regimen for DTG (top figure) and RAL (bottom figure), pooled treatment-naïve



Source: Laboratory ISS dataset

To more fully characterize the renal effect, evaluation of the mean estimated creatinine clearance by the Cockcroft-Gault formula (mL/min) was completed for the treatment-naïve data. As expected, the DTG treatment arm had a mean reduction of 14 mL/min at Week 48 compared to Day 1, as summarized in the following figure. This reduction represents an approximate 11% decline in the overall estimated creatinine clearance in the DTG treatment-naïve population. The figure also shows the variability of the creatinine clearance in this population over time, but for both the RAL and Atripla comparators, there was no significant decline in creatinine clearance by Week 48.

Figure 8: Mean estimated creatinine clearance (mL/min) over 48 weeks, pooled treatment naive

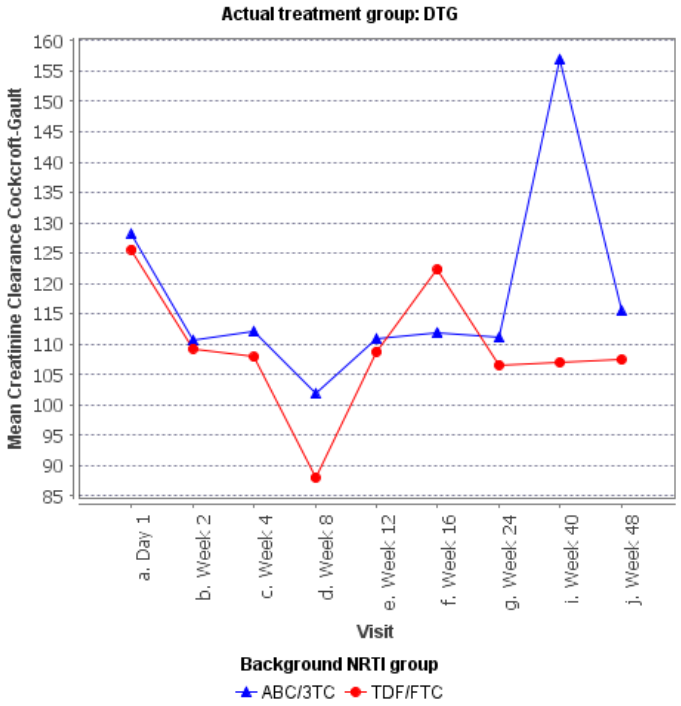


Source: Laboratory ISS dataset

The same analysis as described above was completed for DTG by background NRTI therapy. As displayed in the following figure, the declined in the estimated creatinine clearance occurs in the first 2 weeks, and generally plateaus (although some variability is noted) through Week 48. Additionally, there is no clinically significant difference (approximately 7 mL/min, favoring ABC/3TC at Week 48) between the DTG subjects who received TDF/FTC or ABC/3TC as background therapy. Interestingly, RAL subjects, had a similar approximate 7 mL/min difference in estimated creatinine

clearance favoring ABC/3TC over TDF/FTC (figure not shown) at Week 48. However, as stated previously, these differences are small and likely do not represent a clinically meaningful difference.

Figure 9: Mean estimated creatinine clearance (mL/min) by background NRTI over 48 weeks, pooled treatment naive



Source: Laboratory ISS dataset

Treatment Experienced, INI Naïve

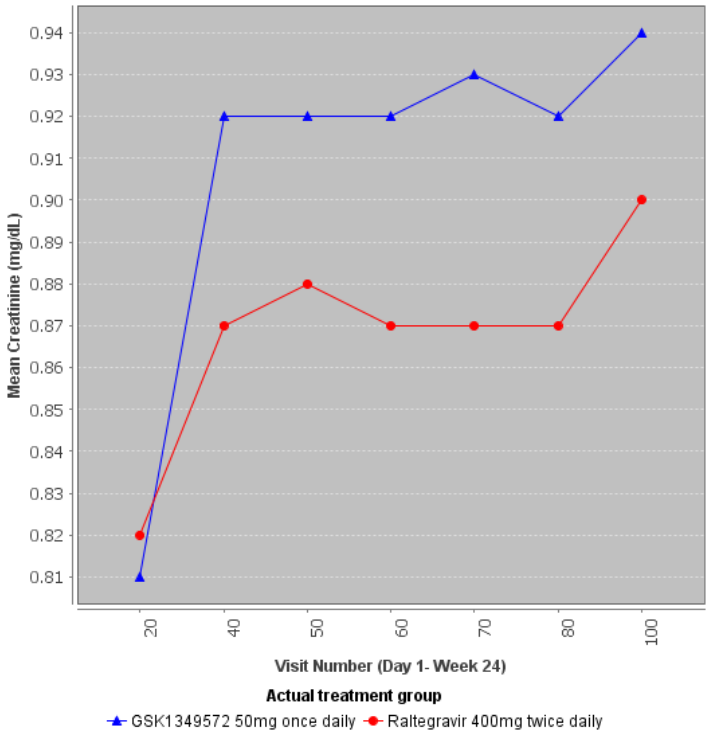
In the DTG arm in Sailing, the mean increase in serum creatinine was 0.1 mg/dL through Week 24, a finding consistent with observations in the treatment-naïve subjects receiving the same DTG dose (Table 56). The mean decrease in creatinine clearance from baseline was 14.4 ml/min through Week 24 in the DTG arm, also consistent in magnitude with effects observed in the treatment naïve trials. No grade 3 or 4 serum creatinine elevations were observed in the DTG arm.

Table 56: Post-baseline renal laboratory abnormalities, Sailing

	DTG N=354	RAL N=361
Creatinine, max toxicity grade from baseline		
Grade 4	0	0
Grade 3	0	1 (<1)
Grade 2	5 (1)	4 (1)
Grade 1	12 (3)	7 (2)
Creatinine (mg/dL) mean change from Day 1		
Week 24	0.1; n=320	0.07; n=326
Creatinine clearance (ml/min) mean change from Day 1		
Week 24	-14.8; n=315	-6.2 ; n=319

These changes in creatinine over time are presented in figure 10 below. In this figure, x-axis represents timepoints of week 2, 4, 8, 12, 16, 20, and 24. In RAL arm in Sailing, small increase in creatinine (0.07 mg/dL) and corresponding decrease in creatinine clearance (6.2 ml/min) were observed; again findings similar to those observed in the RAL arm in Spring-2 treatment naïve trial.

Figure 10: Mean change in creatinine (mg/dL) through Week 24, Sailing



Source: Laboratory ISS dataset

In summary, the creatinine and creatinine clearance changes from baseline observed in the Sailing trial were similar to observations in treatment naïve trials, providing further support of the small magnitude of DTG effect on serum creatinine with the 50 mg QD dose.

Treatment Experienced, INI Experienced

Similar to findings with the 50 mg QD dose, the mean increase in serum creatinine from baseline was 0.13 mg/dL at Week 24 in BID dosed subjects (Table 57). The mean decrease in creatinine clearance from baseline to Week 24 was 8.6 ml/min in BID dosed subjects, slightly lower than Week 24 observations in either treatment naïve trials or the Sailing trial.

Grade 3-4 creatinine toxicity in BID dosed group was observed in 2% subjects compared to 1% rate in subjects receiving DTG QD in the Sailing trial. About 8% of BID dosed subjects developed grade 1 or 2 creatinine toxicity compared to 4% of subjects receiving DTG QD in the Sailing trial. As discussed in the previous subsection, cases

with grade 3-4 creatinine increase were confounded by underlying renal disease or concurrent use of nephrotoxic agents.

Table 57: Post-baseline renal laboratory abnormalities, INI-experienced trials

	Total 50 BID N=207	Viking-3 50 BID N=183	Viking-Pilot 50 BID N=24	Viking-Pilot 50 QD N=27
Creatinine, max toxicity grade from baseline (n, %)				
Grade 4	2 (1)	2 (1)	0	0
Grade 3	2 (1)	2 (1)	0	0
Grade 2	2 (1)	2 (1)	0	3 (11)
Grade 1	17 (8)	14 (8)	3 (13)	1 (4)
Creatinine (mg/dL) mean change from Day 1				
Day 1	82	81	88	89
Week 24	0.13 (n=131)	0.13 (n=109)	0.11 (n=22)	0.12 (n=17)
Creatinine clearance (ml/min) mean change from Day 1				
Day 1	109	109.1	NA	NA
Week 24	-8.6 (n=101)	-8.6 (n=101)	NA	NA

Source: Laboratory ISS dataset

Overall for DTG 50 mg BID group, changes in creatinine from baseline were of similar magnitude as observed with 50 mg QD dose in treatment naïve trials and the Sailing trial. A slightly higher proportion of subjects in 50 BID group had graded creatinine toxicities compared to DTG 50 mg QD subjects in Sailing. However, all cases with grade 3-4 creatinine increase either had ongoing renal disease, or were concurrently using nephrotoxic drugs. Therefore, no conclusive case of renal failure attributable to DTG 50 mg BID was identified in this review. Further, a relationship between DTG exposure and renal failure events or serum creatinine increases was not identified as discussed in section 4.4.2.

3) Proteinuria

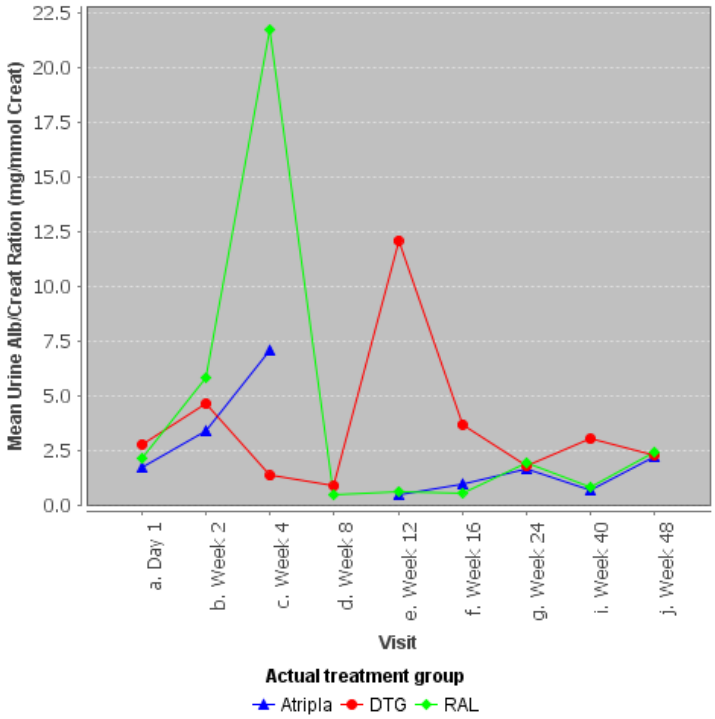
Lastly, evaluation of urine for measurement of urinary albumin-to-creatinine ratio (UACR; mg/mmol creatinine) was completed in the phase 3 protocols to assess for possible renal damage (as indicated by albuminuria or proteinuria). An abnormal result in SI units is ≥ 3.5 mg/mmol creatinine.

Treatment Naïve

Analysis of the mean UACR in treatment-naïve trials showed DTG subjects to be similar to RAL and Atripla over the Week 48 treatment period. The following figure summarizes the findings that through Week 48. There was some variability around Weeks 12-16,

(mostly driven by a few outlying subjects with diabetes or other renal risk factors or events that led to increased UACR), but overall, the mean UACR at Week 48 was similar to the Day 1 mean UACR for all treatment groups.

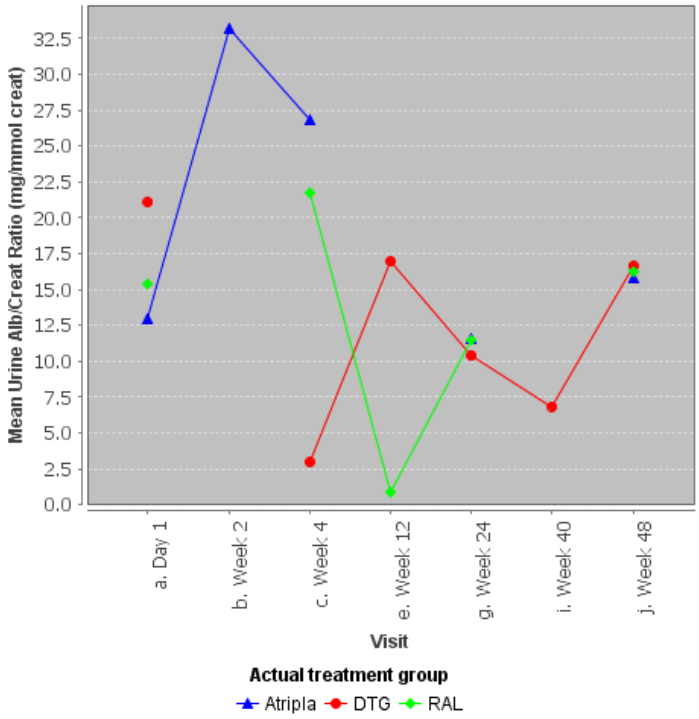
Figure 11: Mean urinary albumin-to-creatinine ratio over 48 weeks, pooled treatment naive



Source: Laboratory ISS dataset

Further analysis was completed by evaluating differences by pre-existing renal risk factors such as diabetes, hypertension and existing renal disease. These analyses were hindered by smaller subgroups and some missing data; but did not reveal any significant differences in the overall trend of similar results for the renal safety data in the treatment-naïve population. As an example, the following figure shows evaluation of mean UACR in the subset of subjects with an abnormal baseline UACR result (≥ 3.5 mg/mmol creatinine). Overall, despite some missing data (demonstrated by gaps in the lines in the graph), there was not a clinically significant increase for the mean UACR from Day 1 through Week 48 for subjects with baseline abnormal UACR on all treatment arms.

Figure 12: Mean UACR in the subset of subjects with an abnormal baseline UACR result



Source: Laboratory ISS dataset

Treatment Experienced, INI-naïve and Treatment experienced, INI-experienced

Increases in UACR were not observed at Week 24 in either the Sailing or Viking-3 trial. Results from Applicant's analysis for Viking-3 are displayed below.

Table 65 Summary of Change from Baseline in Albumin/Creatinine Ratio (mg/mmoL) in ING112574

Treatment (N)	Time	n	Mean	SD	Median	Q1	Q3	Min.	Max.
DTG 50 mg BID N=183	Baseline	160	20.35	59.411	1.75	0.80	8.75	0.2	409.7
	Week 1	149	-5.79	23.947	-0.20	-2.30	0.30	-155.3	46.1
	Week 24	90	-1.31	53.352	-0.10	-1.60	0.70	-290.8	283.5
	Week 48	9	6.38	9.024	2.60	0.60	8.00	-1.4	22.7

Data Source: ISO Table 2.239

Renal Analysis: Overall Summary and Labeling Recommendation

- Small increases from baseline in serum creatinine were observed with DTG in all phase 3 trials. These effects are a result of drug effects on renal tubular secretion of creatinine mediated through OCT2 inhibition, an effect observed with other drugs such as cimetidine and rilpivirine. Creatinine increases were observed within the first weeks of DTG dosing, plateau with a mean change from baseline of 0.1-0.13 mg/dL, and were non-progressive through the dosing period studied up to 48 weeks. Creatinine increases with DTG were observed regardless of background NRTI regimen (TDF/FTC or ABC/3TC), further demonstrating the effects were driven primarily by DTG.
- The observed decline in creatinine clearance from baseline in Phase 3 trials reflects alteration in creatinine transport and not a true decrease in renal function as supported by findings in study ING114819. Glomerular filtration can be accurately measured using iohexol marker, and in this study, DTG did not affect GFR as measured by iohexol clearance.
- A similar magnitude of change in creatinine and creatinine clearance was observed with the 50 mg BID dose up to 24 weeks in INI-experienced subjects.
- Renal AEs were observed at a similar frequency of 4-5% in DTG arms across all Phase 3 trials. The frequency was generally comparable to event rates for the comparator arm in the controlled trials. Events related to renal failure were observed less frequently, in the treatment-naïve trials compared to treatment-experienced trials. No correlation between dose or exposure and renal failure AEs was observed. All renal failure or grade 3-4 creatinine toxicity cases were confounded by virtue of pre-existing ongoing renal disease or because they were concurrently using drugs known to cause nephrotoxicity. In one case, improvement in renal function occurred after DTG discontinuation and tenofovir dose correction; causality to DTG could not be definitively excluded in this case. Based on this case, renal failure should be included in Less Common ADR section 6 of labeling.
- The Applicant's proposal to include information (below) in Drug Reactions section of the label describing effects on creatinine and calculated creatinine clearance is acceptable.

Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 24 to 48 weeks. In treatment-naïve subjects, a mean change from baseline of 0.11 mg/dL (range: -0.60 mg/dL to 0.62 mg/dL) was observed after 48 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects. (b) (4)

Myositis and CK elevations

Rhabdomyolysis and CK elevations are labeled for RAL. A review of AEs related to rhabdomyolysis, and CK elevations was performed to evaluate for potential class-related toxicity. This section initially reviews musculoskeletal AEs of interest focusing on preferred AE terms of myositis, myalgia, and rhabdomyolysis. Grade 3-4 CK elevations are reviewed subsequently to assess trends suggesting muscle toxicity.

Musculoskeletal Adverse Events of Interest

Treatment Naïve

In the treatment-naïve phase 3 trials, the proportions of musculoskeletal AEs were comparable between DTG and RAL and/or Atripla, respectively. Overall, there was only 1 reported case of grade 1 myositis in treatment-naïve subjects which occurred in a subject randomized to Atripla in SINGLE. There were 2 reported SAEs related to musculoskeletal AEs or elevated CKs in the treatment-naïve phase 3 trials. One RAL exposed subject (3441) was reported as having a grade 3 elevated CK and grade 2 myalgia after a seizure event. One DTG subject (5919) had 2 days of muscle pain reported as grade 2 myalgia and considered serious; however the subject had spontaneous resolution of the pain (in 2 days) and remained on study drug throughout the episode.

Additionally, there were 2 DTG subjects (5163 and 5398), both from SINGLE, who reported to have on-treatment grade 2 increased CK. Subject 5163 developed grade 2 CK elevation and grade 1 liver enzyme elevations after 337 days of study drug exposure. Both events were considered not related to study drug and study drug was continued. Subject 5398 had a grade 2 elevation of CK after 57 days of study drug exposure. This event resolved after 23 days while continuing study drug and was considered not related to study drug. These 2 DTG subjects, compares to the Atripla arm in which 2 subjects each were reported as having grade 2, grade 3 and grade 4 events, respectively (total of 6 subjects). In the RAL treatment arm, 2 subjects reported grade 3 CK elevations (including the subject described above).

Treatment Experienced, INI naïve

Musculoskeletal AEs of interest were observed in less than 2% of subjects in either DTG or RAL arm. Among musculoskeletal disorders class, only one AE resulted in drug discontinuation; this was AE myositis in one subject in the DTG arm. Four SAEs in this system organ class were due to AE myositis (DTG), rhabdomyolysis (DTG), intervertebral disc protrusion (RAL), and arthritis (RAL) observed in one subject each.

Myalgia AE was observed in 6 and 7 subjects in the DTG and RAL arm, respectively. None of the DTG myalgia events was assessed as drug-related or resulted in drug discontinuation. The AE of myositis (ID 2809) in the DTG arm was summarized previously in section 7.3.2 Nonfatal SAEs. Briefly, this subject reported strenuous muscular activity and developed muscle pain with grade 3 CK elevation. ARVs were discontinued following which CK improved. Myalgia recurred with CK elevations following two doses of ARVs including DTG. No recurrence was noted subsequently when the subject was restarted on the same regimen without DTG. The investigator assessed the AE related to DTG. Based on available information of positive rechallenge, and lack of recurrence when ARVs were initiated and DTG was withheld suggests causality to DTG; however, it should be noted the case is confounded by reported strenuous muscular activity.

Rhabdomyolysis in one DTG subject was diagnosed during an episode of interstitial pneumonia; the peak CK value was only 2457 IU/L and the episode was not accompanied by hematuria, creatinine elevation or renal failure. The episode was assessed as unrelated to DTG, and treatment was continued. I agree with the investigator's assessment the AE is not related to DTG.

Treatment Experienced, INI Experienced

No myositis or rhabdomyolysis events were reported in INI-experienced trials. Myalgia observed in one subject was a grade 1 AE, assessed as related to study agent, but did not result in DTG discontinuation. One AE of 'CPK increased' resulted in drug discontinuation. This subject (ID 41) had baseline grade 3 CPK elevation of 3333 IU/L at baseline reported strenuous physical activity. He was eventually diagnosed with Macro CK Type 1 syndrome, an abnormal type of CK associated with delayed CK clearance. The event was not associated with muscle pain or renal compromise. CK elevations at Week 12 were also accompanied by grade 3 ALT and AST elevations. The AE was assessed as unrelated to DTG. This case is confounded by pre-existing muscle enzyme disorder; and a causal association with DTG is not evident based on the available information.

Overall, AEs of myalgia, myositis, and CK increased were observed in few DTG subjects receiving 50 mg QD dose; the event rate was generally comparable to controls in individual trials. A higher frequency of these events was not observed with the 50 mg BID dose. With one exception, all DTG events were assessed as not drug-related and DTG treatment was continued. In one case of myositis with 50 mg QD dose, positive rechallenge and lack of recurrence when ARVs were initiated and DTG was withheld suggests causality; however, it should be noted the case is confounded by reported strenuous muscular activity.

Serum Creatine Kinase analysis

Graded CK elevations from baseline were observed in 1-5% subjects across the Phase 3 trials. Majority of elevations were grade 1 or 2, and nearly all were asymptomatic.

Treatment Naïve

The following table provides the summary of grade 3-4 CK elevations in phase 3 treatment-naïve trials. Overall, the total DTG rate of 4% is comparable to RAL (3%) and Atripla (5%). As noted by the scarce AE reports of symptomatic CK elevations across the treatment naïve studies as highlighted above, most of these laboratory reports were considered asymptomatic; all these events resolved without medical intervention and none resulted in discontinuation for DTG subjects (RAL subject above was discontinued but this was due to seizure, CK and myalgias were secondary to this primary event). Additionally, the Applicant reported "Investigators were able to confirm high degrees of physical activity preceding the CPK elevation in the majority of cases."

Table 58: Summary of grade 3 and 4 CK Laboratory Elevations in Treatment-Naïve Subjects

	SPRING-2		SINGLE		
CK Elevations	DTG N=403 n (%)	RAL N=405 n (%)	DTG N=414 n (%)	Atripla N=419 n (%)	DTG total N=817 n (%)
Grade 3-4	20 (5)	13 (3)	9 (2)	19 (5)	29 (4)

Source: Laboratory ISS dataset

Overall, in the treatment-naïve subjects there were no significant cases of symptomatic elevation of CK or myositis that could be considered associated with use of DTG. Additionally, there were no clinical AEs reported that may be related to myositis or rhabdomyolysis.

Treatment Experienced, INI Naïve

As displayed in the following table, grade 3-4 CK elevations were observed in 2% subjects each in the DTG and RAL arms. In DTG subjects, majority were isolated elevations with a normal value observed at subsequent visits or subjects with baseline elevations. Two subjects developed CK of 33,008 IU/L, and CK of 22,785: both were asymptomatic elevations which improved at subsequent visits with continued DTG use. The only symptomatic grade 3 CK elevations was in subject 2809 (myositis/DTG) discussed above.

Table 59: Treatment-emergent CK increases from baseline in Sailing

	DTG N=354	RAL N=361
CK, max toxicity grade from Day 1		
Grade 4	2 (1)	2 (1)
Grade 3	4 (1)	1 (<1)

Source: Laboratory ISS dataset

Treatment Experienced, INI Experienced

In the BID dose group, occurrence of grades 3-4 CK elevations was generally similar to observations with QD dosing in other phase 3 trials (Table 60). Majority of these subjects experienced single episodes of CK elevation with improving or resolved values at the next time point. The only exception was subject 41 discussed above with Macro CK Type 1 disorder.

Table 60: Treatment-emergent CPK increases from baseline

	Total 50 BID N=207	Viking-3 50 BID N=183	Viking-Pilot 50 BID N=24	Viking-Pilot 50 QD N=27
CPK, maximum toxicity grade from baseline (n, %)				
Grade 4	2 (<1)	2 (1)	0	0
Grade 3	5 (2)	5 (3)	0	0

Source: Laboratory ISS dataset

Overall, the grade 3-4 CK profile for DTG 50 mg BID was similar to observations with the DTG QD dose in other phase 3 trials.

CK and Myositis Analysis: Summary and Labeling Recommendation

- Overall, AEs of myalgia, myositis, and CK increased were observed in few DTG subjects receiving 50 mg QD dose; the event rate was generally comparable to controls in individual trials. A higher frequency of these events was not observed with the 50 mg BID dose. With one exception, all DTG AEs were assessed as not drug-related and DTG treatment was continued. In one case of myositis with 50 mg QD dose, positive rechallenge and lack of recurrence when ARVs were initiated and DTG was withheld suggests causality; however, it should be noted the case is confounded by reported strenuous muscular activity.
- Grade 3-4 CK elevations were observed in 2-5% DTG subjects in phase 3 trials; at a frequency comparable to the comparator in controlled trials. The majority of CK elevations were asymptomatic and did not result in drug discontinuation.
- Based on the myositis case, the team recommends this event should be included under Less Common ADRs.

- Applicant's proposal to display grades 2-4 CK elevations in treatment naïve trials in laboratory abnormalities table in section 6 is appropriate.
- The Applicant's proposal [redacted] is not acceptable [redacted]

Psychiatric Disorders

Suicidal ideation and behavior, particularly in subjects with a pre-existing history of psychiatric illness, has been described and is labeled in association with use of RAL. Psychiatric AE analyses were performed to explore for class-related toxicity.

Treatment Naïve

Psychiatric adverse events were more commonly reported for Atripla than for DTG from either phase 3 treatment-naïve trial. In SPRING-2, reporting rates and characterization of the events were generally comparable between the DTG and RAL treatment arms. The following table summarizes the characteristics of the reported psychiatric events. Majority of the reports were considered mild to moderate (grade 1 and 2) and did not lead to a change in study medication dosing. Interestingly, a range from 34-50% of events across the phase 3 treatment arms were considered not resolved at the time of the data cut, reflecting the chronic nature of some of these events (e.g. depression). A higher proportion of psychiatric AEs were considered drug related and resulted in discontinuation for Atripla compared to any other treatment group or for DTG overall.

Table 61: Summary Characteristics of Psychiatric Adverse Events, Treatment-Naïve

	SPRING-2		SINGLE		
	DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)	DTG total N=817 n (%)
Total Subjects with Psychiatric AEs	***74 (18)***	***66 (16)***	***117 (28)***	***152 (36)***	***191 (23)***
Event Characteristics n/n (%)					
Drug – related	18 (25)	11 (17)	80 (68)	110 (72)	98 (51)
Serious	2 (3)	4 (6)	3 (3)	6 (4)	5 (3)
Fatal	0	1 (2)	0	0	0
Grade 3/4	5 (7)	3 (5)	6 (5)	12 (8)	11 (6)
Grade 2	25 (34)	25 (38)	29 (25)	41 (27)	54 (28)
Grade 1	50 (68)	45 (68)	96 (82)	120 (79)	146 (76)
Resolved	40 (54)	26 (39)	72 (62)	103 (68)	112 (59)
Resolving	3 (4)	5 (8)	12 (10)	16(11)	15 (8)
Not Resolved	31 (42)	33 (50)	46 (39)	51 (34)	77 (40)
Resolved with Sequelae	0	4 (6)	5 (4)	5 (3)	5 (3)
Study Drug Discontinued	0	2 (3)	2 (2)	12 (8)	2 (1)
Dose Not Changed	70 (95)	64 (98)	114 (97)	142 (93)	184 (96)
Dose Interrupted/Delayed	4 (5)	0	1 (1)	3 (2)	5 (3)

Source: AE dataset ISS

Further analysis of psychiatric AEs was conducted using any preferred terms that contained the root terms: suicide/suicidal, depression, bipolar/hypomania, nightmare/abnormal dreams, sleep disorders, and insomnia. The following table provides the overall psychiatric adverse events of special interest (AESI).

Table 62: Summary of Psychiatric Adverse Events, Treatment-Naive

Pooled Preferred Terms*	SPRING-2		SINGLE		DTG total N=817 n (%)
	DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)	
Total Subjects with Psychiatric AESI	***74 (18)***	***66 (16)***	***117 (28)***	***152 (36)***	***191 (23)***
Insomnia	22 (5)	19 (5)	66 (16)	45 (11)	88 (11)
Depression, bipolar, suicide/suicidal	25 (6)	24 (6)	27 (6)	34 (8)	61 (6)
Depression	*21 (5)*	*19 (5)*	*23 (6)*	*26 (6)*	*44 (5)*
Bipolar	*0*	*0*	*1 (<1)*	*2 (<1)*	*1 (<1)*
Suicide/suicidal	*4 (1)*	*5 (1)*	*3 (<1)*	*6 (1)*	*7 (1)*
Nightmare, abnormal dreams	18 (4)	10 (2)	39 (9)	89 (21)	57 (7)
Anxiety	15 (4)	22 (5)	15 (4)	27 (6)	30 (4)
Sleep disorder	5 (1)	8 (2)	6 (1)	11 (3)	11 (1)

*Psychiatric AESI terms were pooled and included if the preferred term includes the listed specified term (e.g. insomnia includes: insomnia, initial insomnia, middle insomnia, terminal insomnia)
Source: AE dataset ISS

Generally, DTG was similar to the comparators except for a higher proportion of insomnia in the DTG arm from the SINGLE trial. It is important to note that although the study was blinded, overall a higher proportion of psychiatric AEs were reported in SINGLE, likely due to the known psychiatric AE profile of the comparator Atripla due to the efavirenz component of the FDC regimen. This may have generally increased the adverse events that were reported from this trial. Additionally, SINGLE was the only study in the DTG development program that employed a Global Health Outcomes Symptoms Impact Case Report Form module that questioned subjects about specific potentially bothersome symptoms, including insomnia, at Day 1, Weeks 4, 24, 48 and 96. This survey may have influenced subjects to report insomnia to investigators during study visits; however, no other symptoms included in this questionnaire were found to be proportionally higher from SINGLE. Additionally, while insomnia was observed as a safety signal due to the higher proportion of reporting for DTG from SINGLE, this trend was not observed in any of the other phase 2b/3 studies conducted with DTG.

The Applicant had a pre-specified, exploratory analysis of the 48-week data for SINGLE which indicated a statistically significant higher rate of psychiatric AEs (as identified by the GSK Medical Monitor prior to study unblinding) (p=0.008), and specifically abnormal dreams (p<0.001), in the Atripla arm. In contrast, subjects on DTG with ABC/3TC background therapy were significantly more likely to develop insomnia (RR values and 95% CI were >1) (p=0.029). However, these analyses are exploratory and are not adjusted for multiple comparisons.

Suicidal ideation and behavior, particularly in subjects with a pre-existing history of psychiatric illness, has been described and is labeled in association with use of raltegravir. Overall, the suicidal ideation and behavior reporting rates were similar for DTG and the comparators, RAL and Atripla. All the subjects from the DTG and Atripla treatment groups had a relevant medical history of psychiatric disorders with or without nervous system disorder (e.g. insomnia) and/or alcohol/illicit drug abuse. Two subjects randomized to RAL did not have any related medical history at baseline, and this includes the subject with completed suicide. However, the events in the RAL subjects were also not considered drug related by the investigator. Only suicidal ideation and behaviors reported from Atripla were considered at least possibly related to study drug, as summarized in the following table (Table 63). None of the suicidal ideation or behavior events reported by subjects receiving DTG in the treatment-naïve trials were considered related to study, presumably due to the fact that these subjects all had baseline psychiatric disorder histories.

The following table provides the summary of psychiatric AEs that were considered related to study drug by investigator assessment.

Table 63: Summary of Psychiatric Adverse Events Considered Treatment-Related, Treatment-Naive

	SPRING-2		SINGLE		
Drug Related Pooled Preferred Terms*	**DTG 50 mg QD + 2NRTI N=403 n (%)**	**RAL 400 mg BID + 2 NRTI N=405 n (%)**	**DTG 50 mg + ABC/3TC QD N=414 n (%)**	**Atripla QD N=419 n (%)**	**DTG total N=817 n (%)**
Total Subjects with Psychiatric AE of interest	***74 (18)***	***66 (16)***	***117 (28)***	***152 (36)***	***191 (23)***
Insomnia	6 (1)	3 (1)	43 (10)	24 (6)	49 (6)
Depression, bipolar, suicide/suicidal	*1* (<1)	*1* (<1)	*10 (2)*	14 (3)	*11 (1)*
Depression	*1* (<1)	*1* (<1)	*10 (2)*	*9 (2)*	*11 (1)*
Bipolar	*0*	*0*	*0*	*1(<1)*	*0*
Suicide/suicidal	*0*	*0*	*0*	*4 (1)*	*0*
Nightmare, abnormal dreams	10 (2)	8 (2)	34(8)	74 (18)	44 (5)
Anxiety	1 (<1)	2 (<1)	4 (3)	11 (3)	5 (1)
Sleep disorder	1 (<1)	0	9 (2)	6 (1)	10 (1)

*Psychiatric AESI terms were pooled and included if the preferred term includes the listed specified term (e.g. insomnia includes: insomnia, initial insomnia, middle insomnia, terminal insomnia)
Source: AE dataset ISS

Overall, drug-related psychiatric AEs were more commonly reported for Atripla than for DTG in SINGLE, however, DTG was comparable to RAL in SPRING-2. Again, the pattern of higher reporting rates are observed in SINGLE where DTG/ABC/3TC is being

compared to the efavirenz-based Atripla regimen. The higher proportion of DTG events in SINGLE compared to SPRING-2, is driven by reporting for insomnia and nightmare/abnormal dreams. This may again be related to reporting bias with investigators more commonly attributing sleep complaints in this blinded trial containing Atripla. However, besides insomnia and nightmare/abnormal dreams, overall the reporting rates are generally low and comparable between DTG and RAL and Atripla.

Treatment Experienced, INI Naïve

In this population, treatment-emergent AEs were observed in 11% and 10% of subjects in DTG and RAL, respectively (Table 64). No fatal events were observed. Only one event resulted in drug discontinuation; this was a subject in the RAL arm with recurrent suicidal ideation (details after the table).

Among psychiatric AESI, majority of the events were grade 1 or 2 in severity; with only 1% subjects experiencing grade 3 or 4 AEs in each arm. SAEs were observed in 2% and 1% of subjects in the DTG and RAL arms, respectively. Drug-related events were observed in fewer (4%, 1 out of 27) DTG subjects compared to RAL subjects (38%, 8 out of 21). The median time to onset for these events was 83 days and 68 days in the DTG and RAL arms. About 50% of events in each arm were unresolved reflecting the chronic nature of some events.

Table 64: Summary of Psychiatric AE of interest, Sailing

	DTG N=354	**RAL N=361**
Subjects experiencing ≥ 1 psychiatric AE	40 (11)	35 (10)
Subjects with psychiatric AE of interest	**27 (8)**	**21 (6)**
SAE	6 (2)	2 (1)
Discontinuations	0	1 (<1)
Related	1 (<1)	8 (2)
Grade 3 or 4	4 (1)	3 (1)
Resolved	14 (4)	11 (3)
Time to onset (median, days)	83 (1-268)	68 (1-313)
Insomnia	10 (3)	11 (3)
Depression, bipolar, suicide/suicidal	12 (3)	6 (2)
Depression	8 (2)	6 (2)
Bipolar	0	0
Suicide/suicidal behavior	5 (1)	2 (1)
Nightmare, abnormal dreams	1 (<1)	1 (<1)
Anxiety	4 (1)	5 (1)
Sleep disorder	2 (1)	2 (1)

Source: AE ISS dataset

Insomnia was observed in 3% of subjects in each arm. All DTG events were grade mild or moderate in severity; none resulted in drug discontinuation, and all were assessed as unrelated to study agent. No completed suicides were reported. Suicidal behavior AEs were observed in five DTG and two RAL subjects. All subjects had pre-existing psychiatric disorder including depression, anxiety, bipolar disorder, personality disorder or post-traumatic stress disorder; and all were receiving at least one agent to manage the psychiatric disorder. None of the DTG events were assessed by the investigators as drug-related; none resulted in drug discontinuation; and none of the events were reported to recur. In contrast, treatment was discontinued for suicidal behavior in one RAL subject: this subject experienced recurrent suicidal ideation, initially on day 9 after starting RAL and subsequently on day 235. The investigator assessed the events were related to RAL. The median time to onset of these events was 95 days (7-268 days) for DTG and 56 days (9-102 days) for RAL.

Treatment Experienced INI Experienced trials

In subjects dosed DTG BID, psychiatric AESI were observed in 10% subjects (Table 65). The majority of events were either grade 1 or 2 in severity with a median time to onset of 54 days; and the majority of AEs were considered unrelated to DTG.

Table 65: Psychiatric AEs in INI-experienced trials

	Total 50 BID N=207	**Viking-3 50 BID N=183**	**Viking-Pilot 50 BID N=24**	**Viking-Pilot 50 QD N=27**
Subjects with psychiatric AE	24 (12)	16 (2)	8 (33)	5 (19)
Psychiatric AE of interest	**20 (10)**	**14 (7)**	**6 (25)**	**5 (19)**
Fatality	1 (<1)	0	1 (4)	0
SAE	1 (<1)	0	1 (4)	0
Discontinuation	1 (<1)	0	1 (4)	0
Related	7 (3)	6 (3)	1 (4)	1 (4)
Grade 3 or 4	1 (<1)	0	1 (4)	1 (4)
Resolved	10 (5)	5 (3)	5 (21)	4 (15)
Time to onset (median, days)	54 (1-311)	29 (2-225)	99 (1-311)	171 (1-368)
Insomnia	10 (5)	9 (5)	1 (4)	5 (19)
Depression, bipolar, suicidal	4 (2)	1 (<1)	3 (12)	0
Depression	3 (2)	1 (<1)	2 (8)	0
Bipolar	0	0	0	0
Suicide/suicidal behavior	1 (<1)	0	1 (4)	0
Anxiety	4 (2)	3 (2)	1 (4)	0
Sleep disorder	3 (2)	2 (2)	1 (4)	0
Abnormal dreams, nightmare	5 (2)	4 (2)	0	1 (4)

Source: AE ISS dataset

One completed suicide observed in cohort 2 of Viking-pilot was considered unrelated to DTG (elaborated below). This grade 4 AE was also the only discontinuation in subjects dosed DTG BID.

One completed suicide in cohort 2 of Viking-pilot is described in section 7.3.2 and briefly summarized here. Subject 2463, a 45-year-old male, committed suicide 7 months after initiating treatment with DTG, DRV/r, and ETR. The subject had a history of depression for which he was taking escitalopram. There was no prior history of suicidal ideation or attempts. The event was associated with recent loss of his apartment and job. The cause of death was ethylene glycol and drug intoxication. The investigator assessed the event as unrelated to study drug. In my opinion, the relatively protracted timing of the event since DTG initiation is less suggestive of a drug-induced process. Recent job loss and homelessness suggest social stressors that may have triggered the event. Based on the available information, I agree with the investigator's assessment that the event does not appear related to DTG.

Insomnia AE was observed in 5% subjects. All were mild to moderate in severity, with the median time to onset 11 days. In 4 out of 10 subjects, insomnia was assessed as related study drug, although no subjects discontinued treatment.

Overall, the 24-week psychiatric AE profile in BID dosed subjects was not notably different from observations in treatment-experienced subjects receiving DTG QD in the Sailing trial (frequency 10% in BID subjects and 8% in QD dosed subjects). Event characteristics were also generally similar in terms of severity, time to onset, and proportion resolved by 24 week data cut-off. One completed suicide in a subject with pre-existing depression occurred 7 months after DTG was started. As discussed above, available case information does not suggest deteriorating mental health in the preceding on-treatment period and recent social stressors such as employment loss may have triggered the event. The frequency and characteristics of insomnia with BID dosing were also similar to QD dosed treatment-experienced subjects.

Psychiatric Events Analysis: Overall Summary and Labeling Recommendations

- In the treatment naïve subjects, the frequency of psychiatric events in the DTG arms varied between the two trials despite similar population characteristics. Even though both treatment-naïve trials were double-blind, the relatively higher event reporting in Single, where Atripla was the comparator, may be explained by investigator/participant knowledge that efavirenz-based therapy was a treatment option as well as use of specific psychiatric questionnaires in this trial. Relatively lower event rates in the treatment-experienced trials (11-12% in treatment experienced, 23% in treatment-naïve) may be related to the disproportionate incidence from Single and differences related to the cumulative duration of follow-up (24 vs. 48 weeks). Psychiatric events with DTG occurred less

frequently than with Atripla; and the DTG event rates were generally comparable to RAL.

- Despite incidence differences, the overall event characteristics were similar across trials. Majority of DTG events were mild or moderate in severity, and did not result in drug discontinuation. No striking differences in the frequency or pattern of AEs were observed between subjects receiving DTG QD or BID, and no exposure-response relationships were identified.

- Only one completed suicide was reported in the entire DTG clinical development program in a subject receiving DTG BID. The event occurred in a subject with pre-existing depression about 7 months after treatment initiation. Social stressors including unemployment were reported in the time period preceding suicide, and the event was assessed as unrelated to DTG. No suicidal behavior events were observed in DTG arms in both treatment naïve trials. In the treatment-experienced, INI naive trial, suicidal behavior AEs was observed in 5 and 2 subjects receiving DTG and RAL, respectively. All DTG events occurred in the context of pre-existing psychiatric illnesses. Events were either triggered by recent social stressors, or occurred in association with alcohol or illicit drug abuse, or in subjects with prior history of suicidal ideation. None of the events resulted in DTG discontinuation or were assessed as drug-related. In contrast, one of the 2 RAL events, a case of recurrent suicidal ideation, was considered drug-related and resulted in RAL discontinuation.

  Although an excess of suicidal behavior events were observed with DTG relative to RAL in one trial, Sailing; this trend was not observed in the other trial, Spring-2, comparing DTG and RAL. Importantly, none of the DTG events in Sailing were assessed as causally related or resulted in drug discontinuation. In contrast, one RAL event which recurred on treatment was assessed as drug-related and resulted in RAL discontinuation. Relatively longer median time to onset was observed for DTG events compared to RAL, a finding which also suggests that DTG events were less likely to be drug-related compared to RAL events. Suicidal events are labeled for RAL. At this time, labeling for DTG is not warranted based on the above-mentioned differences in the AE profile of the two drugs.

- Insomnia was the single most frequent psychiatric AE in DTG subjects, observed in 3-11% subjects depending on the trial. The frequency was comparable to RAL; and higher than observed with EFV. Although no discontinuations due to insomnia were reported; some events were assessed as related to DTG. Insomnia events will be displayed in the label in the Common ADR table in section 6.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Analysis of the overall treatment-naïve phase 3 safety database for trends in adverse reporting was completed. The most frequently reported SOCs were Infections and Infestations, Gastrointestinal Disorders and Nervous System Disorders for both SPRING-2 and SINGLE. Additionally in SINGLE, Psychiatric Disorders and Skin and Subcutaneous Tissue Disorders were more frequently reported.

The following figures provide an analysis of the Risk Difference (DTG-Comparator) per 100 subjects by SOC between DTG and the respective comparator arm (RAL or Atripla). For example in SINGLE, for every 100 reported Psychiatric Events, DTG would be expected to have 9.5 less events/100 compared to Atripla. Any dots on the left side of the figure favor DTG and dots on the right side favor the comparator. The size of the dot indicates the proportion of events reported, larger dots mean larger proportion of events (e.g. in SPRING-2, Infections and Infestations DTG= 232/342 events and RAL= 229/345 events compared to Endocrine Disorders DTG=0/342 events and RAL=1/345 events).

These figures highlight that generally, DTG and RAL were comparable across reported safety events. In SPRING-2, DTG is generally comparable to RAL. In SINGLE, Nervous System Disorders (risk difference -24.7 per 100), Psychiatric Disorders (risk difference -9.5 per 100) and Skin and Subcutaneous Tissue Disorders (risk difference -11.6 per 100) all favor DTG with confidence limits not crossing zero. These differences are driven by the higher proportion of reports of the labeled events of dizziness, abnormal dreams and rash experience by Atripla subjects. In contrast, there is a small risk difference favoring Atripla for Infections and Infestations (risk difference 8.3 per 100); however, further analysis of the preferred terms does not reveal any trend or specific infectious etiology related to DTG use. Instead, the difference appears due to a higher overall cumulative reporting rate for DTG (63%) compared to Atripla (55%). This illustrates the need for caution in interpretation of these analyses, particularly because the majority of events are reported at low rates that limit the ability to make meaningful comparisons. However, these analyses are useful to demonstrate the overall trends.

Figure 13: SPRING-2 - Risk Difference per 100 subjects by SOC On-Treatment Events

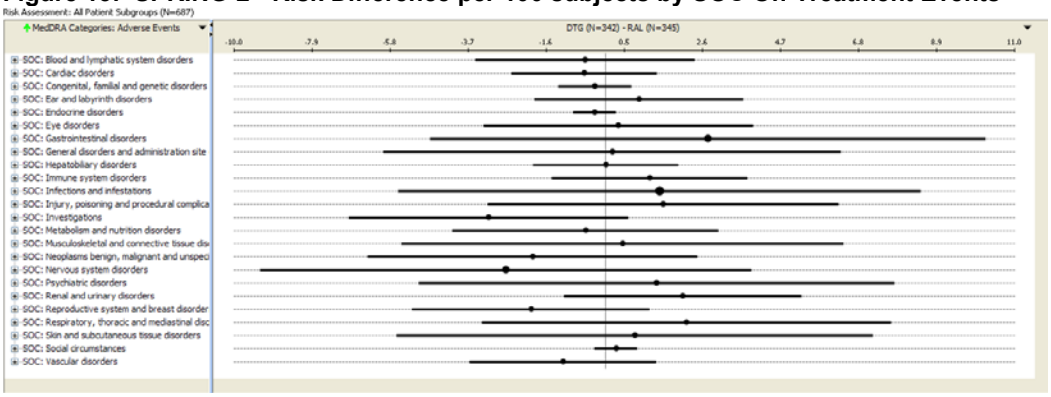
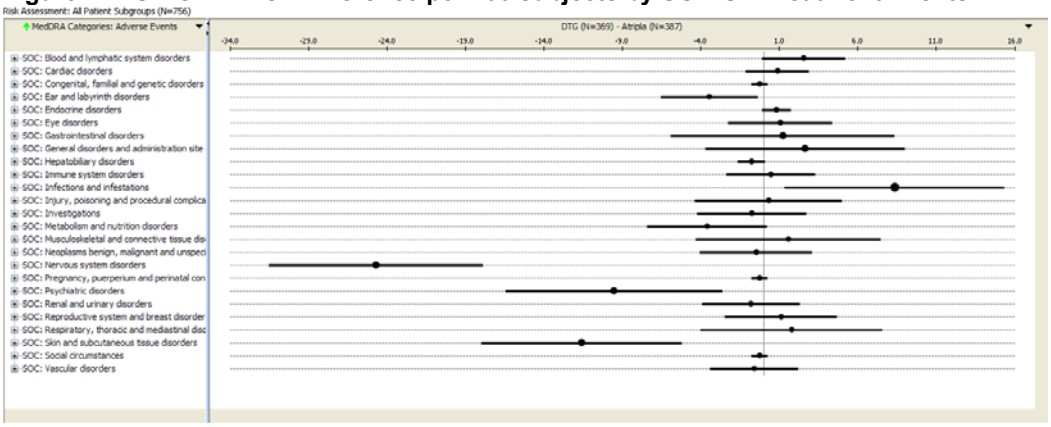


Figure 14: SINGLE- Risk Difference per 100 subjects by SOC On-Treatment Events



Further analysis was completed to determine if events occurring and recorded as pre- and/or post-treatment may show important safety trends and to ensure proper coding of adverse events by the Applicant. As demonstrated in the following figures, there were no significant or alarming trends and the evaluation shows overlapping confidence intervals for these Risk Differences.

Figure 15: SPRING-2 - Risk Difference per 100 subjects by SOC Pre- and Post-Treatment Events

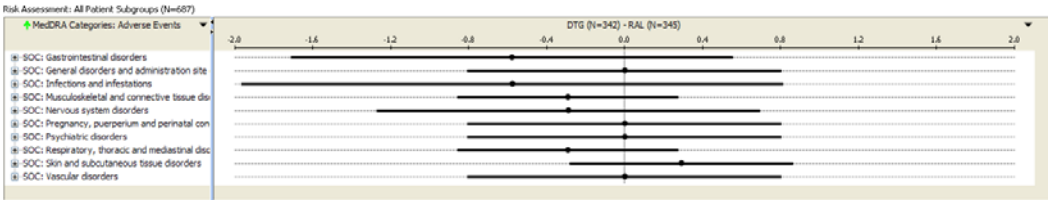
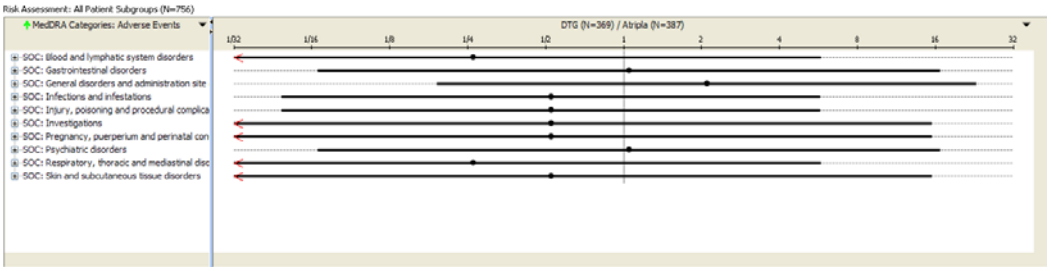


Figure 16: SINGLE- Risk Difference per 100 subjects by SOC Pre- and Post-Treatment Events



Analyses by SOC for on-treatment risk differences for reported AEs were completed for the following subgroups for both SPRING-2 and SINGLE: gender, race, ethnicity, age and Baseline CDC classification (A, B or C). Overall, there were no clinically meaningful observed differences or new safety trends in these subgroup analyses. Additionally, for many of the subgroups, the numbers were too small to allow for meaningful comparisons. The figures from these analyses are included in the Appendix (Section 9.5).

Common adverse events were also evaluated by preferred term. The following analysis evaluates the overall treatment naïve DTG population in comparison to the pooled comparators (RAL and Atripla) to determine if any particular events were reported in a larger proportion of subjects. The following table summarizes the results. As highlighted, only insomnia is observed in a higher proportion of DTG subjects over the comparator arms. Dizziness and abnormal dreams are observed more frequently in the comparator group, which is driven by adverse event reporting for Atripla. All other events are comparable between the treatment groups. Diarrhea, nasopharyngitis, nausea, headache and insomnia were the most common (>10%) AEs reported from the phase 3 treatment-naïve population.

Table 66: Summary of Common AEs, all grades, by Frequency (≥5% of Subjects in the combined DTG group) - Treatment-Naïve Population

Preferred Term	DTG N=817	Comparator N=824
Diarrhea	121 (15)	126 (15)
Nausea	119 (15)	111 (13)
Nasopharyngitis	115 (14)	114 (14)
Headache	108 (13)	106 (13)
Insomnia	*86 (11)*	*61 (7)*
Fatigue	74 (9)	69 (8)
Upper respiratory tract infection	65 (8)	69 (8)
Dizziness	60 (7)	172 (21)
Pyrexia	44 (5)	44 (5)
Depression	44 (5)	45 (5)
Cough	42 (5)	47 (6)
Bronchitis	42 (5)	33 (4)
Abnormal dreams	42 (5)	80 (10)
Back pain	39 (5)	37 (4)
Oropharyngeal pain	38 (5)	29 (4)

Source: AE ISS analysis dataset

Additional analyses were completed to evaluate AEs by preferred terms and events that were considered related to study drug by the Investigator. The following table presents the Adverse Drug Reactions (ADRs; which by definition implies drug relatedness), grade 2 – 4 that were treatment emergent or occurred within 30 days of study drug discontinuation and were at ≥ 2% frequency in any treatment arm. Similar to the overall evaluation of AEs, insomnia is the only event that is reported in a higher proportion of DTG subject compared to Atripla. Nausea, dizziness and rash were reported at higher frequencies in Atripla exposed subjects compared to DTG exposed subjects. In SPRING-2, the ADRs were reported at similar rates for DTG and RAL.

Table 67: Adverse Drug Reactions, Grade 2-4 and Treatment Emergent or Within 30 Days of Discontinuation of Study Drug and ≥2% Frequency

	SPRING – 2		SINGLE		
Preferred Term	**DTG 50 mg QD + 2NRTI N=403 n (%)**	**RAL 400 mg BID + 2 NRTI N=405 n (%)**	**DTG 50 mg + ABC/3TC QD N=414 n (%)**	**Atripla QD N=419 n (%)**	**Total DTG N=817 n (%)**
Any Event	***23 (6)***	***28 (7)***	***53 (13)***	***114 (27)***	***76 (9)***
Insomnia	1 (<1)	1 (<1)	13 (3)	9 (2)	14 (2)
Headache	3 (1)	4 (1)	7 (2)	9 (2)	10 (1)
Nausea	6 (2)	5 (1)	3(1)	12 (3)	9 (1)
Diarrhea	2(<1)	2(<1)	4 (1)	7 (2)	6 (1)
Dizziness	1(<1)	1(<1)	2 (<1)	19 (5)	3 (<1)
Abnormal Dreams	1(<1)	1(<1)	2 (<1)	8 (2)	3 (<1)
Rash	0	3 (1)	2 (<1)	25 (6)	2 (<1)
Vertigo	0	1(<1)	0	7 (2)	0

*Adverse Drug Reaction defined as adverse event caused by the drug
Source: AE ISS analysis dataset

In order to evaluate the adverse reaction label presentation, additional evaluation was conducted to include the grade 1-4 AEs considered related. The rationale for this analysis was to consider whether the more frequently reported drug-related grade 1 events would provide a more comprehensive and clinically relevant description of the observed safety in the treatment-naïve trials. The following table summarizes this overall grade 1-4 analysis.

Table 68: Adverse Drug Reactions, Grade 1-4 and Treatment Emergent or Within 30 Days of Discontinuation of Study Drug and ≥2% Frequency in Any Treatment Arm

	SPRING – 2		SINGLE		
MedDRA preferred term	DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)	Total DTG N=817 n (%)
Nausea	40 (10)	43 (11)	42 (10)	49 (12)	82 (10)
Insomnia	5 (1)	2 (<1)	41 (10)	23 (5)	46 (6)
Headache	18 (4)	16 (4)	22 (5)	31 (7)	40 (5)
Dizziness	11 (3)	16 (4)	28 (7)	133 (32)	39 (5)
Diarrhea	14 (3)	17 (4)	23 (6)	36 (9)	37 (5)
Abnormal dreams	9 (2)	6 *(1)*	26 (6)	64 (15)	35 (4)
Fatigue	4 (1)	11 (3)	26 (6)	26 (6)	30 (4)
Vomiting	10 (2)	7 (2)	9 (2)	10 (2)	19 (2)
Flatulence	8 (2)	4 *(1)*	10 (2)	7 (2)	18 (2)
Pruritus	5 (1)	3 *(1)*	8 (2)	6 *(1)*	13 (2)
Depression	1 (<1)	1 (<1)	10 (2)	9 (2)	11 *(1)*
Abdominal discomfort	8 (2)	1 (<1)	3 *(1)*	2 (<1)	11 *(1)*
pooled RASH	*6* (2)	*9* (2)	*5 (1)*	*50 (12)*	*11 (1)*
Nightmare	2 *(<1)*	1 *(<1)*	8 (2)	14 (3)	10 *(1)*
Abdominal distension	3 *(1)*	4 *(1)*	7 (2)	6 *(1)*	10 *(1)*
Asthenia	2 *(<1)*	8 (2)	8 (2)	5 *(1)*	10 *(1)*
Abdominal pain upper	2 *(<1)*	0	6 *(1)*	7 (2)	8 *(1)*
Gastro-esophageal reflux disease	0	3 *(1)*	8 (2)	0	8 *(1)*
Somnolence	0	2 *(<1)*	7 (2)	19 (5)	7 *(1)*
Sleep disorder	1 *(<1)*	0	6 *(1)*	9 (2)	7 *(1)*
Decreased appetite	2 *(<1)*	5 *(1)*	4 *(1)*	9 (2)	6 *(1)*
Anxiety	1 *(<1)*	2 *(<1)*	4 *(1)*	11 (3)	5 *(1)*
Vertigo	3 *(1)*	4 *(1)*	1 *(<1)*	16 (4)	4 *(<1)*

Source: AE ISS analysis dataset

Based on this analysis, we believe that inclusion of the ADRs that occurred in ≥3% of subjects in any treatment arm highlight the most clinically meaningful differences observed between the treatment arms in the treatment-naïve trials. Therefore, this analysis and cut point will be proposed for product labeling. The above table highlights in yellow ADRs that occurred in ≥ 3% in any treatment arm. When assessing grade 1-4 ADRs, DTG has a higher frequency of reporting for insomnia compared to Atripla or RAL. As shown in the table, for SINGLE, insomnia was reported 5% more frequently in the DTG arm compared to Atripla (10% compared to 5%, respectively). This difference is not appreciable when only grade 2-4 events are included in the proposed labeling ADR table. Additionally, use of the 3% cut point for the ADR table in the proposed labeling will also capture the large difference observed in rash events for Atripla in comparison to DTG in SINGLE. However, the reporting rates for DTG for the remaining grade 1-4 ADRs are either comparable or less frequently observed than for the comparators, RAL or Atripla.

Treatment Experienced, INI Naïve

In the Sailing trial, the same DTG dose 50 mg QD was evaluated in a relatively advanced and treatment-experienced HIV-infected population compared to treatment-naïve trials discussed previously. The profile for common AEs (regardless of causality or grade) was similar to the profile observed in treatment-naïve trials. The profiles for grade 2-4 ADRs and grade 1-4 ADRs in the Sailing trial were also similar to profiles observed in treatment-naïve trials. Based on similar observations in the Sailing trial and the treatment-naïve trials, and because a comprehensive ADR display (grades 1-4 in at least 3% subjects) is recommended for treatment-naïve trials, the team recommends presentation of grade 1-4 ADRs for the treatment-experienced, INI-naïve population in text format in the label.

Frequently occurring common AEs (in at least 5% subjects) and grade 1-4 ADRs in at least 2% subjects in Sailing are discussed below.

Table 69 displays common AEs regardless of causality or grade. At least one AE was observed in 75% and 78% of subjects in the DTG and RAL arms, respectively. Among these, AEs observed more frequently in the DTG arm compared to RAL arm were diarrhea (20% DTG, 17% RAL), upper respiratory tract infection (11% DTG, 9% RAL), headache (9% DTG, 8% RAL), cough (8% DTG, 6% RAL), urinary tract infection (7% DTG, 5% RAL), and nasopharyngitis (6% DTG, 5% RAL).

Table 69: Common AEs (all severity, all causality) in ≥ 5% subjects, Sailing

Preferred Term	DTG N=354	RAL N=361
Subjects with at least 1 AE	**265 (75%)**	**281 (78%)**
Diarrhea	72 (20)	62 (17)
Upper respiratory tract infection	38 (11)	29 (8)
Headache	31 (9)	29 (8)
Cough	29 (8)	23 (6)
Nausea	26 (7)	28 (8)
Urinary tract infection	26 (7)	18 (5)
Influenza	21 (6)	21 (6)
Nasopharyngitis	21 (6)	18 (5)
Rash	18 (5)	17 (5)
Vomiting	17 (5)	20 (6)
Fatigue	15 (4)	23 (6)

*in ≥ 5% subjects in either study arm
Source: AE ISS dataset

Drug-related AEs of grade 1-4severity observed in at least 2% subjects in either treatment arm are presented in table 70. Among these, diarrhea was the only ADR observed more frequently in the DTG arm (8%) compared to RAL arm (6%).

Table 70: Drug-related Grade 1-4 AEs observed in ≥ 2% subjects in either treatment arm week 24, Sailing

Preferred Term	DTG N=354	RAL N=361
Diarrhea	30(8)	22(6)
Nausea	12(3)	16(4)
Vomiting	7(2)	11(3)
Headache	7(2)	7(2)
Dizziness	3(1)	6(2)
Fatigue	4(1)	10(3)
Rash	5(1)	6(2)

Source: AE ISS dataset

Treatment Experienced, INI Experienced

Common AEs (regardless of causality or grade) observed in at least 5% INI-experienced subjects receiving DTG 50 BID are displayed in Table 70. Adverse events were observed in 82% of subjects. Diarrhea was the most common AE observed in 16% of subjects. Overall, these AEs were similar in type to common AEs observed in the DTG arm in Sailing trial (table 64 above), with the exception of greater frequency of bronchitis, pyrexia, injection site reaction and insomnia Of note, apart from insomnia the remaining AEs of bronchitis, pyrexia, and injection site reaction were not assessed to be drug-related in 2 or more subjects (refer to the display in the following table 72). It may

be surmised these events likely reflect co-morbid conditions or concurrent use of injectable agents (e.g., T-20), which is not unexpected for the studied population.

Table 71: Common AEs (all severity, all causality) in ≥ 5% subjects, INI-experienced trials

Preferred Term	Total 50 BID N=207	Viking-3	Viking-Pilot	Viking-Pilot
		50 BID N=183	50 BID N=24	50 QD N=27
Subjects with ≥ 1 AE	**170 (82)**	**147 (80)**	**23 (96)**	**26 (96)**
Diarrhea	34 (16)	25 (14)	9 (38)	5 (19)
Bronchitis	19 (9)	13 (7)	6 (25)	4 (15)
Headache	18 (9)	16 (9)	2 (8)	4 (15)
Pyrexia	18 (9)	13 (7)	5 (21)	4 (15)
Nausea	19 (9)	17 (9)	2 (8)	2 (7)
Cough	17 (8)	13 (7)	4 (17)	3 (11)
Fatigue	16 (8)	12 (7)	4 (17)	1 (4)
Insomnia	10 (5)	9 (5)	1 (4)	5 (19)
Nasopharyngitis	11 (5)	10 (5)	1 (4)	2 (7)
Injection site reaction	11 (5)	9 (5)	2 (8)	1 (4)
URTI	11 (5)	9 (5)	2 (8)	1 (4)
Rash	11 (5)	10 (5)	1 (4)	0
Asthenia	7 (3)	5 (3)	2 (8)	5 (19)

Source: AE ISS dataset

Drug-related grade 2-4 AEs observed in at least 2% subjects receiving DTG BID are displayed in Table 72. These include ADRs of diarrhea and headache, each observed in 2% subjects. In the Sailing trial, which also enrolled treatment-experienced subjects, diarrhea and headache were each observed in 1% or fewer subjects.

Table 72: Drug-related grade 2-4 AEs in ≥ 2% subjects in INI-experienced trials

Preferred Term	Total 50 BID N=207	Viking-3	Viking-Pilot	Viking-Pilot
		50 BID N=183	50 BID N=24	50 QD N=27
Subjects with ≥ 1 AE	**38 (18)**	**35 (19)**	**3 (13)**	**5 (19)**
Diarrhea	4 (2)	4 (2)	0	1 (4)
Headache	3 (2)	3 (2)	0	0

Source: AE ISS dataset

As the higher 50 mg BID dose was evaluated in this population and because of limitations inherent to these trials (limited number of subjects and lack of comparator arm), an additional analysis was performed for grade 1-4 ADRs occurring in at least 2 subjects dosed DTG 50 mg BID. As shown in Table 73 below, the additional ADRs identified in this analysis were similar in type to those observed in treatment-naïve trials or the Sailing trial. The only exception is the AE ‘ALT increased’, a preferred AE term

which represents a laboratory abnormality and not a clinical event. All laboratory abnormalities were reviewed separately as discussed in section 7.4.2, and specifically, hepatic laboratory abnormalities were reviewed in detail in section 7.3.5 under Hepatobiliary Analysis.

Table 73: Treatment-Emergent Adverse Events Considered Related, Grade 1-4, Occurring in ≥ 2 subjects – Week 24 Treatment-Exp, INI-experienced

Preferred Term	Total 50 BID N=207	Viking-3	Viking-Pilot
		50 BID N=183	50 BID N=24
Subjects with ≥ 1 AE	**38 (18)**	**35 (19)**	**3 (13)**
Diarrhea	5 (2)	4 (2)	1 (4)
Headache	4 (2)	3 (2)	1 (4)
Fatigue	2 (1)	2 (1)	0
Insomnia	2 (1)	2 (1)	0
ALT increased	2 (1)	2 (1)	0
Nausea	2 (1)	2 (1)	0
Rash	3 (1)	2 (1)	1 (4)

Source: AE ISS dataset

In summary, grade 2-4 ADRs observed in at least 2% subjects were diarrhea and headache. The ADR profile for DTG 50 mg BID was generally similar to observations in the treatment-naïve and treatment-naïve, INI-naïve populations. The Applicant's proposal to present grade 2-4 ADRs in at least 2% subjects in Viking-3 is appropriate. Further, the review team recommends inclusion of language stating treatment-emergent ADRs in Viking-3 were generally similar to observations with the 50 mg QD dose. Of note, presenting only Viking-3 ADR findings (b) (4) is acceptable (b) (4) For these reasons, the reviewer agrees with presenting Viking-3 data only for treatment-experienced, INI-experienced subjects in label Drug Reactions section.

7.4.2 Laboratory Findings

This section presents results of grade 2-4 laboratory analysis observed in the phase 3 trials. Analysis of the DTG lipid profile, specifically exploring changes from baseline in key lipid parameters, was also performed; results of this analysis are separately presented at the end of the laboratory findings section.

Analysis of Graded laboratory abnormalities

Grade 2-4 analysis of select laboratory parameters occurring in either at least 2% subjects or considered as clinically relevant, are presented below. In general, results of these analyses reveal minor differences (≤1% for some variables) from the Applicant's revised proposed label results (submitted 3/28/2013). These differences are attributable to inclusion or exclusion of some events which occurred in the 30 day post-treatment follow-up window. Of note, liver biochemistries (ALT, AST, total bilirubin) and creatine kinase analysis are presented in the relevant section 7.3.5.

Treatment Naïve

In general, the treatment-emergent laboratory abnormalities for DTG were comparable to RAL and Atripla. Evaluation of grade 1 laboratory abnormalities revealed similar trends to the grade 2-4 results with DTG arms being comparable to RAL and Atripla arms, respectively. The following table provides the grade 2-4 laboratory results for the treatment naïve phase 3 studies that were ≥2% in frequency in any treatment arm. Generally, grade 3 and 4 laboratory abnormalities were reported at a low rate of ≤5% for DTG subjects. Additionally, the reported abnormalities were comparable between DTG and RAL and Atripla, respectively. There were a low proportion of subjects who reported grade 2-4 elevations of lipase and there were no clinical reports of pancreatitis in any DTG exposed treatment-naïve subjects.

Table 74: Treatment Emergent Worst Grade Analysis for Grade 2-4 and in ≥2% of Subjects from Any Treatment Arm

		SPRING-2		SINGLE	
Laboratory Test	**Toxicity grade**	**DTG 50 mg QD + 2NRTI N=403 n (%)**	**RAL 400 mg BID + 2 NRTI N=405 n (%)**	**DTG 50 mg + ABC/3TC QD N=414 n (%)**	**Atripla QD N=419 n (%)**
Cholesterol (MG/DL)	Grade 2	20 (5)	16 (4)	28 (7)	25 (6)
	Grade 3	4 (1)	0	1 (<1)	3 (<1)
Glucose (MG/DL)	Grade 2	23 (6)	19 (5)	30 (7)	19 (5)
	Grade 3	3 (1)	6 (1)	5 (1)	1 (<1)
	Grade 4	0	1 (<1)	0	0
Hyperglycemia (MMOL/L)	Grade 2	20 (5)	16 (4)	27 (7)	18 (4)
	Grade 3	2 (<1)	5 (1)	5 (1)	1 (<1)
	Grade 4	0	0	0	0
LDL Cholesterol calculation (MG/DL)	Grade 2	10 (2)	8 (2)	19 (5)	16 (4)
	Grade 3	4 (1)	2 (<1)	6 (1)	5 (1)
Lipase (U/L)	Grade 2	22 (5)	24 (6)	33 (8)	29 (7)
	Grade 3	3 (1)	7 (2)	7 (2)	5 (1)
	Grade 4	2 (<1)	6 (1)	4 (1)	1 (<1)

Laboratory Test	Toxicity grade	SPRING-2		SINGLE	
		DTG 50 mg QD + 2NRTI N=403 n (%)	RAL 400 mg BID + 2 NRTI N=405 n (%)	DTG 50 mg + ABC/3TC QD N=414 n (%)	Atripla QD N=419 n (%)
Phosphorus, inorganic (MMOL/L)	Grade 2	27 (7)	39 (10)	35 (8)	51 (12)
	Grade 3	4 (1)	5 (1)	5 (1)	11 (3)
Total Neutrophils (GI/L)	Grade 2	12 (3)	11 (3)	9 (2)	15 (4)
	Grade 3	5 (1)	3 (<1)	5 (1)	7 (2)
	Grade 4	3 (1)	3 (<1)	2 (<1)	5 (1)
Triglycerides (MG/DL)	Grade 2	1 (<1)	6 (1)	3 (<1)	8 (2)
	Grade 3	1 (<1)	0	5 (1)	0
	Grade 4	1 (<1)	0	0	1 (<1)

Source: Laboratory ISS dataset

Treatment Experience, INI Naive

Select grade 2-4 laboratory abnormalities observed in the Sailing trial are displayed in the table below. Overall, grade 3-4 toxicities were observed 2% or fewer subjects in the DTG arm. Grade 2 toxicities were also generally balanced between DTG and RAL arms. Analysis of grade 1 toxicities revealed similar findings as observed with grade 2-4 analysis.

Table 75: Select laboratory abnormalities grade 2-4 and maximum toxicity grade change from baseline, Week 24 analysis

	DTG N=354	RAL N=361
Hemoglobin		
Grade 4	1 (<1)	2 (1)
Grade 3	0	1 (<1)
Grade 2	4 (1)	2 (1)
Platelet count		
Grade 4	0	1 (<1)
Grade 3	1 (<1)	1 (<1)
Grade 2	6 (2)	8 (2)
ANC		
Grade 4	3 (1)	3 (1)
Grade 3	7 (2)	4 (1)
Grade 2	9 (2)	8 (2)

	DTG N=354	**RAL** N=361
Lipase		
Grade 4	1 (<1)	3 (1)
Grade 3	3 (1)	3 (1)
Grade 2	19 (5)	23 (6)
Glucose		
Grade 2	33 (9)	24 (7)
Grade 3	3 (1)	7 (2)
Grade 4	0	1 (<1)
Hyperglycemia		
Grade 2	30 (8)	23 (6)
Grade 3	3 (1)	7 (2)
Grade 4	0	1 (<1)
Total cholesterol		
Grade 2	45 (13)	51 (14)
Grade 3	9 (3)	13 (4)
LDL cholesterol calculated		
Grade 2	25 (7)	30 (8)
Grade 3	8 (2)	13 (4)
Grade 4		
Triglycerides		
Grade 2	19 (5)	18 (5)
Grade 3	6 (2)	6 (2)
Grade 4	6 (2)	1 (<1)

Source: Laboratory ISS dataset

Treatment Experience, INI Experienced

In subjects dosed DTG 50 mg BID, grade 2 laboratory abnormalities were observed 2-3% subjects. As displayed in the following table, Grade 3-4 laboratory toxicities were observed in 2% or fewer subjects, with the exception of lipase elevations. Grade 3-4 lipase elevations were observed in 8% of subjects; all were cases of asymptomatic lipase increases. Further, no cases of clinical pancreatitis were reported in the 50 mg BID group. Analysis of grade 1 toxicities revealed similar findings as observed with grade 2-4 analysis. Overall, the laboratory safety profile of DTG dosed 50 mg BID was generally similar to the DTG 50 mg QD arm in Sailing.

Table 76: Select laboratory abnormalities grade 2-4 and maximum toxicity grade change from baseline, Week 24 analysis

	Total 50 BID N=207	Viking-3 50 BID N=183	Viking-Pilot 50 BID N=24
Hemoglobin			
Grade 4	0	0	0
Grade 3	1 (<1)	0	1 (4)
Grade 2	2 (1)	2 (1)	0
Platelet count			
Grade 4	0	0	0
Grade 3	1(<1)	1 (<1)	0
Grade 2	4 (2)	3 (2)	1 (4)
ANC			
Grade 4	2(1)	1 (1)	1 (4)
Grade 3	1(<1)	1 (1)	0
Grade 2	7 (3)	6 (1)	1 (4)
Lipase			
Grade 4	5 (2)	4 (2)	1 (4)
Grade 3	12 (6)	10 (5)	2 (7)
Grade 2	21 (10)	17 (9)	4 (15)
Total cholesterol			
Grade 2	20 (10)	17 (9)	3 (13)
Grade 3	5 (2)	4 (2)	1 (4)
LDL cholesterol calculated			
Grade 2	7 (3)	6 (3)	1 (4)
Grade 3	3 (1)	2 (1)	1 (4)
Triglycerides			
Grade 2	2 (1)	2 (1)	0
Grade 3	3 (1)	1 (1)	2 (8)
Glucose			
Grade 2	22 (11)	21 (11)	2 (8)
Grade 3	4 (2)	4 (2)	0
Hyperglycemia			
Grade 2	22 (11)	20 (11)	2 (8)
Grade 3	4 (2)	4 (2)	0

Source: Laboratory ISS dataset

Lipid Analysis

Dolutegravir effects on the lipid profile were assessed for treatment-naïve trials and for the treatment-experienced, INI naïve trial Sailing. Analysis of the mean change from baseline in fasting total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides was performed. Of note, the analyses did not exclude subjects who initiated lipid-lowering medications during the treatment period. The analyses use observed data and does not exclude or impute subjects who initiate lipid-lowering medications during study. Results for 48 week lipid analysis from treatment-naïve trials are displayed below, followed by 24 week findings for treatment-experienced trials.

Treatment Naïve

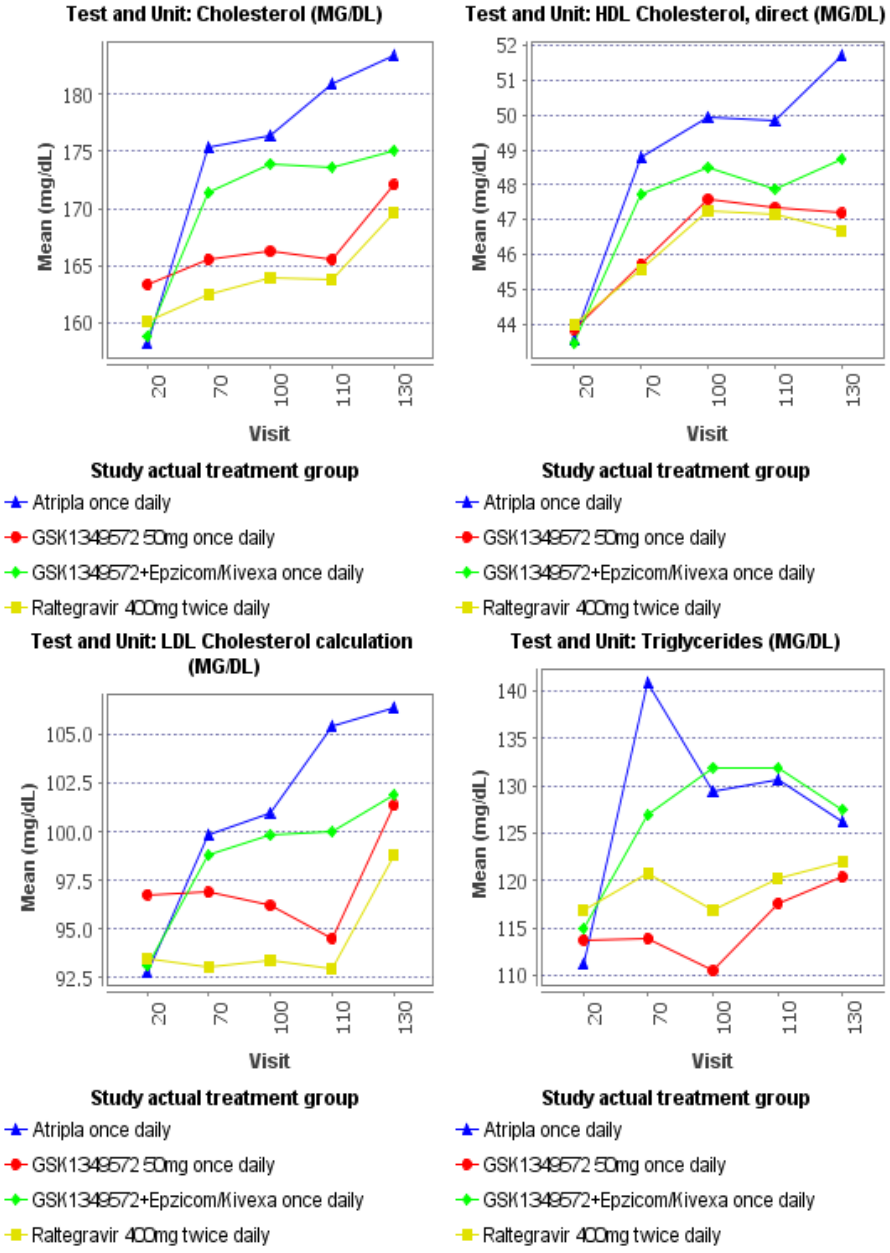
The following table and graphs provide the mean change from baseline for fasting total cholesterol, LDL cholesterol; HDL cholesterol and triglycerides for the treatment-naïve phase 3 trials through Week 48. Generally, there were small increases of total cholesterol, LDL, HDL and triglycerides in all treatment arms over the 48 week treatment period. DTG and RAL subjects experienced similar increases, while generally Atripla exposed subjects had slightly higher increases. It is important to note, however, that these general trends of increases were not associated with an increase in clinical cardiac adverse events. Results of my observed analysis varies from the Applicant's proposed labeling due to the fact that none of the data in my analysis is imputed and represents observed data for subjects who had a value at baseline and Week 48. Additionally, there are likely small differences in the window for the Week 48 analysis and data cut points. However, overall, the differences between the analyses are small, remain proportional between the treatment arms and are not clinically significant differences.

Table 77: Mean Change from Baseline (Observed Data) in Lipid Value in Treatment-Naive Subjects -Week 48 Analysis (Fasting Blood Draws Only)

	SPRING-2		SINGLE	
Laboratory Parameter Preferred Term	TIVICAY 50 mg Once Daily + 2 NRTIs (N = 403)	Raltegravir 400 mg Twice Daily + 2 NRTIs (N = 405)	TIVICAY 50 mg + EPZICOM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
Cholesterol (mg/dL)	8.7	9.5	16.3	25.1
HDL cholesterol (mg/dL)	3.2	2.7	5.3	8.2
LDL cholesterol (mg/dL)	4.6	5.4	8.8	13.6
Triglycerides (mg/dL)	6.6	5.0	12.6	15.0

Source: Laboratory ISS dataset

Figure 17: Changes in mean lipid parameters over 48 weeks, Treatment naive



Source: Laboratory ISS dataset [SPRING-2: DTG in red dot, RAL in yellow square; SINGLE: DTG green diamond, Atripla blue triangle]

Treatment Experienced, INI Naïve

Lipid analysis of 24 week data from treatment-experienced, INI-naïve trial Sailing was also performed. As shown in table 78, small increases from baseline in mean total cholesterol, mean LDL cholesterol, mean HDL cholesterol and mean triglycerides were observed in the DTG arm. Increases of similar magnitude change were also observed in the RAL arm. Overall, the findings were similar to conclusions drawn from analysis of treatment-naïve trial Spring-2 (both trials compared DTG to RAL).

Table 78: Mean Change from Baseline (Observed Data) in Lipid Values in Treatment-Experienced, INI-Naive Subjects -Week 24 Analysis (Fasting Blood Draws Only)

Laboratory Parameter Preferred Term	DTG N=354	RAL N=361
Total Cholesterol (mg/dL)	15.5	17.4
HDL cholesterol (mg/dL)	2.7	1.9
LDL cholesterol (mg/dL)	7.7	10
Triglycerides (mg/dL)	21.2	26.5

Source: Laboratory ISS dataset

Treatment Experienced, INI Experienced

Analysis of 24 week data from subjects in the Viking-3 trial is displayed in Table 79 below. Similar to observations in the Sailing trial discussed above, small increases in individual lipid parameters were observed in subjects dosed DTG 50 mg BID. The mean change in LDL cholesterol from baseline in Viking-3 trial was 15.4 mg/dl, higher than the mean change observed in Sailing trial at week 24. The limited number of subjects in the BID group and lack of a comparator arm limits interpretation of this finding.

Table 79: Mean Change from Baseline in Lipid Values in Viking-3, Week 24 Analysis

Laboratory Parameter Preferred Term	DTG N=183
Total Cholesterol (mg/dL)	16.8
HDL cholesterol (mg/dL)	4.4
LDL cholesterol (mg/dL)	15.4
Triglycerides (mg/dL)	12.2

Source: Laboratory ISS dataset

In summary, there was no indication of clinically significant effect of DTG on lipids observed with the 50 mg QD or BID dose in phase 3 trials. Small mean increases in fasting lipid parameters at weeks 24 or 48 in treatment-naïve or experienced populations were generally similar to those observed with RAL. Treatment-naïve Atripla treated subjects had slightly higher increases in mean change from baseline compared to DTG.

7.4.3 Vital Signs

Vital signs were assessed at Day 1, Week 24 and Week 48 in phase 3 trials. No clinically significant patterns of changes were identified in DTG or comparator treatment groups. No clinically relevant pattern of changes in vital signs (systolic and diastolic blood pressure, pulse) was observed in phase 3 trials.

7.4.4 Electrocardiograms (ECGs)

Thorough QT study (ING111856)

This trial was conducted to evaluate effects of single 250 mg oral dose of DTG on cardiac conduction as assessed by 12-lead ECG compared to placebo and a single oral dose of moxifloxacin. The 250 mg DTG dose was selected to yield exposures 2 to 3 fold higher than steady state exposures achieved with 50 mg BID dosing.

By FDA analysis, the maximum time-matched change from baseline in QTcF was 2.4 msec for DTG with 90% confidence interval -0.2 and 4.9 msec. Both mean change and the upper bound of CI were below the 10 msec threshold of regulatory concern. An appropriate change in QTcF was observed for moxifloxacin (9.48 msec, 90% CI: 7.05, 12.11 msec). In summary, no significant QTc prolongation effect of DTG was detected in the TQT study. Please refer to the review by QT-interdisciplinary review team (IND 75382; dated 8/6/2010) for details.

No adverse events of torsades de pointes were observed in clinical trials. Absolute QTcF exceeding 500 msec was observed in only one subject receiving DTG in all phase 3 trials. This subject 2658 in trial ING111762 with no history of heart disease and normal QTcF 394 msec had an asymptomatic QTcF 516 msec and QTcB 526 msec recorded at week 48 visit. Follow-up ECG approximately 4 weeks later had QTcF of 383 msec and QTcB of 394 msec. The investigator considered the week 48 findings a possible error. Visual inspection of the ECG and manual calculation by the Applicant of QTc using Bazett's formula (results ranged from 384 ms-436 ms depending on the preceding RR interval). The subject was continued on DTG treatment for an additional 5 months after ECG abnormality was observed; the subject eventually discontinued treatment due to protocol-defined virologic failure.

7.4.5 Special Safety Studies

Renal Function Study (ING114819)

This trial was conducted to explore the mechanism for observed increase in serum creatinine with DTG in clinical trials. Specifically, the trial was conducted to evaluate effects of DTG on GFR as measured by iohexol clearance and to evaluate renal plasma flow as measured by para-aminohippurate (PAH) plasma clearance.

In the 14-day study, healthy subjects received DTG 50 mg QD, or 50 mg BID, or placebo. No effects of DTG, either 50 mg QD or 50 mg BID, were observed on GFR or effective renal plasma flow. A decrease in creatinine clearance was observed with both doses; the magnitude of decline was 10% with QD dosing and 14% with BID dosing. Please refer to the clinical pharmacology review by Dr. Su-Young Choi for details.

Findings from this trial demonstrate that DTG does not affect GFR or renal blood flow. In vitro studies have demonstrated that DTG inhibits OCT2, a proximal tubule transporter involved in creatinine secretion. Taken together these observations indicate the serum creatinine elevations observed in clinical trials likely represent OCT2 inhibition and not drug effect on renal filtration.

Hepatic Impairment Study (ING113097)

In this phase 1 trial, DTG pharmacokinetic parameters were observed to be similar between subjects with moderate hepatic impairment and matched controls. Based on these findings, no dose adjustment is recommended for patients with mild to moderate hepatic impairment. Please refer to the clinical pharmacology review by Dr. Su-Young Choi for details.

Renal Impairment Study (ING113125)

In this phase 1 study, moderate decrease in DTG exposure was observed compared to matched healthy controls. The cause for this decrease and the clinical significance of this decrease are not known. No dose adjustment is recommended for HIV-infected patients with mild, moderate or severe renal impairment. Please refer to the clinical pharmacology review by Dr. Su-Young Choi for details.

7.4.6 Immunogenicity

Dolutegravir is not a peptide; therefore, immunogenicity effects were not specifically evaluated during clinical trials. As it is a small molecule, DTG is highly unlikely to have a potential for immunogenicity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

A relationship between key safety concerns and DTG doses 50 mg QD and BID was explored. In summary, no correlation between the events and the DTG dose was identified. These assessments were performed for submission specific primary concerns such as hypersensitivity reaction, rash, gastrointestinal events, hepatobiliary events, renal events, psychiatric events, musculoskeletal events as well as associated laboratory abnormalities. Findings leading to the conclusion of lack of dose dependency are discussed in the individual subsections in section 7.3.5.

As mentioned in section 4.4.2, no relationship was observed between DTG exposure and key adverse events or laboratory abnormalities. Please refer to the clinical pharmacology and pharmacometrics review by Drs. Su-Young Choi, Stanley Au, and Jeff Florian for details.

7.5.2 Time Dependency for Adverse Events

Time to onset analysis was performed for gastrointestinal events, rash, hypersensitivity reactions, and psychiatric events. The findings are discussed in individual subsections in section 7.3.5.

7.5.3 Drug-Demographic Interactions

Safety analysis by gender and race were performed for safety events of interest such as gastric-related events, hepatobiliary events, renal and psychiatric events. The findings are summarized within individual subsections in section 7.3.5. Additionally, the review team assessed safety for the 50 mg QD dose of DTG in key subgroups focusing on AEs by system organ class. A specific pattern of concern was not identified in safety analysis by race, gender, age, and CDC category subgroups. Forest plots depicting the safety profile by gender and race subgroups in treatment-naïve trials are displayed in the appendix section 10. Similar forest plots for the Sailing trial are not included in the appendix as the trial evaluated the same dose 50 mg QD as studied in treatment-naïve trials, and because no outstanding safety issue was identified during review of data from this trial. Similar type of risk assessments were not performed for the 50 mg BID dose given the lack of a comparator arm in the Viking-3 trial.

7.5.4 Drug-Disease Interactions

No definitive drug-disease interactions were observed.

7.5.5 Drug-Drug Interactions

Please refer to Dr. Su-Young Choi's clinical pharmacology review for detail discussions of drug-drug interactions. Key interactions and dose recommendations are outlined below.

Effect of dolutegravir on other drugs

In vitro, DTG inhibits OCT2 and therefore can potentially increase exposures of drugs excreted by OCT2. Agents eliminated by this renal cation transporter include dofetilide, an anti-arrhythmic agent used to treat atrial fibrillation, and metformin, a hypoglycemic agent. No DTG in vivo drug interaction studies were conducted with either drug.

Dofetilide has a narrow therapeutic window. Based on the DTG effects on OCT2, increases in dofetilide exposures and resultant toxicity including life-threatening events can be expected, hence co-administration of dofetilide with DTG is contraindicated. Metformin exposures are expected to increase when it is coadminsitered with DTG. Increased metformin levels can potentially lead to side-effects such as lactic acidosis and hypoglycemia. The Applicant's proposed labeling recommending close monitoring when starting or stopping DTG with metformin and stating that dose adjustment of metformin may be necessary, is acceptable.

Effect of other drugs on dolutegravir

Dolutegravir is primarily metabolized by UGT1A1 and CYP3A4 is a minor pathway. Dose adjustment is necessary when DTG is coadminsitered with moderate or strong metabolic inducers such as fosamprenavir/ritonavir, or efavirenz, or tipranavir/ritonavir, or rifampin. With either of these agents, the recommended DTG dose is 50 mg BID; and caution is warranted when combined with DTG in INI-experienced patients. Enzyme induction effects of etravirine can be offset by concurrent use of ritonavir boosted PI; therefore, DTG should not be used with etravirine without coadministration of ATV/r, DRV/r, or LPV/r.

ATV is a strong UGT1A1 inhibitor. When coadminsitered with ATV/r, plasma DTG AUC, Cmax and Ctrough increased by 62%, 34%, and 121%, respectively, compared to DTG administered alone. When coadminsitered with ATV, plasma DTG AUC, Cmax and Ctrough increased by 91%, 50%, and 180%, respectively, compared to DTG administered alone. Limited safety data are available for these higher DTG exposures achieved with 50 mg BID dose coadminsitered with either ATV or ATV/r. Dosing DTG 50 mg BID with ATV despite increased DTG exposure is supported by 1) lack of exposure-response relationship for safety in phase 3 trials, and 2) overall favorable safety profile of DTG. From the nonclinical perspective, the key nonclinical toxicity GI intolerance was related to local intolerance and not to systemic drug exposures; therefore higher exposures achieved with DTG 50 mg BID plus ATV are not expected to

impact the GI safety profile. Based on above considerations, use of DTG with ATV or ATV/r is acceptable without dose adjustment.

Lastly, DTG undergoes chelation with polyvalent metal cations resulting in reduced absorption; therefore it should be separated when administered with cation-containing antacids.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Dolutegravir clinical trial findings do not indicate the potential for carcinogenicity. The majority of neoplasms in phase 2b/3 clinical trials were either benign or were categorized as AIDS-related opportunistic infections which were not unexpected in the trial population. As mentioned in section 4.3, DTG was not carcinogenic in long-term studies in mice and rat species.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant women were excluded from DTG clinical trials, and pregnancy was a pre-specified withdrawal criteria in these trials. At the time of NDA data cut-off, a total of 15 pregnancies were reported in subjects receiving DTG. Of these, 2 were reported as ongoing, 6 pregnancies resulted in live term births, 4 were elective terminations, 1 pregnancy resulted in spontaneous abortion, and the outcome was unknown for 2 pregnancies.

No adequate and well-controlled trials of DTG have been conducted in the pregnant population. No teratogenicity was observed in animal studies. Effects on male or female fertility, parturition, or maternal behavior were not observed in animal reproductive and developmental toxicity studies. Dolutegravir falls under Category B for use in pregnancy. Because animal reproduction studies are not always predictive of human response, and DTG was shown to cross the placenta in animal studies, this drug should be used during pregnancy only if the potential benefit justifies the potential risk.

7.6.3 Pediatrics and Assessment of Effects on Growth

Refer to section 8 for review of data supporting the indication in the adolescent pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

One case of DTG overdose was reported in clinical trials: a subject reported taking 150 mg DTG on one occasion instead of 100 mg dose in cohort II of Viking trial; this

overdose was not associated with AEs. The highest DTG dose administered in clinical trials was the single dose of 250 mg in ING111856, the TQT study; and no unexpected AEs were observed in this trial.

There is no known antidote specifically for treatment of DTG overdose. Dialysis is unlikely to result in significant removal of the active substance because DTG is highly protein bound.

There were no reports of drug dependence, withdrawal or rebound effects of DTG during clinical trials.

7.7 Additional Submissions / Safety Issues

None.

8 Pediatric Review

This section of the clinical review summarizes the pediatric clinical trial findings to support an indication in pediatric patients 12 to less than 18 years of age and weighing at least 40 kg. This review highlights the supporting pharmacokinetic, safety and efficacy (antiviral activity) data in adolescent subjects. Please also refer to section 1.2 for the overall risk benefit discussion in pediatric subjects.

Typically the review process for HIV pediatric trials involves matching pediatric and adult pharmacokinetic data which in turn is used to extrapolate efficacy between adults and pediatric patients. We do this because we presume the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c). Thus, one can rely on the pharmacokinetics data to extrapolate efficacy; that is, the goal would be to target the exposure(s) (AUC) that are similar to the observed exposures (AUC) from the approved (or to-be marketed) adult dose(s). Although AUC is the primary pharmacokinetic parameter targeted when selecting pediatric dose(s), C24 may also be an important pharmacokinetic parameter for some antiretroviral drugs with regards to establishment of exposure-response relationship. In the case of DTG, both AUC and C24 were considered pivotal data when selecting the pediatric once daily dosing. The clinical efficacy (antiviral activity) data obtained from pediatric trials, when available, are used as supportive data. For this NDA efficacy data was available for 23 subjects. In addition, safety data cannot be extrapolated between adults and pediatric subjects; therefore, safety data are required and were available for 23 subjects.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two endpoints HIV RNA and CD4 cell counts. Antiretroviral drugs including NRTIs, NNRTIs, INIs and PIs have been shown to lower HIV RNA, improve CD4 counts (or percentage) and improve general clinical outcome in adult and pediatric subjects and treatment

recommendations are very similar across all age groups (refer to Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1-134. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf. for a review of studies and references).

This pediatric trial is conducted in collaboration with the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), together with the National Institute of Allergy and Infectious Diseases (NIAID), NIH. The purpose of the trial is to determine the appropriate dose (and formulations) of DTG for use in pediatric subjects with HIV-1 infection. The goal of the study is to determine pediatric dose(s) that approximates adult exposure (AUC24 and C24h) observed at the 50 mg QD dose; the primary PK endpoint is the AUC24, with C24h as secondary endpoint. Safety and efficacy (antiviral activity) were also collected during the study. Although the trial is designed to evaluate DTG in multiple age cohorts (i.e. 6 weeks to less than 18 years of age), the focus of the current pediatric submission is Cohort I- adolescent subjects 12 to less than 18 years of age.

The study is designed to have two stages. During Stage 1, intensive PK, tolerability and short term safety data were collected. Ten subjects were enrolled in Stage 1 of Cohort 1. These subjects continued on treatment to allow evaluation of the long-term safety and efficacy of DTG. In stage 2, long-term (e.g. 24 weeks) safety and antiviral activity data were to be collected. Additional 13 adolescent subjects were enrolled in Stage 2 of Cohort 1. Thus in total, 23 adolescent subjects were enrolled in Cohort 1 to provide long-term safety and antiviral activity of DTG.

The data allowing review of the safety and efficacy of DTG in adolescent subjects were submitted in two parts. The first, submitted at the time of the NDA, contained intensive PK data from 10 subjects who enrolled into Stage 1 and who then continued on treatment; thus, long-term safety (minimum of 24-weeks) and Week 24 efficacy data were also included for these 10 subjects. The first submission also contained efficacy and safety data ranging from Week 4 to Week 52 for the remaining 13 adolescent subjects enrolled in Stage 2 of Cohort 1. The second submission was submitted as part of the Safety Update Report. It provided additional safety and efficacy data so that a minimum of 24 Week safety and efficacy data would be available for the remaining 13 subjects. In addition, the raw datasets for these 13 subjects was also provided. Therefore, the two submissions combined provided a minimum of Week 24 safety and efficacy data for all subjects enrolled in Cohort 1 (i.e. n=23).

The proposed dosing regimen for pediatric patients 12 to less than 18 years of age and weighing at least 40 kg is 50 mg QD, taken orally. No dosing is proposed for INI-experienced pediatric patients because 50 mg twice daily was not evaluated.

The current application partially addresses the pediatric study requested under BPCA (Pediatric Written Request, PWR). Per PWR, GSK is to conduct “Multiple-dose

pharmacokinetic, safety and antiviral activity study(ies) of GSK1349572, in combination with other antiretroviral agents, in HIV-infected pediatric patients from birth to 18 years of age".

Data supporting the adolescent treatment indication come from study P1093. This study is designed to have two stages. During Stage 1, intensive PK, tolerability and short term safety data were collected. Ten subjects were enrolled in Stage 1 of Cohort 1. These subjects continued on treatment to allow evaluation of the long-term safety and efficacy of DTG. In stage 2, long-term (e.g. 24 weeks) safety and antiviral activity data were to be collected. Additional 13 adolescent subjects were enrolled in Stage 2 of Cohort 1. Thus in total, 23 adolescent subjects were enrolled in Cohort 1 to provide long-term safety and antiviral activity of DTG.

Summary of Pharmacokinetic Data

For Cohort 1, 10 subjects were enrolled in Stage 1. The weight based dose (~ 1mg/kg/day) administered was as follows:

- DTG 50 mg QD if ≥ 40 kg
- DTG 35 mg QD if <40 kg

Most subjects (nine) received 50 mg QD dosing while one subject, who weighed <40kg received 35 mg QD. As mentioned above, the primary and secondary PK targets were to match the adult AUC24 and C24 observed at the 50 mg QD, respectively. The exposure goal for AUC24 is 46 mcg*h/mL (range: 37-67 mcg*h/mL) and the exposure goal for C24 is 0.96 mcg/mL (range: 0.77-2.26 mcg/mL). The ranges were defined as: lower limits of 80% of the geometric means (37 mcg*h/mL for AUC24 and 0.77 mcg/mL for C24h); upper limits of 90th percentile around the AUC24 and C24 (67 mcg*h/mL for AUC24 and 2.26 mcg/mL for C24) observed in treatment-naive adult subjects in SPRING-1 trial. The maximal exposure target is 92 mcg*h/mL for AUC24, which is 2 times the geometric mean value at 50mg QD in adults (46 mcg*h/mL) and is also comparable to exposures with 50 mg BID or co-administration of DTG 50mg QD with atazanavir. The maximum lower limit is defined as AUC24 25mcg*h/mL and C24h 0.5mcg/mL based on the Applicant's defined EC90. Of note, the observed AUC24 and C24 in the adult Phase 3 trials were slightly higher than what was observed in the SPRING-1 (Phase 2) trial- i.e. AUC24 and C24 are 53.5 mcg/mL and 1.11 mcg/mL, respectively.

Please refer to the Clinical Pharmacology/Pharmacometrics review by Drs. Su-Young Choi, Stanley Au and Jeff Florian.

The following question was addressed by the clinical pharmacology and pharmacometrics group:

- Does the proposed DTG dose of 50 mg QD achieve exposures in adolescents within the targeted exposure range?

In sum, DTG 50 mg QD achieved exposures in adolescents within the pre-defined targeted exposure range, as defined by the SPRING-1 data. The geometric mean for AUC24 and C24 were 46 mcg*h/mL and 0.9 mcg/mL, respectively. The %CV were 43.1 and 58.6, respectively. These exposures however were lower than what was observed in the adult Phase 3 data (adult Phase 3 data: AUC24 and C24 are 53.5 mcg/mL and 1.11 mcg/mL, respectively). Of note, one adolescent subject experienced a very low DTG exposure; no explanation was provided for the low exposure. When the exposure analysis is conducted after excluding this subject, the AUC24 and C24h are similar to what was observed in the Phase 3 adult trials (i.e. the exposures for AUC24 and C24 are 52.9 mcg/mL and 1.06 mcg/mL, respectively).

Efficacy Evaluation

The mean and median age for the 23 subjects is 14 years with range of 11 to 17 years. Most (74%) are female and approximately 50% are black or African American, 35% are White and 13% are Asian. Majority (71%) are non-Hispanic. All subjects are treatment-experienced. The following table summarizes the historical ARV use.

Table 80: Historical ARV Use

Prior ARV use, n, (%)	**N=23**
Prior NRTI use	23 (100)
Prior NNRTI use	11 (48)
Prior PI use	
1	7 (30)
≥2	11 (48)
Prior CCR5 use	1 (4)
Prior T-20 use	1 (4)

Source: AE ISS dataset

The efficacy results for the 23 subjects at Week 24 are as follows: At Week 24, 65% of the subjects reached HIV RNA <50 copies/mL.

Table 81: Virologic Outcome at Week 24 based on Snapshot Algorithm

Cohort 1	DTG 50 mg QD (n=23)
Virologic success (HIV RNA <50 copies/mL)	15 (65%)
HIV RNA ≥ 50 copies/mL	8 (35%)

Source: Snapshot ISS dataset

Although cross-trial comparisons should be viewed with caution, the response rate in adolescents was numerically lower than the response rate observed in adults from the SAILING trial (79%). However, the response rate observed in this trial is generally comparable to results from other trials in treatment-experienced, adolescent subjects.

Out of the eight subjects who did not reach HIV RNA <50 copies/mL, 5 had HIV RNA ≥400 copies/mL. At the time of this review, resistance information is available for 2 of the 8 subjects. Per Applicant, neither of the 2 subjects developed INI associated resistance substitution.

Improvements in mean CD4 count and percent were observed from baseline through Week 24, as shown in table 82 below.

Table 82: Change in absolute CD4 count and CD4 percent at Week 24

CD4 count	Week 0	Week 24	Change from Baseline
N=23			
Mean	527	598	+71
Median	466	582	+116
Min-max	11-1025	74-963	
CD4%			
N=23			
Mean	23%	28%	+5%
Median	22%	28%	+6%
Min-max	1-39%	7-39%	

Source: Laboratory ISS dataset

Safety

As stated previously, this NDA contains a minimum of 24-Week safety data for 23 subjects. In addition, Safety Update Report (SUR) summarizes all the AEs reported from time of initiation of treatment through the data cut-off date of January 15, 2013. Overall, the AE profile and laboratory abnormalities including changes in serum creatinine were similar to what was reported in adults. No new or unexpected toxicities were observed. The overall safety profile from the 23 adolescent subjects is acceptable and supports the overall favorable benefit risk assessment for this population.

All 23 pediatric subjects reported at least one AE. All clinical adverse events were Grade 1 or 2 and none led to treatment discontinuation. There were no deaths or clinical SAEs. Of note, the only serious or Grade 3 events reported are related to laboratory toxicity and include increase in lipase in one subject (Grade 3) and an increase in total bilirubin (Grade 3).

Nine subjects reported adverse events that were considered by the investigators to be at least possibly related to treatment. The events were diarrhea (n=3), nausea (n=2), abdominal pain (n=2), dizziness (n=1), headache (n=1), rash (n=1), leg cramp (n=1), and decreased appetite (n=1). All were Grade 1, except 3 events were Grade 2: abdominal pain in 2 subjects, diarrhea in 1 subject, and rash in 1 subject (see further discussion on rash below).

The most common AEs (by preferred term, regardless of severity, causality, reported in at least 5%) were as follows: diarrhea (n=6), fever (n=5), abdominal pain (n=4), decreased appetite (n=4), myalgia (n=4), nausea (n=3) and pharyngitis (n=3), fatigue (n=2) and disseminated rash (n=2).

Four subjects had adverse events related to musculoskeletal pain including leg cramp, lower extremity pain and upper extremity pain. All were Grade 1 events and none discontinued treatment. None of the subjects had reported graded increase in CK. However, in addition to these subjects, there was one subject who had Grade 1 increase in CK but this subject did not have reported clinical symptoms.

The adverse events of special interests evaluated for this pediatric trial include rash-, renal-, neuropsychiatric- and hepatic- events.

Rash was reported in five subjects. The terms included ‘macule’, ’papule’, ‘rash disseminated’, and ‘generalized urticaria’. All were Grade 1 or 2 and none led to treatment discontinuation or interruption. Of note, one of the subjects reported to have ‘rash disseminated’ had the event prior to initiation of treatment and continued to have the rash throughout the treatment period. The subject also had concurrent diagnosis of ‘presumed scabies’ throughout the treatment period. This rash event was considered to be possibly related to treatment by the investigator. However, given the event was present at Week 0 and the subject had presumed scabies diagnosis, it is not likely that the rash is related to study drug. Of note, three of the subjects were also receiving other ARVs that could possibly explain the rash events: DRV/r (n=2) and Epzicom (n=1).

Similar to what was observed in the adult clinical trials, in this pediatric trial, the mean serum creatinine increased during treatment compared to baseline. As summarized in Table 83, by Week 4, the mean serum creatinine (Scr.) increased by approximately 0.1 mg/dL, when compared to baseline. By Week 24, no additional significant increase is noted. Comparing the Week 4 data to the last observed time-point, which ranges from Week 24 to Week 72, the mean serum creatinine remains relatively stable, i.e. the mean and maximum changes are approximately 0.1mg/dL when compared to baseline.

Table 83: Mean changes in Serum Creatinine Compared to Baseline

N=23	Mean	median
Baseline	0.58 mg/dL (0.4- 0.9)	0.58 mg/dL
Week 4	0.66 mg/dL (0.4-0.95)	0.6 mg/dL
Change from Baseline	0.08 (0-0.05)	
Week 24	0.73 mg/dL (0.51-1.03)	0.7 mg/dL
Change from Baseline	0.15 (0.11-0.13)	
Last observed (W24 - W72)	0.7 mg/dL (0.44-1.0)	0.67 mg/dL
Change from Baseline	0.12 (0.04-0.1)	

Source: Laboratory ISS dataset

Except for one subject who had Grade 1 increase in serum creatinine, no other subjects were reported to have Grade 1 or higher increase in serum creatinine. The subject had normal baseline value of 0.68 mg/dL (ULN is 0.9 mg/dL); at Week 4, S Cr was 0.95 mg/dL and by Week 8, S Cr increased to 1.02 mg/dL (Grade 1). The highest reported value, 1.03 mg/dL, was at Week 24, and the last recorded value at Week 48 was 0.86 mg/dL. Subject's phosphorous and potassium remained normal throughout the study period. Subject's co-medications included DRV/r, Truvada, and etravirine. Although the event was not considered to be treatment related by the investigator, the contribution of DTG cannot be excluded for certain. In addition, Truvada, an ARV known to have an affect on renal function, cannot be ruled out as a contributor to the graded event.

The only other reported renal adverse event that non laboratory-related hypertension ('renal hypertension') in one subject. The event (always Grade 2) started around Week 24 and continued up to Week 40. The subject continued on treatment without discontinuation and the event was not considered to be treatment-related.

Integrase inhibitors such as raltegravir have been associated with neuropsychiatric events such as depression. Thus, neuropsychiatric events were considered to be Adverse Events of Special Interest. Three subjects experienced psychiatric events, including depression, anxiety and ADHD. All were Grade 1 or 2 and none were considered to be treatment related. None led to treatment discontinuation.

No hepatobiliary events (excluding laboratory-related events) were reported as clinical adverse events. Please refer to laboratory section for liver-related laboratory toxicities.

Laboratory toxicities

There were no graded hemoglobin or platelet toxicities. However, several subjects experienced white blood cells-related toxicities: one subject had Grade 1 decrease in WBC and five subjects had Grade 1 or 2 decrease in neutrophils or absolute neutrophil count. Of these, one subject had abnormal baseline value (Grade 1). Of note, none of the subjects were receiving zidovudine during the treatment period.

Liver- and pancreas-related laboratory abnormalities are summarized in the table below.

In summary, there were no Grade 3 or 4 increases in ALT or AST. One subject (SID 690529) had Grade 3 increase in total bilirubin (TB), with accompanying increase in indirect bilirubin (IB: observed 1.8; ULB 0.4) and direct bilirubin (DB: observed 0.8; ULN 0.5). However, no associated toxicity (i.e. Grade 1 or above) were reported for alkaline phosphatase, ALT or AST. No clinical jaundice event was reported for this subject. Grade 3 increase in Lipase was reported in one subject (ID 8500394). The increase in lipase was first noted at Week 40 (Grade 2), which then increased to G3 by Week 48; at the last recorded visit, Week 54, the toxicity had decreased back to Grade 2. The subject continues to be on treatment without discontinuation and no clinical pancreatitis was reported for this subject.

Table 84: Selected Worst Grade Laboratory abnormalities

Laboratory parameters, toxicity grade, n	N=23
ALT	3(13)
Grade 1	3(13)
AST	3(13)
Grade 1	3(13)
TB	3(13)
Grade 1	1(4)
Grade 2	1(4)
Grade 3	1(4)
IB	
Abnormal	4(4)
DB	
Abnormal	2(8)
Lipase	1(4)
Grade 1	0
Grade 2	0
Grade 3	1(4)

Source: Laboratory ISS dataset

9 Postmarketing Experience

None.

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10 Appendices

10.1 Literature Review and References

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10.2 Labeling Recommendations

Key recommendations by the clinical review team are outlined here. Refer to Team Leader memo by Dr. Kim Struble for labeling changes recommended (if any) after this review was entered in DARRTS.

- Indication and Usage section 1: recommend to include the following language to emphasize presence of Q148 substitutions resulted in reduced response rates, and presence of Q148 plus 2 INI substitutions resulted in poor response. Detailed information for INI substitutions should be included here because it is clinically relevant and therefore should be prominently displayed. This information is also recommended in the Highlights section.

(b) (4)

- Warnings and Precautions section 5:
  - Recommend a separate warning for liver biochemistry elevations and recommend monitoring of liver enzymes for hepatotoxicity in HBV/HCV coinfected patients.

    Effects on serum liver biochemistries
    Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY. In some cases the elevations in transaminases were suggestive of immune reconstitution syndrome or HBV reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY is recommended in patients with underlying hepatic disease such as hepatitis B or C.

  - Recommend deletion of the following paragraph proposed to the existing warning for Immune Reconstitution Syndrome.

(b) (4)

- Recommend Fat Redistribution warning, which is ARV class warning, be included in the label

- Adverse Reactions section 6:
  - Recommend inclusion of the ADRs (b) (4) to highlight the most clinically meaningful differences observed between the treatment arms in the treatment-naïve trials.
  - Recommend inclusion of language stating treatment-emergent ADRs in Viking-3 trial were generally similar to ADRs observed with DTG 50 mg QD dose in clinical trials.
  - Recommend presentation of selected laboratory analysis with grades 2-4 toxicities and combining grade 3-4 toxicity to allow ease in display.
  - Recommend inclusion of (b) (4) 'myositis' in Less Common ADRs.
  - Recommend deletion (b) (4) in Less Common ADRs
  - Recommend deletion (b) (4)

- Clinical Studies section 14
  - Recommend to delete (b) (4)
  - Recommend to delete (b) (4).

10.3 Advisory Committee Meeting

An advisory committee meeting was not held for this NDA because there are two previously approved drugs in this ARV class, topline safety presented at the pre-NDA did not reveal particular issues that were unexpected for the class, and efficacy results from phase 3 trials did not pose particular concerns.

10.4 Clinical Investigator Financial Disclosure Review

Application Number: 204790

Submission Date: December 17, 2012

Applicant: GSK

Product: Dolutegravir

Reviewers: Charu Mullick, Wendy Carter, Yodit Belew

Date of Review: May 17, 2013

Covered Clinical Studies: ING113086, ING114467, ING111762, ING112574, P1093

Was a list of clinical investigators provided:	Yes x	No ☐ (Request list from applicant)
Total number of investigators identified: 468		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 (honoraria payment) Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes x	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes x	No x☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: n/a	Yes ☐	No ☐ (Request explanation from applicant)

Four investigators, each enrolling (b) (6) subjects in individual phase 3 trials entered into financial arrangement with the Applicant. One investigator enrolled (b) (6) subjects (b) (6) ; the investigator received $25,250 as honoraria for each study. The second investigator enrolled (b) (6) subjects (b) (6) ; this investigator received up to $93,215 as honoraria for each study. A third investigator enrolled (b) (6) subjects (b) (6) the investigator received up to $40,650 honoraria for each study. The fourth investigator enrolled (b) (6) subjects (b) (6) ; the investigator received $53,700 as honoraria in each study.

This financial disclosure information is not likely to affect the overall results because each investigator enrolled (b) (6) subjects in each trial. In addition, efficacy for the pursued HIV treatment indication relies on an objective endpoint, HIV viral load, based on laboratory results and not subjective investigator-based endpoints, thereby limiting ability of investigators to impact the efficacy results. Lastly, any investigator related bias is unlikely to influence overall outcomes because phase 3 trials supporting this NDA were large, multicenter, double-blind trials.

Subgroup Analyses Effects of Gender and Race on Treatment-Naïve Common Adverse Events by SOC

SPRING-2

The figure 18 provides the overall Relative Risk Ratio (with a zero events correction of 0.5) of all reported on-treatment AEs by MedDRA SOC level in SPRING-2. The overall events are reported at similar rates and there are no SOCs that significantly favor DTG over RAL, or RAL over DTG.

Figure 18: Relative Risk Ratio of treatment-emergent AEs by MedDRA System Organ Class SPRING-2

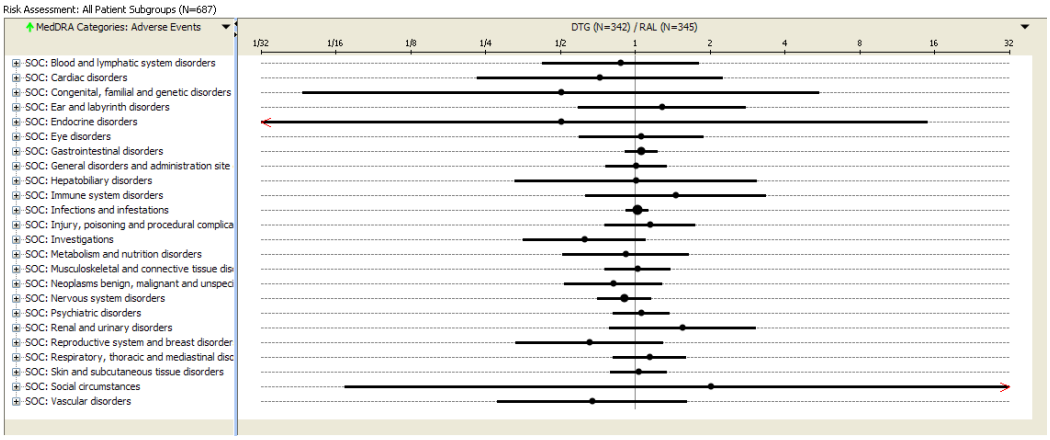
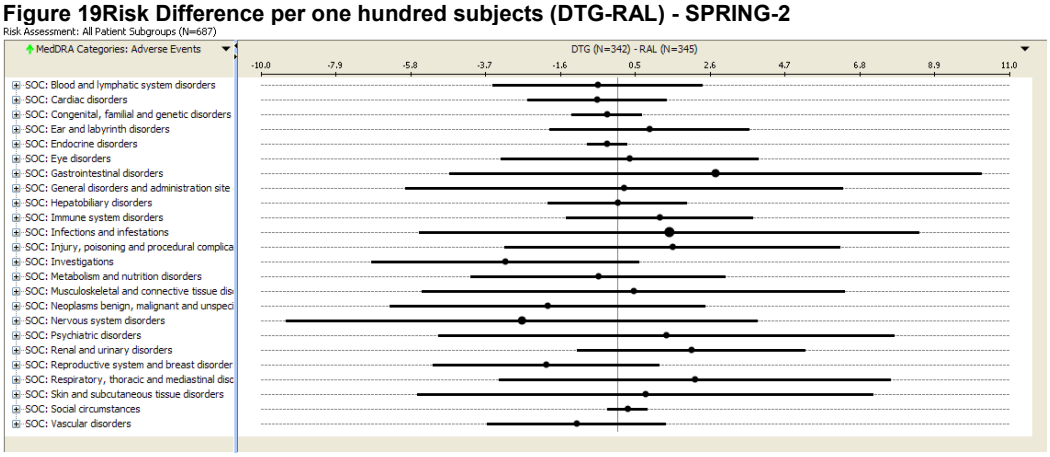


Figure 19 provides the same data; however, evaluating the risk difference per one hundred subjects.

Figure 19Risk Difference per one hundred subjects (DTG-RAL) - SPRING-2



The following 2 figures provide the risk difference per one hundred subjects by gender. There is no significant effect on the common AEs by SOC when evaluated by gender. Similar analyses were completed for preferred terms and again, no trends or specific safety issues were identified related to gender.

Figure 20: Risk Difference (DTG-RAL) per one hundred subjects by SOC (Female)

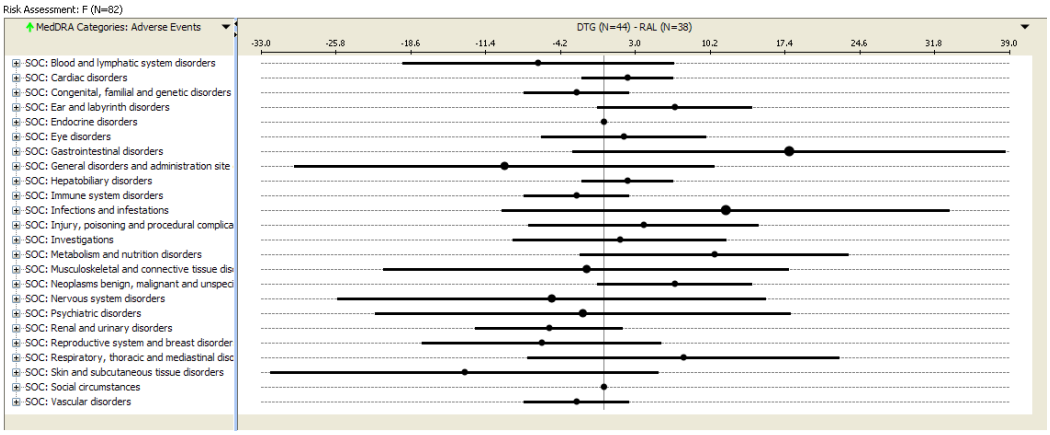
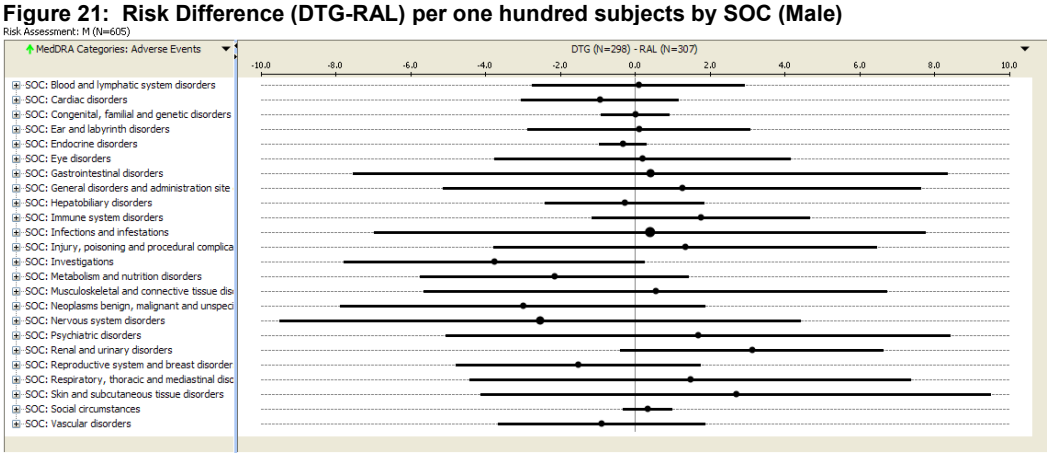


Figure 21: Risk Difference (DTG-RAL) per one hundred subjects by SOC (Male)



The following 4 figures provide the risk difference per one hundred subject by race (African American/African Heritage, White, Other) and ethnicity (Hispanic or Latino). Again, no significant trends by race or ethnicity were observed when comparing DTG to RAL. Interestingly, the was a higher reported risk for GI disorders for DTG compared to RAL which is driven by more events of nausea reported in African American/African subjects exposed to DTG (16/46, 35%) compared to RAL (5/35, 14%). However, this is a small subgroup which limits meaningful comparisons.

Figure 22: Risk Difference (DTG-RAL) per one hundred subjects by SOC (African American/African)

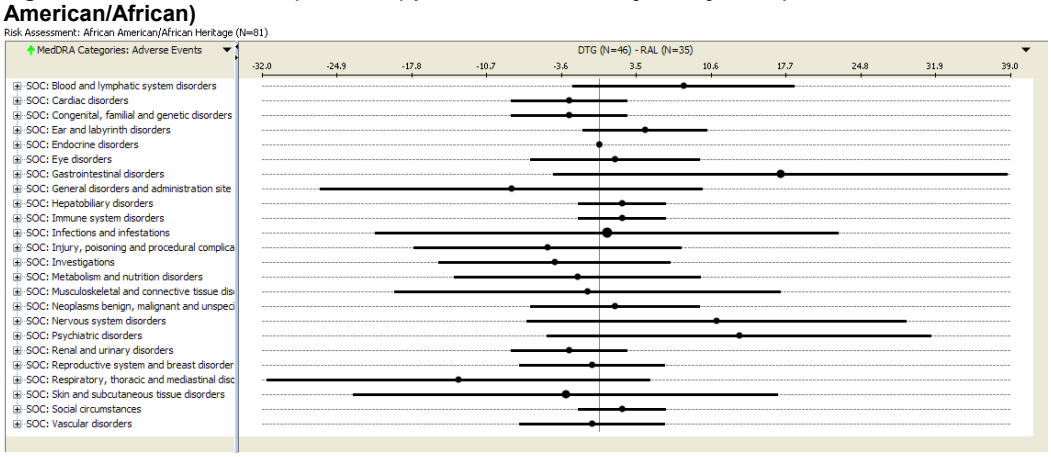


Figure 23: Risk Difference (DTG-RAL) per one hundred subjects by SOC (White)

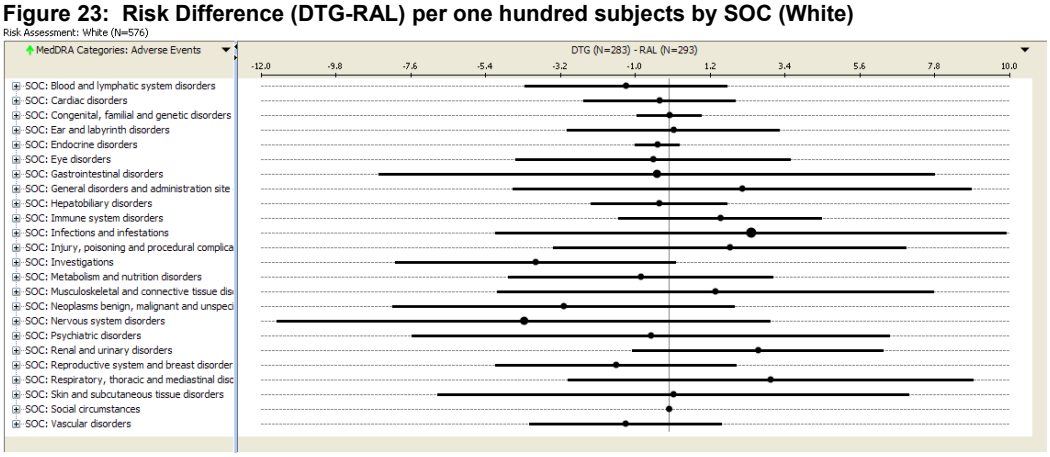


Figure 24: Risk Difference (DTG-RAL) per one hundred subjects by SOC (Race)

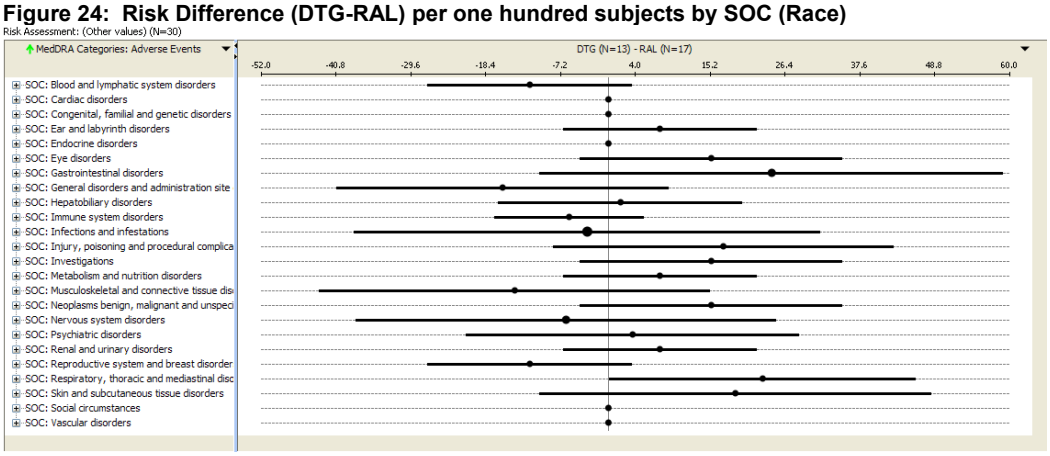
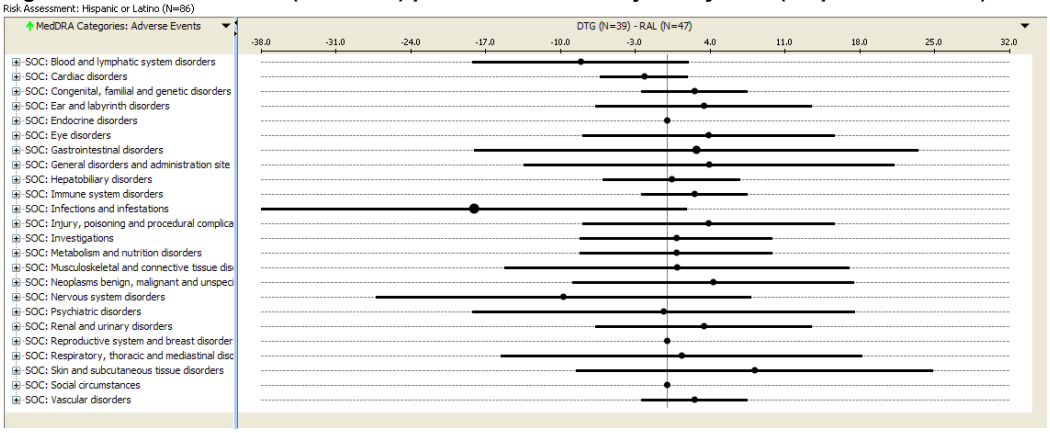


Figure 25: Risk Difference (DTG-RAL) per one hundred subjects by SOC (Hispanic or Latino)



SINGLE

The following figure provides the overall Relative Risk Ratio (with a zero events correction of 0.5) of all reported on-treatment AEs by MedDRA SOC level in SINGLE. The next figure provides the risk difference per one hundred subjects for the on-treatment AEs by SOC. In the risk difference plots, the vertical line represents zero in the scale and the scale shifts according to the subgroup analysis. In both the overall risk ratio and the risk difference figures, the trend favors DTG compared to Atripla for nervous system disorders (risk difference -24.7 per 100), psychiatric disorders (risk difference -9.5 per 100) and skin and subcutaneous tissue disorders (risk difference -11.6 per 100). There is a small risk difference favoring Atripla for Infections and Infestations (risk difference 8.3 per 100). There is no specific safety trend that emerges when further analysis by preferred terms is completed, instead, an overall larger proportion of subjects in the DTG arm compared to the Atripla arm reported events coded to Infections and Infestations (DTG 63% compared to Atripla 55%).

Similar patterns are observed for risk difference when the safety database of SINGLE is evaluated by gender and race. There are no new safety patterns or events, other than those described above, specific to the subgroups evaluated that favor DTG over Atripla, or Atripla over DTG. The following figures provide these analyses.

Figure 26: Risk Ratio (DTG/Atripla) by SOC in SINGLE

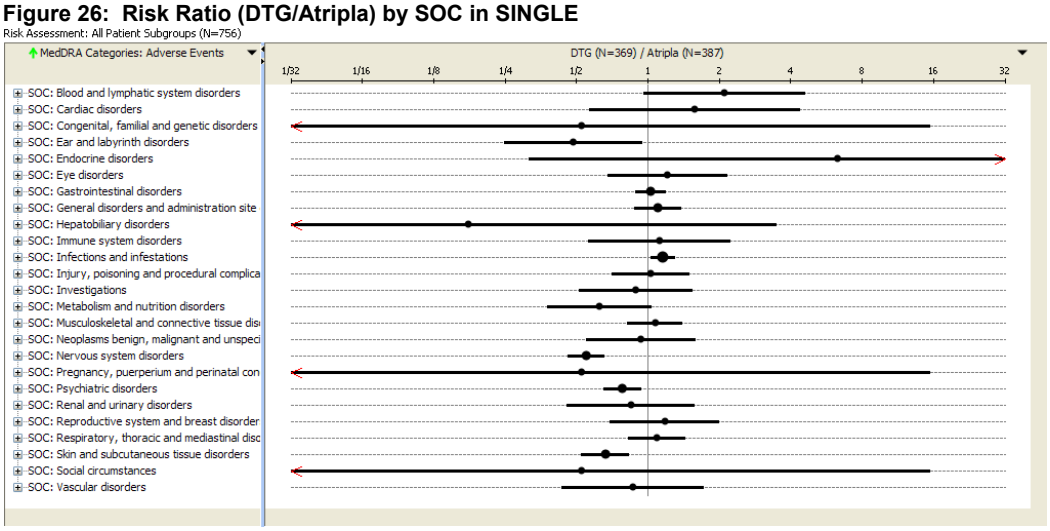


Figure 27: Risk Difference (DTG-Atripla) per one hundred subjects – SINGLE

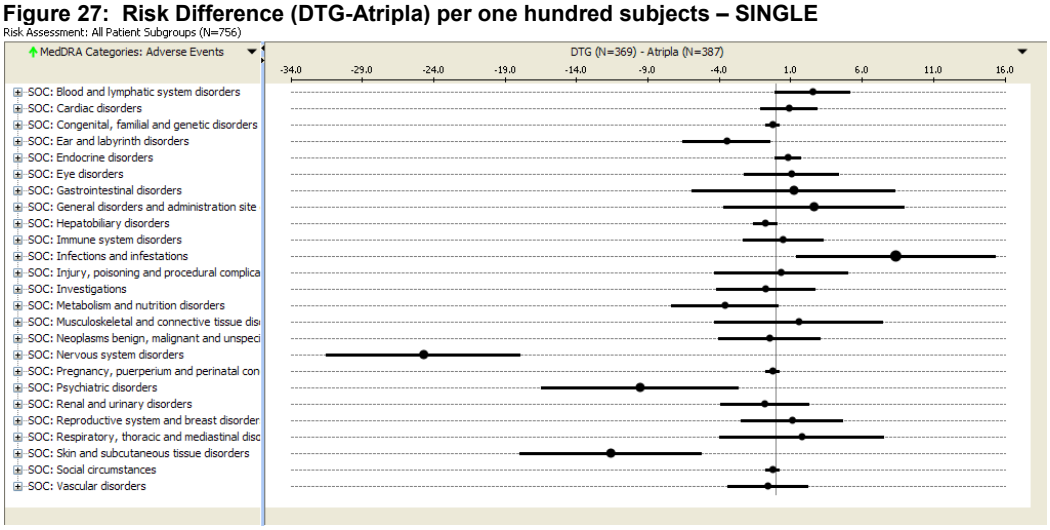


Figure 28: Risk Difference (DTG-Atripla) per one hundred subjects by SOC (Female)

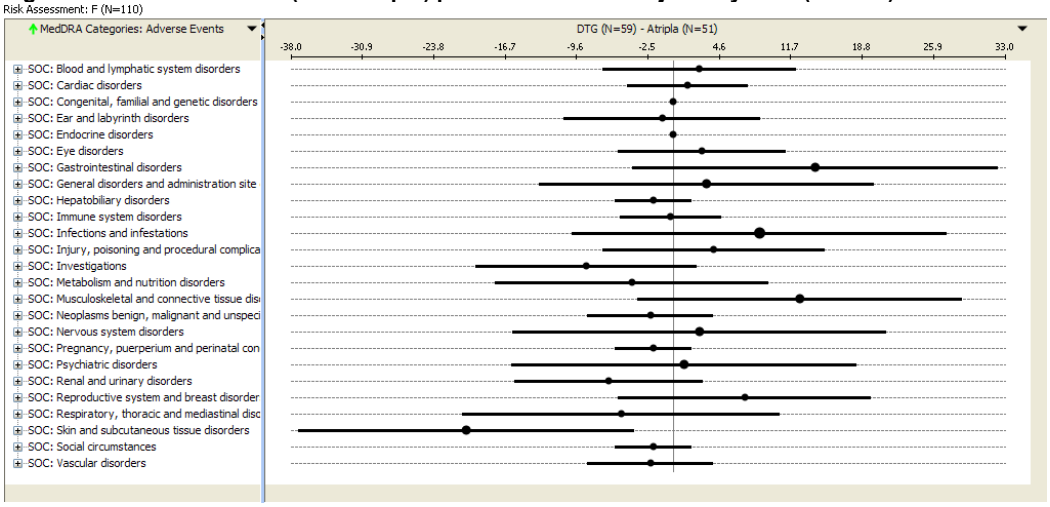


Figure 29: Risk Difference (DTG-Atripla) per one hundred subjects by SOC (Male)

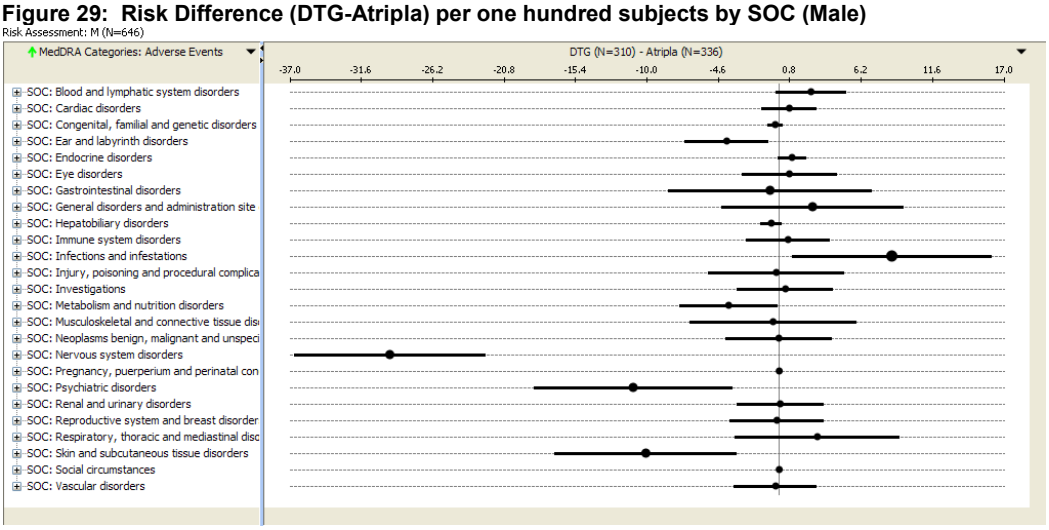


Figure 30: Risk Difference (DTG-Atripla) per one hundred subjects by SOC (African American)

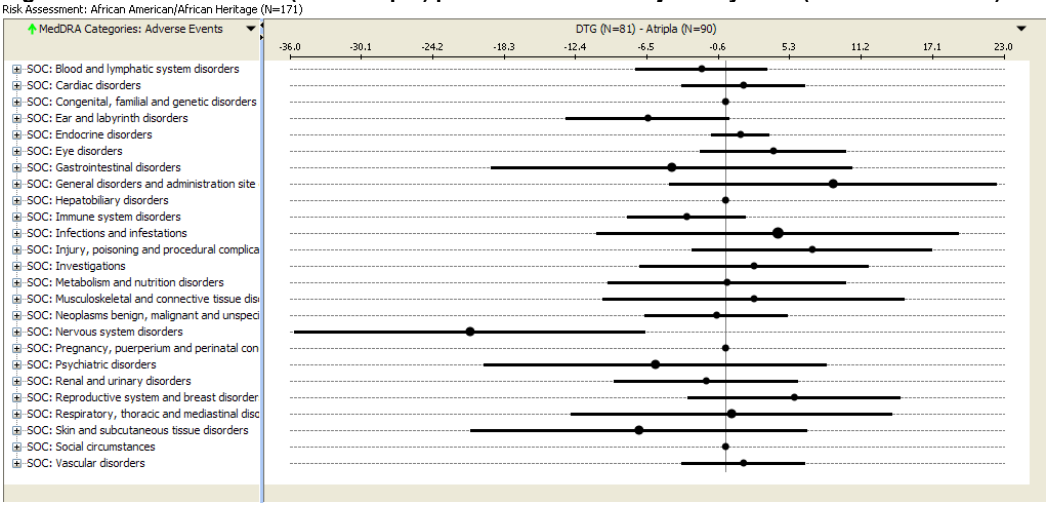


Figure 31: Risk Difference (DTG-Atripla) per one hundred subjects by SOC (White)

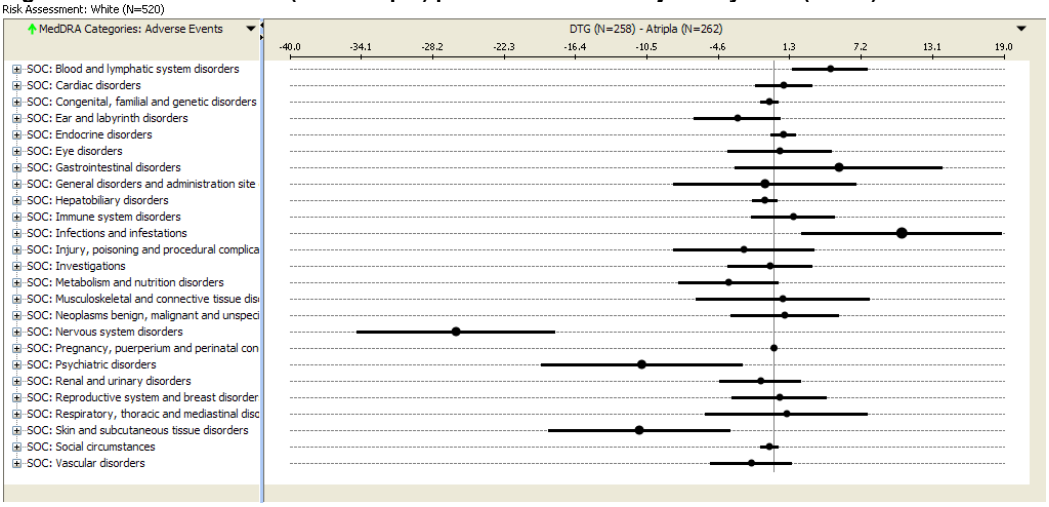


Figure 32: Risk Difference (DTG-Atripla) per one hundred subjects by SOC (Other Race)

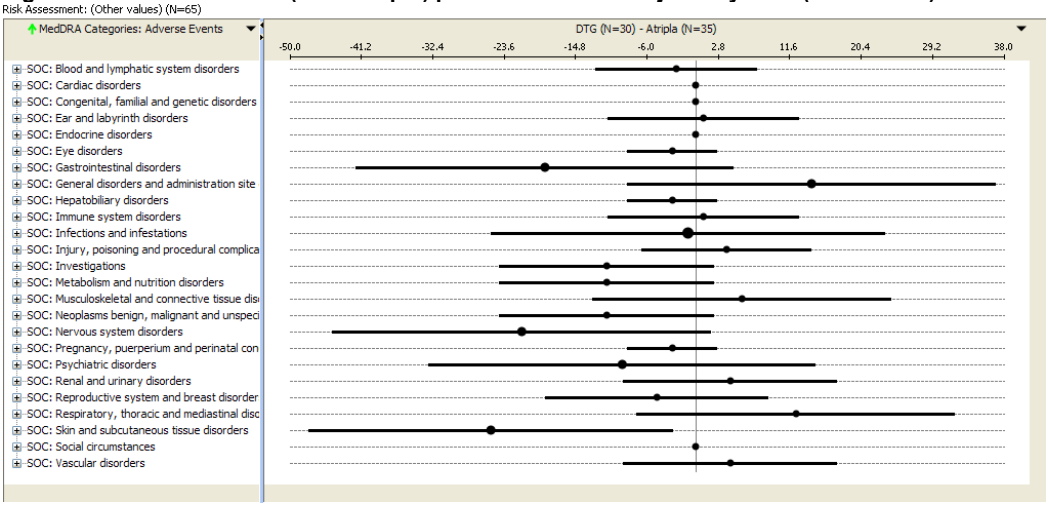
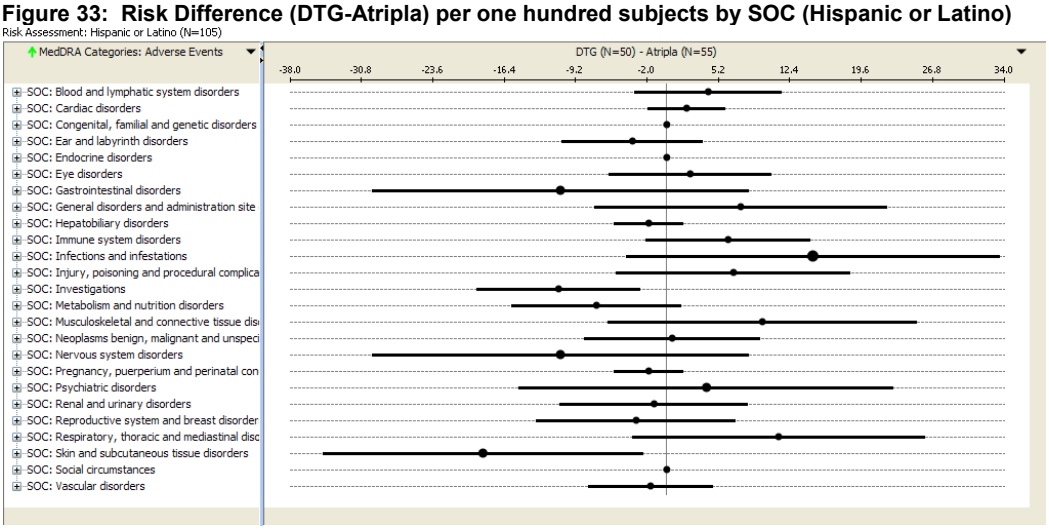


Figure 33: Risk Difference (DTG-Atripla) per one hundred subjects by SOC (Hispanic or Latino)



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/s/

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