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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Clinical Review

Date	June 2, 2014
From	Yodit Belew, M.D. Charu Mullick, M.D.
Subject	Clinical Review
NDA/BLA # Supplement#	205551 000
Applicant	GSK
Date of Submission	October 22, 2013
PDUFA Goal Date	August 22, 2014
Proprietary Name / Established (USAN) names	Triumeq abacavir/dolutegravir/lamivudine (ABC/DTG/3TC)
Dosage forms / Strength	Fixed dose combination tablet containing 600mg/50mg/300mg of ABC/DTG/3TC
Proposed Indication(s)	Treatment of HIV-1 infection
Recommended:	Approval

1. Introduction

Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI) developed by GSK, was approved for the treatment of HIV-1 infection on August 12, 2013 under NDA 204790. GSK has co-formulated dolutegravir with two nucleoside reverse transcriptase inhibitors (NRTIs) abacavir and lamivudine to create a fixed dose combination (FDC) drug product, Triumeq. No new clinical safety and efficacy trials were conducted with Triumeq. Rather, in support of the approval of Triumeq, contents of NDA 205551 include a relative BA trial and one pivotal Phase 3 trial. The Phase 3 trial SINGLE (ING114467) evaluated the safety and efficacy of DTG, co-administered with ABC/3TC. Results from the Week 48 data were previously reviewed under NDA 204790; this NDA submission contains Week 96 data for SINGLE. An additional clinical trial supporting use of Triumeq for the treatment of HIV includes Week 48 data from SAILING (ING111762).

NDA 204790 containing several pivotal trials was submitted on December 17, 2012 supporting approval of dolutegravir for treatment of HIV infection. Dolutegravir 50 mg once daily is indicated for the treatment of HIV infection in treatment - naïve or - experienced but INSTI-naïve patients. The dose of dolutegravir for INSTI-experienced patients is 50 mg twice daily. Week 48 data from SINGLE and SPRING-2 were reviewed to support the indication in the naïve population. The two trials were similar in design

except for the background ARVs used to complete the regimen. In SINGLE, all subjects were treated with DTG plus ABC/3TC while either ABC/3TC or TDF/FTC was allowed for use as background regimen in SPRING-2. Week 24 data from SAILING was also submitted to support the indication in treatment-experienced (INSTI-naïve) adults. Additionally, data from VIKING-3 supported use of dolutegravir in INSTI-experienced population. Please refer to clinical, virology, pharmacology, CMC and pharmacology/toxicology reviews for NDA 204790 for full details.

A supplemental NDA has also been submitted for NDA 204790 containing 96-week data for the treat-naïve population, 48-week data for the treatment-experienced, INSTI-naïve population, and a full 48-week data for the INSTI-experienced population.

As stated above, contents of NDA 205551 include data from the relative BA trial and data from the SINGLE and SAILING trials. Contained in the NDA are also longer-term data for SPRING-2 (96 Week data) as well as data for a new Phase 3b trial (FLAMINGO) comparing DTG to darunavir. The review team concluded that these two additional trials in treatment naïve populations are not necessary to support approval of the FDC drug product because the background regimen in these trials was not limited to ABC/3TC and sufficient data is available from the SINGLE trial in treatment naïve subjects. Data from the SAILING trial, which evaluated DTG in combination with ARVs, was included in this review as supportive evidence for use of DTG in treatment experienced, INSTI naïve subjects. Limited number of subjects received DTG with ABC/3TC in SALING trial. Nonetheless, the effectiveness of Triumeq in patients who are treatment- experienced but INSTI-naïve can be extrapolated as long as the virus harbored by patients is susceptible to dolutegravir, abacavir and lamivudine. Such conclusions are supported by the following: 1) analysis from Week 24 data for SAILING demonstrated that DTG 50 mg QD, in combination with other ARVs is effective for treatment of HIV in treatment-experienced, INSTI-naïve subjects; 2) previous clinical trials have demonstrated that abacavir and lamivudine in combination with other ARVs can be effective in treatment-experienced subjects providing patients' virus is susceptible to ABC/3TC. Therefore, we did not require additional data with Triumeq to support the broad indication – 'treatment of HIV infection'.

In summary, the discussion in this review is focused on the Week 96 results from SINGLE and Week 48 results from SAILING trials. The data from the Phase 3 trials (SPRING-2 and FLAMINGO) in treatment naïve subjects are considered supportive trials evaluating the safety and efficacy of DTG-containing regimens. Therefore the results for these supportive trials are not included in this review. Further, in the Triumeq label, summary sentences and references to the Tivicay label will be included, where appropriate, to provide the additional details for these supportive trials. The clinical review for sNDA 204790 (Tivicay) will address results from all the Phase 3 trials.

This clinical review presents the main findings for dolutegravir in combination with ABC/3TC, highlighting safety, efficacy and overall risk/benefit assessment to support my recommendation for approval for NDA 205551. References are made throughout the review to the dolutegravir NDA as well as to GSK's abacavir and lamivudine NDAs to

support safety and efficacy of each individual drug product, when used in combination or with other ARVs.

Although the fixed dose combination product under review contains three antiretroviral agents, limited discussions are included for abacavir and lamivudine as these NRTIs have been approved for use for many years. Abacavir (Ziagen®) was originally approved on 17 December 1998 (GSK; NDA 020977 for the tablet formulation); lamivudine (Epivir®) was originally approved on 17 October 1995 (GSK; NDA 020564 for tablet formulation). Epzicom®, the FDC drug product containing abacavir and lamivudine was approved on 2 August 2004 (GSK; NDA 021652). Prescribers are familiar with the safety profiles for these individual drugs. Please refer to the individual drug products reviews for additional safety information.

2. Background

The estimated number of people infected with HIV or AIDS worldwide is approximately 33 million, which pleads for continuing the need for development of new treatments. Currently available HIV treatment includes six different antiretroviral drug classes- comprised of over 27 approved single agents (not including FDC products). The drug classes include: nucleoside reverse transcriptase inhibitors (NRTI), non- nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors, CCR5 receptor antagonists, and integrase strand transfer inhibitors.

Abacavir and lamivudine are a carbocyclic synthetic nucleoside analogue and belong to the class nucleoside reverse transcriptase inhibitors (NRTIs). Both are approved for treatment of HIV infection in combination with other ARVs.

Dolutegravir, an INSTI is indicated for treatment of HIV-1 infection in combination with other ARV. Dolutegravir was the third and the latest INSTI to be approved for treatment of HIV infection. Previously approved INSTIs include raltegravir and elvitegravir (as part of the FDC drug product, Stribild). Although there are no labeled class-related toxicities identified with the INSTI class, several overlapping toxicity trends have been noted. Raltegravir and dolutegravir are associated with development of serious skin reactions (including hypersensitivity reactions for DTG). Neuropsychiatric events have also been noted for both drugs: while psychiatric events including suicidal ideation and depression were noted for both drugs, insomnia was the most common neuropsychiatric ADR for dolutegravir. Other safety issues of interest for DTG include increase in serum creatinine and serum creatinine kinase. Myopathy, rhabdomyolysis, and creatinine kinase elevations have also been reported with raltegravir use. Elvitegravir is associated with musculoskeletal events and sleep disorders. 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 gastrointestinal side-effects such as diarrhea and nausea.

Dolutegravir was approved for treatment of HIV infection on 17 August, 2013. The

approval was supported by four clinical trials: two Phase 3 trials in treatment naïve-subjects, one Phase 3 trial in treatment-experienced, INSTI naïve subjects, and one single arm Phase 3 trial in INSTI-experienced subjects. The two phase 3 trials in treatment naïve adults (SINGLE and SPRING-2) are ongoing, randomized, double-blind, double- dummy, active controlled international trials and are identical in design except for the comparator drug and for the background regimens. The active comparators for SINGLE and SPRING-2 are efavirenz and raltegravir, respectively. The two trials differ in the background regimen: SINGLE included a fixed regimen of abacavir/lamivudine; whereas in SPRING-2, either abacavir/lamivudine or tenofovir/emtricitabine was allowed. The safety data from these three active-controlled trials includes approximately 1171 subjects treated at the marketed, 50 mg QD dose for at least 48 weeks (in naïve subjects) or 24 weeks (in INSTI naïve subjects). In Viking-3, 50 mg BID was evaluated; while 183 subjects were enrolled for the trial, 114 subjects had 24 week data at the time of the NDA review. Please refer to NDA 204790 for details.

GSK has submitted an efficacy supplement to NDA 204790 (Tivicay) containing 96 Week data for SINGLE and SPRING-2 and 48 Week data for SAILING. In addition, results from Week 48 data from a new Phase 3b trial (FLAMINGO) conducted in treatment naïve adults are also included. The comparator arm for this trial is darunavir/ritonavir, with background regimen limited to ABC/3TC or TDF/FTC. Additionally, Week 48 data are also included from the VIKING-3 trial.

Triumeq, a FDC drug product containing ABC/DTG/3TC represents a new complete regimen administered as a single tablet, taken once daily for the treatment of HIV-1 infection in (b) (4) resistance to components of the FDC drug product. The dose of DTG in Triumeq is insufficient (b) (4).

This NDA review focuses on two Phase 3 trials, SINGLE and SAILING. The interim results from these trials were previously reviewed under NDA 204790 (48 week data for SINGLE and 24 week data SAILING). The Week 96 data (SINGLE) and Week 48 data (SAILING) are discussed in this review.

The financial disclosure information was provided by the Applicant with NDA 204790 and reviewed by the clinical review team (see Appendix 1). There is no new financial information for the pivotal Phase 3 trials.

3. CMC

Please refer to ONDQA's Chemistry review by Dr. Maotang Zhou and Biopharmaceutics review by Dr. Elsbeth Chikhale for full details. In summary, issues related to stability, microbial testing, and product quality have been adequately addressed by the Applicant. The dissolution method and acceptance criteria are also acceptable. The Office of Compliance (Office of Scientific Investigation) has inspected the bioequivalence trial site. A recommendation is pending.

NDA 205551 provides data for Triumeq FDC drug product. The drug product has a shelf life of 24 months when stored at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature]. Triumeq tablets are purple, biconvex and debossed with '572 Tri' on one side. Each film-coated tablet contains abacavir sulfate equivalent to 600 mg of abacavir, dolutegravir sodium equivalent to 50 mg of dolutegravir, and 300 mg of lamivudine.

The proposed dissolution medium [REDACTED] (b) (4) was not considered adequate for the dissolution testing of abacavir and lamivudine. A full dissolution profile data for abacavir and lamivudine has been requested by the ONDQA's Biopharmaceutics team and is currently under review. Additionally, several information pertaining to drug substance specifications have been requested and are currently under review.

4. Nonclinical Pharmacology/Toxicology

Extensive programs of nonclinical studies with ABC, DTG, and 3TC have been previously conducted. In view of the nonclinical safety profiles for each of these compounds, additional nonclinical combination safety studies with ABC, DTG and 3TC are not considered necessary to support this application. Therefore, no new nonclinical pharmacology/toxicology data were submitted.

The preclinical evaluation of DTG included trials to assess the safety pharmacology, pharmacokinetics, general toxicology, carcinogenicity, genetic toxicology, and reproductive and developmental toxicology. Please refer to the review by Dr. Mark Seaton for details of nonclinical toxicology findings under NDA 204790.

Please refer to the individual drug NDAs for abacavir and lamivudine for further details.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Dr. Stanley Au's Clinical Pharmacology Review and Dr. Elsbeth Chikhale's Biopharmaceutics Review for details.

Absorption, Food effects and Bioavailability

Relative BA Study ING114580

The Applicant conducted a relative BA study to support the FDC drug product. Please refer to the individual study review by Dr. Stanley Au, Clinical Pharmacology reviewer for details regarding the food effect evaluation for the FDC drug product and the Biopharmaceutics review by Dr. Elsbeth Chikhale for details regarding the bioequivalence of the FDC tablet compared to the individual drug products.

The primary objective of the study was to evaluate the relative BA of a FDC tablet

compared to the individual drug products taken concurrently under fasted conditions. The FDC tablet provided similar exposures compared to the individual components administered concurrently under fasted conditions (90% CIs were within 80%-125% for ABC, 3TC and DTG C_{max} and AUC_[0-inf]); thus the FDC is bioequivalent to the individual drug products, pending the results of the OSI inspection for the trial.

Triumeq may be taken with or without food. In healthy adults, when compared with fasted conditions, the high-fat mean condition resulted in decreased C_{max} (23%) for abacavir and increased C_{max} (37%) and AUC (48%) for dolutegravir. Lamivudine exposures were not affected by food.

Refer to the Individual drug NDAs and Prescribing Information for additional information with regards to additional Clinical Pharmacology information for each component of Triumeq.

Metabolism, Elimination, Half-life

Dolutegravir: Dolutegravir is metabolized primarily by the UDP-glucuronosyltransferase, UGT1A1, pathway and CYP3A4 is a minor pathway. Approximately 53% of DTG is excreted in feces and 31% is excreted in urine. The average terminal half-life is approximately 14 hours and steady-state is achieved after approximately 5 days with repeat dosing. Please refer to dolutegravir NDA and prescribing information for details.

Abacavir: Following oral administration of 600mg tablet, abacavir is rapidly absorbed and extensively distributed. The primary routes of elimination are alcohol dehydrogenase. Observed elimination half-life was 1.54 ±0.63 hrs in single dose trials. Refer to prescribing information and NDA review for abacavir for details.

Lamivudine: Following oral administration of 300mg tablet, lamivudine is rapidly absorbed and extensively distributed. Approximately 70% of intravenous dose of lamivudine is recovered as unchanged drug in the urine. In most single dose trials, the observed mean elimination half-life ranged from 5 to 7 hrs. Refer to the NDA review and prescribing information for lamivudine for details.

Dose Selection

The dose for the individual drug products were determined in their respective development programs and subsequently approved under their corresponding NDAs. The FDC product contains the approved doses of abacavir 600mg, dolutegravir 50 mg and lamivudine 300 mg. Thus no additional dose exploration trials are needed to support the FDC drug product.

Drug-drug interactions (DDI)

Please refer to Dr. Stanley Au's Clinical Pharmacology Review for details. In summary no new DDI studies were conducted using the FDC drug product. Summaries are provided below highlighting the major DDI based on trials from the individual drugs:

Dolutegravir: Certain ARVs decrease the exposure of dolutegravir 50mg QD. These ARVs include efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, and rifampin. When dolutegravir 50mg once daily is co-administered with any of aforementioned ARVs, the recommended dolutegravir dosage regimen is 50 mg twice daily. Co-administration of dofetilide with dolutegravir is contraindicated due to the potential for increased dofetilide exposure and risk for serious and/or life-threatening events. Refer to dolutegravir USPI for additional details.

Abacavir: Ethanol decreased the elimination of abacavir, causing an increase in overall exposure. Methadone has no clinically significant effect on abacavir.

Triumeq: No DDI trials were conducted using the FDC drug product. However, all the relevant DDI from the individual drug products are included in the proposed Triumeq label. Specifically, based on DDI studies with DTG, the following recommendations are included in the proposed label:

Dosing Recommendation With Certain Concomitant Medications

(b) (4) the dolutegravir (b) (4) (50 mg (b) (4) in TRIUMEQ is insufficient when co-administered with (b) (4) that may decrease dolutegravir concentrations, the following dolutegravir dosage regimen is recommended.

Coadministered Drug	Dosing Recommendation
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50-mg tablet, separated by 12 hours from TRIUMEQ, should be taken.

Thorough QT trial or other QT assessment

Dolutegravir: A TQT 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. 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. Please refer to the review by QT-interdisciplinary review team (IND 75382) for details.

The effects of abacavir or lamivudine as single entities or the effect of Triumeq on the QT interval have not been evaluated.

Critical intrinsic factors: age, gender, hepatic insufficiency and renal impairment.

Dolutegravir

The safety of DTG was assessed during review of NDA 204790. Included in the review are several key subgroups analysis to evaluate intrinsic factors such as age, gender, hepatic and renal functions. A specific pattern of concern was not identified during the safety analyses by race, gender or age. Based on the hepatic impairment trial results, no dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Similarly, based on the renal impairment trial results, no dose adjustment is recommended for patients with mild to moderate renal impairment.

Abacavir: A dose reduction is required in patients with mild hepatic impairment. No trials have been conducted establishing safety, efficacy, and pharmacokinetics of abacavir in patients with moderate or severe hepatic impairment. Thus, abacavir is contraindicated in patients with moderate or severe hepatic impairment.

Lamivudine: A dose reduction is required in patients with creatinine clearance <50 mL/min.

Triumeq: Because Triumeq contains abacavir and lamivudine, Triumeq cannot be administered to patients with hepatic or renal impairment. For example, if a dose reduction of lamivudine is required for patients with creatinine clearance <50 mL/min, Triumeq should not be used. Similarly, if a dose reduction of abacavir is required due to hepatic impairment, Triumeq should not be used. The individual drugs or alternative ARV regimen should be considered under these scenarios.

The labeling recommendations for Triumeq reflect the above information in the appropriate sections, including:

(b) (4)
Triumeq (b) (4) patients with creatinine clearance less than 50 mL/min (b) (4)
(b) (4).

4.0 Contraindications

Triumeq is contraindicated in patients with moderate or severe hepatic impairment.

Exposure-response and Exposure-safety analyses

Dolutegravir

Please refer to reviews of NDA 204790 for details on the exposure-response and exposure-safety analyses. Specifically, please refer to the clinical pharmacology and pharmacometrics reviews by Drs. Su-Young Choi, Stanley Au, and Jeffry Florian for details. No further exposure-response and exposure-safety analyses were conducted for the FDC drug product.

The analyses conducted under NDA 204790 evaluated DTG in treatment-naïve subjects where DTG 50 mg QD was administered. In summary, no exposure-response relationships were observed for DTG. Of note, the analyses for the naïve subjects included DTG data irrespective of background regimens (ABC/3TC or TDF/FTC) because the background NRTIs have no effect on DTG exposures. Thus, the overall conclusions with regards to exposure- response or exposure-safety analyses for DTG remain unaltered. In the treatment-experienced, INI-naïve subjects, an apparent exposure-response relationship was observed when analysis included all subjects from the trial; however, the results were not reproducible following exclusion of subjects whose background regimen (BR) included moderate to strong metabolic inducers (such as TPV/r or EFV which reduce DTG exposures) or in subjects who were noncompliant.

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.

6. Clinical Microbiology

The clinical microbiology section addresses details pertaining to dolutegravir. Please refer to the respective NDAs and the prescribing information for details on the microbiology profile of abacavir and lamivudine.

Dolutegravir

Please refer to clinical and virology reviews of NDAs 205551 and 204790 for additional details. Please also refer to the prescribing information for Tivicay for additional information.

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.

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 trial- SINGLE

Based on resistance analysis in a subset of subjects (i.e. those with HIV RNA >400 copies/mL at failure or last visit through Week 96 and who have a resistance data available, n=8), no subject from DTG treatment arm had a decrease in susceptibility to DTG or background NRTIs.

Treatment-experienced, INI naïve trial- SAILING

At 48 weeks, 6% and 13% subjects in the DTG and RAL arms respectively met protocol specified virologic failure criteria. Among 28 DTG subjects who had resistance data available at failure, six subjects had treatment-emergent INSTI resistance substitutions. In comparison, among 49 RAL subjects with resistance data available at failure, 21 subjects had emergent INSTI resistance substitutions. Only one isolated from the DTG failure subjects with emergent INSTI resistance substitutions had phenotypic resistance to DTG and RAL. This isolate had RAL resistance substitutions at baseline with additional emergent INSTI resistance substitutions at failure. The other 5 isolates from DTG failure subjects with emergent INSTI resistance substitutions had <2-fold change in dolutegravir phenotypic susceptibility. All RAL failure subjects with emergent INSTI

resistance substitutions had phenotypic resistance to RAL.

Cross-resistance

No new data were submitted with the current NDA. In summary, the single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a >2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a >2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference).

Abacavir and Lamivudine

Please refer to prescribing information for Ziagen and Epivir for details. The antiviral activity of abacavir against HIV-1 was assessed in a number of cell lines including in primary monocytes/macrophages and PBMCs. EC₅₀ values ranged from 3.7 to 5.8 μM (1 μM = 0.28 mcg/mL) and 0.07 to 1.0 μM against HIV-1_{IIIB} and HIV-1_{BaL}, respectively, and was 0.26 ± 0.18 μM against 8 clinical isolates. The antiviral activity of lamivudine against HIV-1 was assessed in a number of cell lines including monocytes and PBMCs using standard susceptibility assays. EC₅₀ values were in the range of 0.003 to 15 μM (1 μM = 0.23 mcg/mL). HIV-1 isolates with reduced susceptibility to the combination of abacavir and lamivudine have been selected in cell culture with amino acid substitutions M184V/I, K65R, L74V, and Y115F in HIV-1 RT. Substitution at M184I or V causes high-level resistance to lamivudine and approximately 2-fold decreased susceptibility to abacavir. Substitutions K65R, L74M, or Y115F with M184I or V conferred a 7-fold to 8-fold reduction in abacavir susceptibility, and combinations of three substitutions were required to confer more than an 8-fold reduction in susceptibility. Cross-resistance has been observed among NRTIs. The combination of abacavir/lamivudine has demonstrated decreased susceptibility to viruses with the substitutions K65R with or without the M184V/I substitution, viruses with L74V plus the M184V/I substitution, and viruses with thymidine analog mutations (TAMs: M41L, D67N, K70R, L210W, T215Y/F, K219 E/R/H/Q/N) plus M184V. An increasing number of TAMs is associated with a progressive reduction in abacavir susceptibility.

The proposed label for Triumeq reflects all the pertinent microbiology points discussed above.

7. Clinical/Statistical- Efficacy

No efficacy trial was conducted with Triumeq tablet. The efficacy of dolutegravir, the anchor/ third agent for the FDC, is established primarily based on the SINGLE trial and supported by the SAILING trial and other Phase 3 clinical trials previously reviewed under NDA 204790. The SINGLE trial is the pivotal trial supporting the Triumeq because all subjects enrolled in the trial received DTG plus ABC/3TC. Please refer to NDA 204790 for full details on trial design attributes, demographics, baseline characteristics and results for all the Phase 3 trials.

This review focuses on results from SINGLE and SAILING. Note, Week 48 (SINGLE) and Week 24 (SAILING) results were also reviewed under NDA 204790. This NDA provides longer-use data for the two trials – Week 96 (SINGLE) and Week 48 (SAILING) - and support approval of Triumeq for treatment of HIV infection. This review will focus on outcomes at Week 96 (SINGLE) and Week 48 (SAILING) results. For results from the Week 48 (SINGLE) and Week 24 (SAILING) analysis, please refer to the clinical review by Drs. Charu Mullick and Wendy Carter under NDA 204790.

Overview of the Trial Designs

SINGLE (Treatment Naïve)

SINGLE is an ongoing phase 3, randomized, double-blind, double-dummy, active-controlled, international, non-inferiority trial in HIV-1 infected treatment-naïve adults. This trial was designed to demonstrate the non-inferiority of DTG 50 mg plus ABC/3TC FDC compared to FDC Atripla consisting of EFV, TDF, FTC, both administered once daily over 144 weeks. The primary analysis was at Week 48 and reviewed under NDA 204790. The Week 96 results are reviewed in this NDA and future submission for the open-label Week 96-144 result is expected. Key inclusion criteria included HIV-1 infected treatment-naïve adults ≥ 18 years of age with plasma HIV-1 RNA ≥ 1000 copies/mL at Screening and 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 $\leq 100,000$ copies/mL or $> 100,000$ copies/mL and CD4 cell count \leq or > 200 cells/mm³. The primary efficacy objective was to demonstrate non-inferiority of treatment with DTG 50 mg plus ABC/3TC QD compared to Atripla at Week 48, with a pre-specified NI margin of 10%. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 using the FDA 'snapshot' algorithm (Missing, Switch or Discontinuation=Failure). A total of 788 subjects were planned for enrollment; 844 subjects were randomized, and 833 subjects received at least one dose of trial medication.

SAILING (Treatment-experienced, INSTI naïve)

SAILING is a randomized, double-blind, active controlled trial in treatment-experienced INSTI-naïve subjects. Subjects with resistance to at least two or three ARV classes, and having at least one fully active ARV (in addition to DTG or RAL) to construct a background regimen were enrolled. Subjects were randomized to DTG 50 mg once daily or RAL 400 mg twice daily, each taken with an optimized background regimen. Darunavir use in the OBR was restricted to maximum of 60 participants. Randomization was stratified by screening HIV RNA \leq or $> 50,000$ copies/mL, presence of two or $<$ two fully active ARVs in the OBR, and DRV use (no DRV/r use, or DRV/r used with or without primary PI mutations). The primary endpoint is proportion of subjects with HIV RNA < 50 copies/mL at 48 weeks.

A total of 719 subjects were enrolled. As extensively discussed under NDA 204790,

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subjects enrolled from Russian site 083523 were excluded from analysis. This site was closed by the Applicant after Good Clinical Practices (GCP) violations were discovered. Post exclusion, data from 715 subjects were included in analyses. This included 354 and 361 subjects in the DTG and RAL arms, respectively.

Demographics and Baseline Characteristics

SINGLE

The intent to treat population (ITT) for SINGLE included 833 subjects, 414 of whom received DTG and 419 received Atripla. Baseline characteristics, including gender, race and age were comparable between the two groups. The majority of the participants were male (84%) and Caucasian (68%). Overall, 68% of subjects had a baseline viral load of \leq 100,000 copies/mL and 86% had CD4 cell counts above 200 cells/mm³. 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.

Table 1: Demographic and Baseline Characteristics

	DTG + ABC/3TC QD N=414 n (%)	Atripla QD 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)
Median baseline HIV-1 RNA	4.7	4.7	4.7
Baseline HIV RNA group			
≤100,000 copies/mL	280 (68)	288 (69)	568 (68)
>100,000 copies/mL	134 (32)	131 (31)	265 (32)
Median Baseline CD4 (cells/mm³)			
<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)

*One subject with missing data from Atripla arm

[†] Subjects with hepatitis B were excluded from enrollment

Source: demography population flags, viral HIV-1 analysis dataset- SINGLE

SAILING

The treatment arms were balanced with respect to age, gender, and race. The treatment arms were also balanced with respect to baseline CD4 count, baseline plasma HIV RNA, ARV class resistance, baseline GSS, and DRV/rtv use in OBR. Thirty-two percent of subjects were female and 50% were non-white. Overall 51% subjects had two-class resistance; the remaining had resistance to three or more classes. The majority, 52% of subjects had baseline GSS of 1 to < 2, while 42% had baseline GSS of 2. Overall, 41% of subjects received a DRV containing regimen. Among these, 21% subjects received DRV/rtv and did not have primary PI mutations at baseline.

Efficacy Results

Please refer to statistical review by Dr. Tom Hammerstrom for additional details, including details on secondary efficacy endpoint analyses, subgroup analyses and sensitivity analyses.

SINGLE

Table 2 below summarizes the efficacy outcome at Week 96 based on FDA's snapshot algorithm. The findings from the Week 96 analyses were consistent with the findings from the Week 48 analyses. Overall, the proportion of subjects with viral load <50 copies/mL was 80% and 72% for the DTG and Atripla arms, respectively. The treatment difference was 8% (95% CI: 2.3%, 13.8%). The overall efficacy result demonstrated the superiority of DTG-containing regimen over Atripla- containing regimen in this trial. The primary reason for the difference noted between the two arms is the higher rate of discontinuation due to adverse events in the Atripla arm (11% vs. 3%). Similar findings were noted at the Week 48 analysis; the proportion of subjects with HIV RNA <50 copies/mL was 88% and 81% in the DTG and Atripla arm, respectively. The treatment difference at Week 48 and 95% CI was 7.4% (2.5%, 12.3%).

Table 2: Efficacy Outcome at Week 96

Efficacy outcome Week 96	DTG + ABC/3TC QD N=414 n(%)	Atripla QD N= 419 n(%)
HIV RNA <50 copies/mL*	332 (80)	303 (72)
HIV RNA ≥ 50 copies/mL	31(7)	33 (8)
Data in window not below threshold	13 (3)	7 (2)
Discontinued for lack of efficacy	9 (2)	11 (3)
Discontinued for other reason while not below threshold	9 (2)	15 (4)
No Virologic Data	51 (12)	83 (20)
Discontinued due to AE or Death	13 (3)	48 (11)
Discontinued for Other Reasons	36 (9)	35 (8)
Missing data during window but on study	2 (<1)	0
Subgroup Analysis		
Baseline HIV RNA (copies/mL)		
≤ 100,000	239 (85)	209 (73)
>100,000	94 (73)	94 (71)
Gender		
Female	51 (76)	35 (56)
Male	282 (81)	268 (75)
Race		
Caucasian	225 (79)	219 (77)
African-American or African Heritage	79 (81)	62 (63)
Other	29 (91)	21 (60)

*Treatment difference: 8% (95% CI: 2.3- 13.8%).
Source: Snapshot dataset for SINGLE

Efficacy outcome was also evaluated based on baseline CD4 count, plasma HIV RNA (≤ vs. > 100,000 copies/mL), gender and race.

A difference in virologic response rate was noted within the DTG arm when efficacy was assessed based on baseline HIV RNA; response rates were 85% and 73% in subjects with baseline HIV RNA ≤ 100,000 copies/mL and >100,000 copies/mL, respectively. The primary reason for this observed difference is the number of virologic failures, 4% and 14% in subjects with baseline HIV RNA ≤ 100,000 and >100,000 copies/mL, respectively.

A difference in treatment response was also noted between the two treatment arms when efficacy outcome was evaluated based on baseline HIV RNA; among subjects with baseline HIV RNA ≤ 100,000, the proportion of subjects who were suppressed was higher in the DTG arm compared to the Atripla arm, 85% and 73%, respectively. The difference was driven by a higher rate of treatment discontinuation due to adverse events in the Atripla arm (4% DTG vs. 12% Atripla). Among subjects with baseline HIV RNA

>100,000 copies/mL, the two arms performed similarly (71% DTG, 72% Atripla). The reason for this finding does not appear to be due to virologic failure but may be due to missing data. The proportion of subjects who had no virologic data due to reasons such as withdrew consent, lost to follow-up, moved, and protocol deviation was 10% in the DTG arm and 6% in the Atripla arm. Discontinuation due to adverse events continues to be higher in the Atripla arm (10%), compared to 2% in the DTG arm.

SAILING

At week 48, 71% and 64% of subjects in the DTG and RAL arms, respectively, had HIV RNA < 50 copies/mL by snapshot analysis. The treatment difference was 7% with 95% CI 0.7%, 14.2%, demonstrating superiority of DTG containing regimens over RAL regimens. The week 48 findings support week 24 results. Of note, the background regimen in SAILING was not limited to ABC/3TC. Among subjects enrolled in the SAILING trial, 8 received DTG with ABC/3TC. Although few in this trial received the components of Triumeq, the effectiveness of Triumeq in patients who are treatment-experienced, INSTI-naïve can be extrapolated as long as the virus is susceptible all the components of Triumeq. Additionally, previous clinical trials have demonstrated the effectiveness of abacavir and lamivudine for the treatment of HIV infection in treatment-experienced subjects with susceptible virus.

Table 3: Efficacy Outcome at Week 48

Efficacy Outcome Week 48	DTG+ BR QD n(%)	RAL+ BR QD n(%)
	N=354	N=361
HIV RNA <50 copies/mL	251 (71)	230 (64)
HIV RNA ≥ 50 copies/mL	71 (20)	100 (28)
Data in window not below threshold	35 (10)	48 (13)
Discontinued for lack of efficacy	19 (5)	35 (10)
Discontinued for other reason while not below threshold	7 (2)	7 (2)
Change in ART	10 (3)	10 (3)
No virologic data at the week 48 window	32 (9)	31 (9)
Discontinued study drug due to AE or death	9 (3)	13 (4)
Discontinued for other reasons and last available HIV RNA > 50 c/ml	16 (5)	14 (4)
Missing data during window but on study drug	7 (2)	4 (1)

*Treatment difference: 7% (95% CI: 0.7- 14.2%).
Source: Snapshot.xpt, Pop.xpt - SAILING

- Key subgroup analysis
 - The trend of higher response rate in the DTG arm compared to RAL was

observed across the majority of subgroups. Results of analysis for subgroups by stratification factors are provided below for the various subgroups.

- No DRV/rtv use: response rates for DTG and RAL were 67% (143/214) and 60% (126/209) respectively.
- DRV/rtv use without primary PI substitutions, response rates for DTG and RAL were 69% and 70% respectively.
- DRV/r use with primary PI substitutions, response rates for DTG and RAL were 85% and 67% respectively.

The reason for differential DTG response in subgroups where DRV/rtv was used without or with primary PI substitutions (69% and 85%) is not known. It should be noted these subgroups were small with approximately 68-77 subjects in each, which limits interpretability of the results. Importantly, DRV is a potent PI and results from the no DRV/rtv use subgroup indicate the overall response observed in the trial was not driven by DRV effects.

- Subgroup analysis was also performed for the remaining two stratification factors. As mentioned previously, the SAILING trial enrolled treatment-experienced subjects failing an ARV regimen with screening HIV RNA at least 400 copies/ml. For this particular population, enrollment was stratified by screening HIV RNA \leq or $>$ 50,000 copies/ml to ensure adequate representation of the higher baseline HIV RNA category. Analysis by the baseline HIV RNA category, \leq or $>$ 50,000 copies/ml, showed higher response rates for DTG compared to RAL in each group. For subgroups with PSS 2 or $<$ 2, higher response rates were observed with DTG compared to RAL in each group.

- Secondary endpoints

Analyses of secondary endpoints also support the primary efficacy findings: the proportion of subjects with HIV RNA $<$ 400 copies/mL was 79% and 71% in DTG and RAL arms, respectively. Mean increases in CD4 count were 162 cells/mm³ and 153 cells/mm³ in the DTG and RAL arms, respectively.

Efficacy summary and conclusions

In summary, dolutegravir, when used in combination with ABC/3TC, is efficacious for treatment of HIV-1 infection in naïve or experienced (INSTI-naïve) subjects. The SINGLE trial provided robust data in treatment naïve subjects, where all subjects received DTG in combination with ABC/3TC. The efficacy of DTG in treatment experienced, INSTI naïve adults is demonstrated in SAILING trial. Although few were enrolled in the SAILING trial with ABC/3TC as background regimen, the effectiveness of Triumeq in patients who are treatment-experienced but INSTI naïve can be extrapolated as long as the virus is susceptible to dolutegravir, in addition to abacavir/ lamivudine.

The use of Triumeq alone is not recommended in patients who are not susceptible to each components of the FDC product. Moreover, the dose of dolutegravir contained in Triumeq is not sufficient for patients who may have INSTI-associated resistance

substitutions or clinically suspected INSTI resistance. In patients with certain INSTI-associated resistance substitution, DTG 50 mg twice daily is required. Please refer to NDA 204790 and Prescribing Information for Tivicay for additional details. These facts should be considered when treatment is initiated with ABC/DTG/3TC FDC drug product. The Prescribing Information for Triumeq reflects these limitations under the Usage and Indications section and Microbiology section.

1.0 Indications and Usage

TRIUMEQ is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection.

Limitations of Use:

- TRIUMEQ alone (b) (4) in patients with current or past history of resistance to any components of TRIUMEQ [see Microbiology (12.4)].

- (b) (4)

8. Safety

Abacavir and lamivudine have been marketed for over 15 years. The safety profiles of these drugs are well known. Dolutegravir is a new ARV, approved in August 2013, thus the focus of the safety review for this NDA will highlight adverse reactions associated with dolutegravir. Please refer to NDA 204790 review for extensive discussions on the safety and tolerability of dolutegravir when used in combination with ARVs.

Please refer to abacavir and lamivudine NDAs and the individual Prescribing Information for additional details on the safety and tolerability of these NRTIs.

The SINGLE and SAILING trials evaluated the safety profile of DTG 50 mg taken once daily, in treatment naïve and treatment-experienced, INSTI naïve subjects. The DTG safety profile appears similar across the two populations. While subjects in SINGLE all received ABC/3TC as background regimen, few received ABC/3TC in SAILING. For subjects in SAILING who received DTG with ABC and 3TC, no new or unexpected safety concerns were observed.

Disposition

SINGLE

Subjects were randomized to DTG+ABC/3TC or Atripla and completed 96 weeks in the double-blind phase of the trial. At Week 96, subjects were unblinded and given the opportunity to continue into the open-label phase through to Week 144 or discontinue from the trial. A total of 833 subjects were randomized (1:1) and received at least one dose of trial medication, 414 in the DTG arm and 419 in the Atripla arm. As summarized in Table 4 below, through Week 96, more subjects discontinued Atripla (28%) compared to the DTG (18%). 'Adverse events' was the most common reason for discontinuation for both arms -3% and 12% in the DTG and Atripla arms, respectively. Similar to the Week

96 finding, at Week 48, more subjects discontinued in the Atripla arm due to adverse events compared to the DTG treatment arm – 2% (DTG) vs. 10%

(Atripla).

Table 4. Disposition, Week 96

Disposition events n(%)	DTG/ABC/3TC QD N=414	Atripla QD N=419
Number of subjects who discontinued	73 (18)	116 (28)
Lack of efficacy	18 (4)	15 (4)
Lost to follow-up	17 (4)	18 (4)
Adverse event	14 (3)	52 (12)
Protocol deviation	14 (3)	14 (3)
Withdrew consent	9 (2)	15 (7)
Investigator discretion	1 (<1)	2 (<1)

Source: Disposition analysis dataset- SINGLE

SAILING

A total of 719 subjects were enrolled and randomized 1:1 to DTG (n=360) or RAL (n=364). Five subjects withdrew prior to dosing (3 DTG, 2 RAL). Four additional subjects (3 DTG, 1 RAL) enrolled at Russian site were excluded from analysis. The ITT population includes 354 and 361 subjects in the DTG and RAL arms respectively. After completion of 48 weeks treatment, subjects in the DTG arm had the option of continuing treatment in an open-label phase. At the time of data cut-off for 48 week analysis, 16% and 22% of subjects in the DTG and RAL arms had withdrawn from the trial. This includes 6% and 12% subjects in the DTG and RAL arms respectively who discontinued for lack of efficacy; therefore, a total of 1% and 3% subjects in the DTG and RAL arms respectively discontinued due to an AE.

General Safety Analysis

The following table provides summary of the overall characteristics of AEs reported during SINGLE trial. The characteristics of the adverse events in the SAILING trial were generally similar to those observed in the SINGLE trial. In addition, for both SINGLE and SAILING, the overall safety analysis did not significantly change with regards to types of AEs or frequency of AEs between the interim analysis time point (Week 48 SINGLE; Week 24 SAILING), and the current analysis time point (Week 96 SINGLE; Week 48 SAILING).

Table 5: Overview of Adverse Events, Week 96

Overview of Adverse Eventsn(%)	DTG +ABC/3TC QD N=414	Atripla QD N=419
Death	0	2 (<1)
SAE	47(11)	53(13)
SAE and related	1(<1)	9(2)
Discontinuations	14(3)	53(13)
Subjects experiencing ≥ 1 AE	376 (91)	394 (94)
Maximum Toxicity		
Grade 1	143(35)	138(33)
Grade 2	176(43)	173(41)
Grade 3	56(14)	79(19)
Grade 4	7(2)	10(2)

Source: adverse events analysis dataset- SINGLE

Deaths and other SAEs

SINGLE

Through the Week 96 data cut-off, two fatalities were reported; both were in the Atripla treatment group and were discussed during the Week 48 analysis. No additional fatalities were reported since then.

Throughout the 96 weeks treatment period, the numbers of subjects reporting a SAE were similar between the two arms; 47(11%) and 53 (13%) in the DTG and Atripla arms, respectively. This finding is generally similar to the Week 48 observation- 9% in the DTG arm and 8% in the Atripla arm. Among the SAE, few occurred in more than 1 subject at both analyses time points. At Week 96, the SAE reported in at least 2 subjects in the DTG arm include pneumonia (n=3) and syphilis (n=2); this is identical to the Week 48 findings, with exception of an extra subject who reported pneumonia. The SAE reported in at least 2 subjects in the Atripla arm at Week 96 include drug hypersensitivity, suicide attempt, depression, pneumonia, and appendicitis.

Treatment-related SAEs occurred in 10 subjects, one of whom was treated with DTG. The subject in the DTG arm experienced drug hypersensitivity and was previously discussed during the Week 48 data review. Briefly, a 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. The culprit for the hypersensitivity remains to be definitively identified. Either abacavir or dolutegravir could have led to the hypersensitivity reaction.

Additional analysis for other medically serious events, as qualified by FDA's Designated Medical Events (DME) was performed to identify new events since the Week 48 SINGLE trial data review. The identified designated terms include 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. Events identified in the DTG arm during the Week 48 review include deafness and angioedema. No additional events have been identified in the DTG treatment arm post-Week 48 analysis review. In the Atripla arm, a case of anaphylactic reaction (1 subject) and a case of acute renal failure (1 subject) were reported since the Week 48 data review.

SAILING

Overall, three treatment-emergent fatalities were observed through the 48 weeks. All events were in the RAL arm and none were assessed as drug-related. Deaths were attributed to metastatic adenocarcinoma (n=1), cervical carcinoma (n=1), and acute hepatic and renal failure (n=1).

Nonfatal SAEs were observed in 9% and 11% subjects in the DTG and RAL arms, respectively. Among these, only one SAE was observed subjects taking ABC/3TC with DTG: this was an SAE 'cerebrovascular disease' that was considered not related to study treatment, and did not result in drug discontinuation.

Discontinuations due to AEs

SINGLE

Throughout the 96-week treatment period, fewer subjects in the DTG arm (n=14(3%)) discontinued treatment compared to Atripla treated subjects (n=52(12%)). Compared to Week 48, an additional 3 subjects in the DTG arm and 5 subjects in the Atripla arm discontinued treatment due to AEs. The post Week-48 events in the DTG arm include abnormal dreams, nightmare, pulmonary TB and colon cancer. Abnormal dreams and nightmare were considered treatment-related and are further discussed under 'Adverse Events of Special Interest'.

During the overall treatment period, psychiatric disorders was the most common SOC leading to discontinuation in both arms, 4 (<1%) and 23 (5%) in DTG and Atripla arms, respectively. In the DTG arm, no SOC was identified as having $\geq 1\%$ subjects leading to discontinuation. In addition to Psychiatric Disorders, the following SOCs had more than 1 subject discontinuing DTG due to an adverse event: Skin and subcutaneous tissue disorders (n=2), Immune system disorder (n=2), Infection and infestations (n=2), Injury, poisoning and procedural complications (n=2). By preferred terms, adverse events that

led to DTG discontinuation include drug hypersensitivity, hypersensitivity, rash, memory impairment, depressed level of consciousness, abnormal dreams, nightmare, depression, and renal failure. Of note, memory impairment, depressed level of consciousness and abnormal dreams all occurred in one subject. This subject is further discussed under 'Adverse Events of Special Interest' section. .

SAILING

At 48 weeks, 2% and 4% subjects in the DTG and RAL arms discontinued treatment due to an AE. One additional discontinuation after 24 week analysis was due to the AE 'back pain' in a DTG subject. This subject was subsequently diagnosed with gastrointestinal adenocarcinoma with metastases, and back pain was considered to be due to possible spinal metastatic infiltration.

Adverse Drug Reactions

Adverse drug reactions are defined as events considered treatment-related to study drug, as assessed by the investigator.

SINGLE

Since the Week 48 analysis, the frequency of ADRs, by SOC, regardless of severity, did not change by more than 2% for either treatment arm. Overall, throughout the 96 weeks treatment period, the most common ADRs (by SOC) reported in the DTG arm, regardless of severity, were gastrointestinal disorder (22%), psychiatric disorders (21%), nervous system disorders (16%), general disorders and administration site conditions (10%) and skin and subcutaneous tissue disorders (7%). In the Atripla arm, the most common ADRs by SOC were nervous system disorders (42%), psychiatric disorders (30%), gastrointestinal disorders (22%), skin and subcutaneous disorders (18%), and general disorders and administration site conditions (11%).

The table below summarizes ADRs by preferred terms that were at least Grade 2 and reported in at least 2% of subjects in either arm over the 96 weeks period. Overall, insomnia, fatigue and headache were the most common ADRs with Grade 2 or higher severity reported in the DTG arm. Compared to Week 48, the percentage of subjects with ADRs as defined above remained the same in each arm, with the exception of depression and fatigue. By Week 96, one additional subject in the DTG arm experienced fatigue, thereby increasing the incidence from 1% to 2%. During the Week 48 review, five subjects (1%) in each arm experienced depression (at least Grade 2 and considered treatment related). By Week 96, an additional four subjects in the Atripla arm reported depression with at least Grade 2 severity and considered treatment related, increasing the overall depression incidence to 2% for the Atripla arm.

Table 6: Adverse Events with at least Grade 2 Severity, Related, and Reported at least in 2% of Subjects, by Preferred Term Through Week 96

Adverse Events n(%)	DTG +ABC/3TC QD N=414	Atripla QD N=419
Psychiatric		
Insomnia	14 (3)	10 (2)
Depression	5 (1)	9 (2)
Abnormal dreams	3 (<1)	8 (2)
Nervous System		
Dizziness	2 (<1)	21 (5)
Headache	8 (2)	9 (2)
Gastrointestinal		
Nausea	3 (<1)	12 (3)
Diarrhea	3 (<1)	7 (2)
General Disorders		
Fatigue	7 (2)	7 (2)
Skin and Subcutaneous Tissue		
Rash ^a	2 (<1)	22 (6)
Ear and Labyrinth		
Vertigo	0	7 (2)

a: includes: rash, rash generalized, rash macular, rash maculo-papular.
Source: Adverse events analysis dataset- SINGLE

SAILING

The only event meeting the criteria for grade 2 in severity and observed in at least 2% subjects was diarrhea (2% DTG, 1% RAL) as the only event meeting the criteria.

In summary, the ADR at Week 96 (SINGLE) and Week 48 (SAILING) are generally similar to the results previously observed during NDA 204790 review. Analyses of related events, at least Grade 2 in severity and with at least ≥ 2% frequency in either treatment arm were conducted. Since the Week 48 review, two additional terms, depression and fatigue, met the qualification criteria and are now included in the proposed product labeling. Although depression and fatigue were previously described with use of Tivicay, these terms did not meet the analysis criteria for inclusion into the ADR table in the prescribing information for Tivicay. Specifically, the frequency of depression increased to 2% for the Atripla arm, while the frequency of fatigue increased to 2% in both DTG and Atripla arms. Otherwise, the terms and frequencies of ADRs described in Table 2 of the proposed Triumeq label through Week 96 are generally similar to the 48 week data as described in the Tivicay label. The label for Tivicay, including the ADR table will be updated with the supplemental NDA that is currently under review to include the 96 week data.

Adverse events of interest:

Based on signals from nonclinical toxicity studies or previously identified potential INSTI drug class effect, adverse events identified for further safety evaluation for dolutegravir included hypersensitivity reactions and rash, neuropsychiatric events, hepatobiliary events, renal events, and musculoskeletal events. Hypersensitivity reaction is a well-established event for abacavir; thus the proposed labeling for Triumeq includes the abacavir associated warnings and precautions. Hypersensitivity reactions have also been described with use of DTG; detailed reviews of these events were conducted with the Tivicay NDA.

Hypersensitivity reactions and Rash

Hypersensitivity reactions and rash have been previously described in ARVs such as efavirenz, raltegravir and abacavir. A serious and life threatening hypersensitivity reaction (ABC HSR) is associated with use of ABC, especially in those who carry the HLA-B*5701 allele. The drug product labeling for ABC includes wording under Warnings and Precautions, in addition to a boxed warning. Recommendation for HLA allele screening prior to initiation of therapy with abacavir is also included. Hypersensitivity reactions and rash were also observed during review of DTG. Similarly, the Prescribing Information for DTG includes language under Warning and Precaution.

Triumeq contains both abacavir and dolutegravir. Consistent with abacavir labeling, 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. Of note, although the presence of the HLA allele significantly increases the risk of having a hypersensitivity reaction, rash and hypersensitivity reactions have been previously documented in subjects who are negative for HAL-B*5701. Therefore, in the setting of a hypersensitivity reaction or rash events during treatment with ABC/DTG-containing regimen, it may be clinically challenging to differentiate the causal relationship between the specific drug and the event.

The following preferred terms were included for evaluation for rash: rash, exfoliative rash, rash erythematous, rash follicular, rash generalized, rash macular, rash papular, rash maculo-papular, rash pruritic, rash vesicular, and drug eruption. Hypersensitivity was evaluated by including preferred term containing 'hypersensitivity' (e.g. hypersensitivity, drug hypersensitivity) and anaphylactic reaction. For treatment-experienced population analyses, additional AE term of 'angioedema' was included.

SINGLE

Table 7 summarizes characteristics of rash and hypersensitivity-related AEs. Rash AEs were more frequently reported in the Atripla arm compared to the DTG arm, 20% vs. 8%, respectively. The majority of the rash events were mild or moderate, were not treatment-related and resolved without treatment interruption or discontinuation. No DTG subjects were reported to have a grade 4 rash AE. A total of 8 subjects in the DTG treatment arm reported rash-related terms after the Week 48 analysis timepoint. The terms included rash, maculo-papular rash, and pustular rash. All were non-serious, not-related and did

not lead to DTG discontinuation. All but 2 events were Grade 1; one event was Grade 2 (rash), and one of the pustular rash was Grade 3 in severity. In the Atripla arm, a total of 9 subjects reported rash events since the Week 48 review including rash, generalized-rash, pruritic rash, urticaria, and pustular rash. Most were Grade 1 or 2, and none led to treatment discontinuation; one event (rash) was considered treatment-related. Rash occurring after the first four to six weeks of therapy are likely to be due to other causes and less likely to be study drug related.

With regards to hypersensitivity events, overall, most of the hypersensitivity events were reported in the first 48 weeks of treatment and these cases have been previously discussed. Please refer to the clinical review for NDA 204790 for details. In summary, for the DTG arm, 4 subjects had reported hypersensitivity events, all of which occurred before Week 48. Of those, two were considered to be a SAE, although one was revised to non-serious by the investigator at a later date. The rationale for revising the event as non-serious was not provided (see below). No new events were reported since the Week 48 review. In the Atripla arm, 5 subjects reported hypersensitivity reactions at the time of the Week 48 review. An additional 2 subjects experienced hypersensitivity reactions by Week 96; the preferred terms were hypersensitivity (one subject) and anaphylactic reaction (one subject).

Table 7: Skin and Hypersensitivity Events, Week 96

Skin and Hypersensitivity Events n(%)	DTG +ABC/3TC QD N=414	Atripla QD N=419
Number of Subjects with AE	32(8)	83(20)
Event characteristics		
SAE	1	1
Discontinuation	4(1)	9(22)
Drug-related	7(2)	53(13)
Toxicity		
Grade 1	25(6)	48(12)
Grade 2	6(1)	34(8)
Grade 3	2(1)	5(1)
Grade 4	0	0
Outcome		
Resolved		
Not resolved	6(1)	5(1)
Preferred AE Terms		
Drug eruption	0	4 (1)
Drug hypersensitivity	1 (0.2)	1 (0.2)
Hypersensitivity	3 (1)	4 (1)
Rash	19 (5)	60 (14)
Rash generalized	0	9 (2)
Rash macular	2 (1)	1 (0.2)
Rash maculo-papular	2 (1)	5 (1)
Rash papular	2 (1)	0
Rash pruritic	5 (1)	2 (1)
Rash pustular	0	1 (0.2)
Urticaria	0	3 (1)

Source: Adverse events analysis dataset- SINGLE

Below is a brief summary of the hypersensitivity cases reported in the DTG arm; detailed summary is included in the NDA 204790 review:

Hypersensitivity (serious): Subject 6929 received DTG/ABC/3TC; after 2 doses she 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 of the visit.

Hypersensitivity (non-serious): 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.

SAILING

One subject in the DTG arm discontinued treatment due to hypersensitivity reaction; the case was confounded by concurrent use of etravirine and darunavir/rtv. Please refer to Tivicay NDA review for details. No additional concerning cases were observed after the 24 week analysis.

In summary, no significant changes were noted during the Week 96 analysis for SINGLE compared to the Week 48 review. Findings in the HSR-related cases in SAILING were generally similar to the observations in SINGLE. No new additional labeling language is recommended under Warnings and Precautions section. However, the Triumeq label will contain all the pertinent hypersensitivity language for abacavir. The ADR table under Section 6 will reflect the incidence of rash events during the 96-week treatment period.

Hepato-biliary events

The analysis for hepato-biliary events included any hepatobiliary clinical event and liver serum biochemistries. Of note, because subjects with HBV co-infection were excluded from enrollment into SINGLE trial, this analysis was not conducted for SINGLE in this review. Refer to NDA 204790 for analysis on HBV reactivation with use of DTG in combination with other ARVs.

SINGLE

Treatment emergent hepatobiliary events, regardless of causality or severity, were similar between the two treatment groups (1% each). While no events were reported in the DTG arm during the Week 48 review, 5 subjects experienced hepatobiliary events between Week 48 and 96. The events reported include cholelithiasis (n=3), gallbladder polyp (n=1) and hepatic steatosis (n=1). None were serious; all were mild or moderate and none were considered to be treatment related or led to treatment discontinuation. The AEs in the Atripla arm include cholelithiasis (n=1), cholecystitis (n=1) and autoimmune hepatitis (n=1) and all were reported at the time of the Week 48 data review.

Overall, the incidence of liver biochemistry abnormalities was similar between Week 48 and Week 96 review. Based on the analysis of the laboratory datasets, the incidence of Grade 3 and 4 increases in ALT were < 1% for the DTG and Atripla arms. Grade 3 AST elevations were reported in 1% and 2% of DTG and Atripla treated subjects, respectively. The incidence of Grade 1 and 2 ALT or AST elevations were similar between the two treatment arms: Grade 1 ALT (10% vs. 13% in the DTG and Atripla arms, respectively); Grade 2 ALT (2% vs. 5% in the DTG and Atripla arms, respectively); Grade 1 AST (12%

in each arm); Grade 2 AST (3% in each arm). Most total bilirubin (TB) elevations were Grade 1 and occurred in 4% and <1% in the DTG and Atripla arms, respectively. No Grade 4 TB toxicities were reported for either treatment arms and very few (<1%) had Grade 2 or 3 elevation in either treatment arms. No subjects in either group had concurrent elevation of ALT >3xULN, total bilirubin >2xULN and ALP <2xULN.

SAILING

Overall, hepatic-related adverse events observed in DTG and RAL arms were jaundice (2% vs. 1%), hepatitis (1% vs. <1%), hepatocellular injury (1% vs. none), cholelithiasis (<1% vs. <1%), hepatotoxicity (<1% in each arm), bile duct stone (<1% vs. none), liver disorder (<1% vs. none), acute hepatic failure (none vs. <1% RAL), and biliary colic (none vs. <1%). Analysis of hepatic laboratory parameters was performed. The frequency of graded laboratory abnormalities was similar in the DTG and RAL arms. Analysis by HBV and/or HCV coinfection showed a higher proportion of graded laboratory abnormalities in coinfecting subjects compared to mono-infected subjects in DTG treated subjects. This finding was also observed in the 24 week analysis. Analysis for Hy's law cases was performed. Four subjects met laboratory criteria for potential Hy's law cases including 3 subjects in the DTG arm and 1 subject in the RAL arm. All were confounded by either hepatitis B reactivation, hepatitis C infection, or alcohol abuse. The four cases are presented in detail in the Tivicay original NDA review.

In summary, with the exception of the HBV co-infected subset, which were not enrolled in SINGLE, the AEs and laboratory toxicities observed in SAILING were similar to events reported with DTG once daily dosing in SINGLE. For both SINGLE and SAILING trials, the incidences of hepatobiliary events were generally similar to the findings during NDA 204790 review. No new hepatic-related safety issues have been identified.

Neurologic and psychiatric disorders

Neuropsychiatric (NS) events have been reported with use of Isentress and Stribild. At the time of the dolutegravir (Tivicay) review special consideration was given to neurologic and psychiatric disorders. Please refer to review under NDA 204790 and Prescribing Information for Tivicay for details.

SINGLE

Overall, throughout the 96-weeks treatment period, more subjects treated with Atripla developed a neurological event (all causality, severity) compared to DTG treated subjects, 54% and 30%, respectively. The finding was similar to the Week 48 reporting – 27% and 51% in the DTG- and Atripla- treated subjects, respectively, reported neurologic events. Among the neurologic events of interest reported after the Week 48 review, few were serious, Grade 3 or 4 in severity, or considered treatment-related.

Overall, the most common neurologic events reported in the two treatment arms include dizziness and headache. The incidence of dizziness (all cause, all severity) was approximately 3.5 times higher in the Atripla group (37%) compared to the dolutegravir group (10%); this observed difference in dizziness between the treatment arms is the primary reason for the overall difference in the number of subjects reporting neurologic

events between the two treatment arms. Other preferred terms reported in at least 2% of subjects randomized to the DTG treatment arm include (all causality, severity): headache (approximately 15% in each arm); paraesthesia (3% in the DTG arm and 2% in the Atripla arm); and somnolence (2% in the DTG group and 6% in the Atripla group). Most neurologic events were Grade 1 or 2 in severity. Approximately 1% in the DTG arm and 2% in the Atripla arm reported SAE. One subject in the DTG arm discontinued treatment due to neurologic-related events (see below) while 17 (4%) discontinued treatment in the Atripla arm.

Subject 5359 (further discussed below under psychiatric events) was randomized to the DTG arm. During the course of the treatment, he reported several neuropsychiatric events, including memory impairment and depressed level of consciousness which led to treatment withdrawal. Other reported NS events in this subject included dizziness, headache, and abnormal dreams. All events were non-serious and mild to moderate in severity. All were considered to be treatment-related and have resolved since treatment discontinuation.

The number of psychiatric events of special interest reported for the two treatment arms at Week 96 was 33% and 41% in the DTG and Atripla treatment arms, respectively. At Week 48, the incidences reported in the two treatment arms were 28% (DTG arm) and 36% (Atripla arm). The most common preferred term (all causality, all severity) reported in the DTG treatment arm was insomnia (17%). Between Week 48 and 96, the frequency of insomnia increased by 1% in the DTG group. The frequency of insomnia did not change between Week 48 and 96 for the Atripla group. Abnormal dreams were the most commonly reported psychiatric preferred term in the Atripla arm (17% at Weeks 48 and 96). Other adverse events (all causality, all severity) reported in at least 2% of subjects in the DTG arm include the following: depressive disorders (10% DTG; 12% Atripla), abnormal dreams (8% DTG; 17% Atripla); anxiety (7% DTG; 8% Atripla), nightmare (3% DTG; 5% Atripla), libido decreased (2% DTG; 1% Atripla), and sleep disorder (2% DTG; 4% Atripla). Most were mild to moderate and nonserious. Few were Grade 3 or 4 events – Grade 3 events were reported in 2% of DTG treated subjects and in 3% of Atripla treated subjects; approximately 1% in each arm had Grade 4 events.

Approximately 20% and 29% of subjects in the DTG and Atripla arm, respectively, had AEs considered to be at least possibly related to study drug; of these, <1% in the DTG arm and 4% in the Atripla arm were reported after the Week 48 timepoint. By preferred term, the most common drug related AEs (regardless of severity) reported in at least 2 and DTG-treated subjects include the following: abnormal dreams (7% DTG; 16% Atripla), depressive disorders (3% DTG; 5% Atripla), nightmare (2% DTG; 4% Atripla), sleep disorder (1% DTG; 2% Atripla), anxiety (1% DTG; 3% Atripla), nervousness (1%DTG; <1% Atripla), and initial insomnia (1% DTG, 0 Atripla).

The number of subjects who discontinued treatment due to psychiatric events of special interest was 4 (1%) in the DTG arm and 6% in the Atripla. The four subjects in the DTG arm experienced nightmare (1), insomnia (1), abnormal dreams (1) and depression (1). Of the four subjects who discontinued in the DTG arm, two subjects (nightmare (n=1),

abnormal dreams (n=1)) discontinued after the Week 48 data review (see below).

Subject 5359 is a 35 years old Caucasian male with past medical history of anxiety and depression. Immediately upon initiation of treatment with DTG, he experienced several neuropsychiatric events; starting on Day 1, he experienced 'decreased level of consciousness', headache and dizziness. All were mild to moderate, non-serious but considered to be treatment-related. By Day 246, subject also complained of memory impairment ('short term memory problems') and by Day 424, subject was experiencing abnormal dreams ('vivid dreams'). These latter two events were Grade 2 in severity, non-serious but considered treatment-related. The events that ultimately led to treatment discontinuation approximately around Week 78 are abnormal dreams, memory impairment and decreased level of consciousness. All events resolved after treatment discontinuation.

Subject 5754 is a 27 year old Caucasian male with no reported significant past medical history. On Day 366, he experienced nightmare, which was non-serious, Grade 3 and not considered to be treatment-related. This event is ongoing despite permanent discontinuation of the study drug on Day 508. Other neuropsychiatric events the subject experienced during study treatment include insomnia (Grade 2, non-serious, not treatment related) and libido decreased (mild, non-serious and not treatment related). Both events occurred starting on Day 1 of treatment; while decreased libido has resolved, insomnia is an ongoing event. This subject also experienced restlessness on Day 153; event was Grade 2, non-serious but considered to be treatment-related; symptom was treated by temporary interruption of DTG. DTG was resumed after symptom resolution.

SAILING

In general, the neuropsychiatric events described during the SAILING trial were similar to those observed in the SINGLE trial. Please refer to NDA 204790 review and Prescribing Information for Tivicay for additional details.

In summary, the incidences and types of neuropsychiatric events were generally similar to the Week 48 SINGLE analysis and the Week 24 SAILING) analysis. However, treatment-related, Grade 2 or higher depressive disorders increased in incidence to at least 2% in the Atripla arm, qualifying the term to be included in the ADR table; the ADR table for Triumeq has been revised to include depression. There appears to be some neuropsychiatric events, specifically depressive disorders, which may be universal to use of integrase inhibitor class drugs. Depression in "subjects with pre-existing depression or psychiatric illness" is included in the raltegravir label, under 'Less Common Adverse Reactions' section. There is ongoing review for Stribild, which will likely lead to the inclusion of 'suicidal ideation/attempt' in "subjects with pre-existing depression or psychiatric illness" under 'less common adverse reactions' section. Additional analysis will be conducted with the sNDA for Tivicay an (b) (5)

Renal events

Results from the Phase 2b trial in treatment-naïve subjects suggested that DTG may have an effect on the secretion of creatinine. Grade 1 increase in serum creatinine (SCr) was noted more frequently in the DTG arm than in the comparator, EFV arm. The mechanism of action is blockage of the renal tubular transporter OCT2, thereby affecting the secretion of creatinine from the renal tubules, leading to an increase in SCr. No effects on GFR and renal plasma flow were identified. Please refer to NDA 204790 for details.

The renal events analysis was performed by evaluating renal AEs and graded creatinine toxicities. In addition, calculations of the changes in serum creatinine compared to baseline values were performed.

SINGLE

Overall, throughout the 96-week treatment period, the incidence of renal related AEs (regardless of severity, causality) was 6% in the DTG group vs. 7% in the Atripla group. The event rates at Week 48 were 4% and 5% in the DTG and Atripla treatment arms, respectively. By preferred terms, the most common AE (regardless of severity, causality) at Week 96 was dysuria (1% in each arm). Other AEs reported in at least 2 subjects receiving DTG include nephrolithiasis (1% each arm), urinary urgency (1% each arm) and hematuria (1% each arm).

Most events were Grade 1 or 2; three subjects had Grade 3 events (1 in DTG arm and 2 in Atripla arm); none reported Grade 3 events after the Week 48 analysis. No subject had a Grade 4 event. One subject in the DTG arm (urinary urgency) and 3 subjects in Atripla arm had a SAE reported, as previously reported with the Week 48 data. In addition, 1 subject in the DTG arm and 5 in the Atripla arm had events considered to be treatment-related. Micturition urgency was the treatment-related event reported in the DTG-treated subject; the event, reported after the Week 48 review, was Grade 1, non-serious and resolved without consequence. One subject from each arm discontinued due to renal-related events: 'renal failure' in the DTG arm and 'chronic renal failure' in the Atripla arm. These events were previously reviewed under NDA 204790. Briefly, the DTG treatment subject (7802) had pre-existing renal risks with diabetes, hypertension and proteinuria at baseline. During the trial, 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.

The following table summarizes the graded serum creatinine toxicity during the 96-week treatment period. Most were Grade 1 events and no Grade 4 toxicity was reported for either treatment arm. The mean serum creatinine change from baseline continues to remain stable over the 96 week treatment period.

Table8: Serum Creatinine, Maximum Treatment-emergent Toxicity

	DTG + ABC/3TC QD N=414	Atripla QD N=419
SCr, maximum treatment emergent toxicity n(%)		
Grade 1	9 (2)	5 (1)
Grade 2	4 (1)	1 (<1)
Grade 3	0	1 (<1)
SCr, mean change from baseline		
Baseline mmol/L (mg/dL)	75 (0.98)	75(0.98)
Week 4	+11(0.14)	+0.2 (~0)
Week 24	+13 (0.17)	+0.5 (~0)
Week 48	+10 (0.13)	-0.7 (0.01)
Week 96	+12.6 (0.15)	+1.4 (0.02)

Source: laboratory analysis dataset- SINGLE

SAILING

The types of renal-related adverse events reported in SAILING trial were similar to those observed during the SINGLE trial. The changes in mean SCr from baseline and the reported creatinine maximum treatment-emergent toxicity were also similar to the changes reported in the SINGLE trial.

In summary, based on the analyses conducted, the change in serum creatinine appears be stable. No new labeling language is recommended for renal-related events.

Myositis and elevation in CK

Rhabdomyolysis and CK elevations are events observed with raltegravir. Elvitegravir (Stribild) is also associated with musculoskeletal events. To evaluate for potential class-related toxicity, review of adverse events related to rhabdomyolysis and CK elevations was conducted for dolutegravir. Refer to NDA 204790 clinical review for details. Myalgia, myositis and CK elevation were noted but most were mild and did not lead to treatment discontinuation. Most CK elevations were asymptomatic. The current prescribing information for Tivicay includes 'myositis' under less common ADRs and CK elevation is included in the laboratory toxicity table.

SINGLE

Overall, 27% and 22% of the DTG and Atripla treated subjects, respectively, experienced musculoskeletal (MS) disorders. Compared to Week 48, the incidence of MS disorders increased by 6% and 12% for the DTG and Atripla treatment arms, respectively. Among the events reported since the Week 48 review, none were considered treatment-related in the DTG arm, while 1 subject in the Atripla arm experienced treatment-related myalgia. In addition, similar to the Week 48 findings, no subject in the DTG arm discontinued treatment due to MS-related event; one subject discontinued Atripla as previously described during the Week 48 review. No 'rhabdomyolysis' or 'myositis' preferred terms

were reported since the Week 48 review for either arm while myalgia and MS pain continue to be reported in both treatment arms.

Overall, throughout the 96-week treatment period, there were few reported SAEs (2 in the DTG arm and 7 in the Atripla arm); most MS-related events were Grade 1 or 2 and none reported a Grade 4 event. Overall, six subjects in the DTG arm and 8 in the Atripla arm reported treatment-related events, including arthralgia, flank pain, muscle spasm and pain in extremity for the DTG arm; the events in the Atripla arm included arthralgia, flank pain, muscle twitching/tightness and synovitis.

Most elevations in CK were limited to Grade 1 or 2 and the incidence was similar between the two treatment arms. The proportion of subjects with Grade 1 elevation in CK was approximately 11% in each treatment arm. Grade 2 events were reported in 5% of the DTG arm and 3% of the Atripla arm. Grade 3 events were reported in 3% of each arm while Grade 4 events were slightly higher in the Atripla arm (4% vs 2%).

SAILING

The events and frequencies related to MS disorders were generally similar to those reported in the SINGLE trial. In musculoskeletal disorders class, AEs were observed in 14% and 20% subjects in the DTG and RAL arms respectively. Among the events of interest, one additional AE of rhabdomyolysis was observed after 24 weeks. The event occurred in the setting of resolving pneumonia, was confounded by use of other concomitant medications including moxifloxacin, and was assessed by the investigator as not related to DTG. Briefly, a subject (ID 627) was hospitalized for community acquired pneumonia and developed lower extremity stiffness and neck pain. Creatine kinase levels are not available. Serum creatinine and GFR, which are available, were normal during the episode. Myalgia was observed in 6 and 7 subjects, respectively, in the DTG and RAL arms. Myositis was observed in one subject in the DTG; none were reported in the RAL arm. For both myositis and myalgia, no additional AEs occurred after 24 weeks.

In summary, based on the results from the current review, no changes are recommended to the prescribing information for Tivicay or the FDC drug product.

Common AEs

SINGLE

Overall, the treatment-emergent adverse events (regardless of causality, severity) at Week 96 were similar to those reported during the Week 48 analysis. Most (91% DTG, 94% Atripla) reported at least 1 adverse event by Week 96, while 89% and 92% in the DTG and Atripla arms experienced an adverse event during the Week 48 review. The most commonly reported AEs in the DTG arm was diarrhea (20% at Week 96, 17% at Week 48) while dizziness was the most common AE in the Atripla arm (37% at Week 96, 36% at Week 48). For the DTG arm, dizziness was reported in 10% and 9% of subjects at Week 96 and 48, respectively). In the Atripla arm, 20% and 17% of subjects reported

diarrhea at Weeks 96 and 48, respectively. By Week 96, other commonly reported AEs in at least 10% of subjects in the DTG arm include, nasopharyngitis (18% DTG, 16% Atripla), insomnia (17% DTG, 11% Atripla), nausea (16% DTG, 15% Atripla), headache (15% each), fatigue (15% DTG, 13% Atripla), and upper respiratory infection (12% DTG, 13% Atripla). These findings were generally similar to the Week 48 analyses. Most were Grade 1 or 2, non-serious and did not lead to treatment discontinuation.

SAILING

The incidence of common adverse events reported in SAILING is similar to those reported in SINGLE. At least one AE was observed in 79% of subjects in each arm. Diarrhea was the most frequently observed event in both arms (19% DTG, 18% RAL).

Grade 3 and 4 AEs

SINGLE

The number of subjects with Grade 3 AEs by Week 96 were 53 (13%) and 73 (17%) in the DTG and Atripla arms, respectively. The frequency of Grade 3 and 4 events at Week 48 were 7% and 10%, in the DTG and Atripla arms, respectively. The number of subjects with Grade 4 AEs (non-laboratory-related events) were 4(<1%) and 10(2%) in the DTG and Atripla arms, respectively at Week 96; no new Grade 4 events were reported for the DTG arm after the Week 48 review while 1 subject in the Atripla arm had Grade 4 depression. For the subjects in the DTG arm, the Grade 3 AEs include subdural hematoma (n=1), priapism (n=1), homicidal ideation and suicidal ideation (n=1) and intentional overdose and suicide attempt (n=1). All of the events were also reported as SAEs, none were considered to be treatment related, and none resulted in death. One subject (subdural hematoma) discontinued study drug.

Laboratory

SINGLE

The following are selected laboratory toxicities to be included in the Triumeq label. Grade 2-4 will be displayed in the label. Liver- and renal- related laboratory toxicities, and CK elevations are discussed in their respective sections above. Overall, the laboratory toxicities reported at Week 96 were similar to the Week 48 findings.

Table 9: Selected Laboratory Parameters, Maximum Treatment-emergent Toxicities

n(%)	DTG/ABC/3TC QD N=414	Atripla QD N=419
Lipase (u/L)		
Grade 1	47(11)	44(11)
Grade 2	39(9)	40(10)
Grade 3	10(2)	11(3)
Grade 4	6(1)	2(<1)
Hyperglycemia (mg/dL)		
Grade 1	65(16)	65(16)
Grade 2	30(7)	21(5)
Grade 3	8(2)	2(<1)
Total Neutrophil counts		
Grade 1	43(10)	41(10)
Grade 2	12(3)	21(5)
Grade 3	8(2)	7(2)
Grade 4	2(<1)	7(2)

Source: laboratory analysis datasets

No new additional signals are identified with analysis of the SAILING data.

Safety Update Report and Postmarketing Reports

The data cutoff for the 120 day safety update was January 20, 2014. This safety update report was submitted 90 days after the submission of NDA 205551. The content includes listings and a brief discussion of serious adverse events (SAEs), deaths and pregnancies in subjects who received DTG + ABC/3TC. The following trials were included to provide the safety update.

- ING114467 (SINGLE)
- ING112276 (SPRING-1; Phase 2b trial in treatment naïve subjects)
- ING113086 (SPRING-2; Phase 3 trial in treatment subjects)
- ING111762 (SAILING)
- ING114915 (FLAMINGO; Phase 3b trial in treatment naïve subjects)
- ING116070 (A small trial evaluating the PK profile of DTG in CSF)
- ING112578 (P1093; pediatric trial children 12 years and older)
- ING117172 (ARIA; trial in pregnant women).

SAE considered possibly related to DTG were reported in 4 subjects and included: adverse drug reactions shakiness, weakness, confusion, ataxia and nystagum in the setting of DDI (see below); suicide attempt; flatulence; and osteonecrosis. None discontinued treatment with DTG. With regards to events of special interests, no subject

had a hypersensitivity reaction, IRIS or rash. One subject had hepatotoxicity in the setting of acute HCV infection; four subjects had MS disorders (back pain, osteonecrosis, intervertebral disc protrusion). Three subjects developed nephrolithiasis and one subject had renal mass. Psychiatric events were reported in two subjects and included suicide attempt, depression, suicidal ideation and paranoid schizophrenia. The subject with suicide attempt (also considered serious and possibly related to DTG) is further discussed below.

Subject 5400 is a 62 year-old male enrolled in SINGLE trial and randomized to on (b) (6) to the DTG treatment arm. He completed the blinded phase and entered the open-labeled phase on (b) (6). His past medical history includes hypertension, anxiety and insomnia; concomitant medications at time of the event included meclizine hydrochloride and nortriptyline. On (b) (6), 924 days after the start of study drug and 251 days after the start of the open-label phase, he reported feeling “terrible” and was noted to be shaky, weak and confused, with nystagmus and mild gait ataxia. He was hospitalized and treatment with DTG+ABC/3TC was continued. The investigator considered that the drug reaction may have been caused by interaction between the concomitant medications, meclizine hydrochloride, doxycycline and nortriptyline, however a possible relationship to study drug was not ruled out. Of note, side effects reported with use of nortriptyline include weakness, ataxia, lack of coordination, blurred vision, and tinnitus. Use of Meclizine is associated with blurred vision, dizziness and drowsiness. The event resolved on (b) (6). The subject was instructed not to take his meclizine continually, but only when an onset of vertigo as present, to lower the chance of the interaction of meclizine with nortriptyline occurring again.

Subject 6115 is a 42 year-old male with past medical history of psychiatric disorder (NOS) and anxiety was enrolled in SINGLE trial and randomized on (b) (6) to receive DTG+ABC/3TC FDC; he completed the blinded phase of the trial and entered the open label phase on (b) (6). Concomitant medications included atorvastatin calcium, hydrochlorothiazide and amlodipine. On (b) (6), 973 days after the start of study drug, 302 days after Week 96 (or end of blinded study phase) and 301 days after the start of the open label phase, the subject attempted suicide by intentional ingestion of multiple drugs. Alcohol was also ingested during the episode. The subject was hospitalized and was treated. Treatment with DTG+ABC/3TC was continued. The investigator considered that there was a reasonable possibility the suicide attempt may have been caused by study drugs, as well as concomitant medications, atorvastatin calcium, hydrochlorothiazide and amlodipine. The event was unresolved at time of the SUR report.

Based on the last submitted postmarketing report (reporting date upto February 11, 2014), increase in lipase and pancreatitis were identified in one subject. In addition, one subject reported depressed level of consciousness, disorientation, and feeling abnormal. None of these terms are labeled events for DTG. Based on the available information for

these cases, continued pharmacovigilance is recommended at this time, without changes to the prescribing information. Other reported terms in the postmarketing reports were confounded by other concurrent medical condition and/or the events occurred years/months after initiation of DTG, making the contribution of DTG to the events difficult to interpret.

Safety Summary

Review of the 96 Week data from SINGLE and 48 Week data from SAILING demonstrated that DTG, in combination with other ARVs is generally safe and tolerated. Overall, there were no significant changes observed when the results are compared to the Week 48 (SINGLE) and 24 (SAILING) results previously reviewed under NDA 204790.

The SAILING trial evaluated the safety profile of DTG 50 mg taken once daily, which is the same as the dose administered in treatment naïve trials. The DTG safety profile in the treatment-experienced INSTI naïve subjects appears similar to observations in the treatment-naïve population. In subjects who received DTG with ABC and 3TC, no new or unexpected safety concerns were observed. Of note, the number of subjects with ABC/3TC background regimen enrolled in SAILING is few; however, the safety profile of DTG regardless of the background regimen used, was similar in treatment-naïve and treatment-experienced, INSTI-naïve subjects. This collective data along with the safety of individual drugs in other clinical trials and post-marketing experience support the use of the FDC in treatment experienced, INSTI-naïve population.

In the SINGLE trial, there were no new deaths reported since the Week 48 review. The two deaths previously described during the Week 48 review occurred in the Atripla arm. Among subjects with SAEs, few were considered treatment-related. Specifically, one subject in the DTG arm and nine subjects in the Atripla arm experienced treatment-related SAEs. The subject in the DTG arm experienced drug hypersensitivity, which was previously described during the Week 48 review; no new treatment-related SAEs were reported in the DTG arm after the Week 48 review. Few subjects discontinued treatment since the Week 48 analysis (3 in the DTG arm and 5 in the Atripla arm). Overall, throughout the 96-week treatment period, fewer subjects in the DTG arm (14(3%)) discontinued therapy compared to the Atripla arm (52 subjects (12%)). Similar to the Week 48 findings, psychiatric disorder was the most common SOC leading to treatment discontinuation in both treatment arms – 4(<1%) and 23(5%) in the DTG and Atripla arms, respectively.

Treatment-related adverse events or ADRs were generally similar between Week 48 and 96 analysis periods. Similar to the Week 48 findings, ADRs with at least moderate severity and reported in at least 2% of subjects randomized to the DTG arm were insomnia (3% and 2% in DTG and Atripla arms, respectively), headache (2% in each arm) and fatigue (2% in each arm).

The most common treatment emergent AE (regardless of causality, severity) at Week 96 were diarrhea for the DGT arm (20%) while dizziness was the most commonly reported

AE for the Atripla arm (37%) . These findings are similar to the Week 48 reporting. Most were mild to moderate and did not lead to treatment discontinuation.

The safety of the individual drugs contained in Triumeq were previously established during the review cycle of the respective NDAs. In addition, abacavir and lamivudine have well described pre and post marketing safety profiles. Triumeq is bioequivalent to the individual drugs; and the doses contained in the FDC product are the same as the approved doses for the individual drugs. Therefore, previously described safety finding for the individual drugs is applicable to the FDC drug product; no unique or new safety signal are expected to arise for Triumeq. The proposed labeling for Triumeq sufficiently describes the AE profiles for ABC/DTG/3TC. Further, references to the prescribing information for the individual drugs will be included to provide additional sources for details. As DTG is a relatively newly approved ARV, further or additional safety evaluation will be conducted with the currently submitted sNDA . Continued routine postmarketing pharmacovigilance is recommended with the approval of the FDC formulation.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Although DTG is approved for use in HIV infected children 12 years of age and older, Triumeq is not recommended in any pediatric population because once daily abacavir/lamivudine is not approved in children. (b) (5)

(b) (5), (b) (4)

Of note, for the FDC drug product, the Agency is waiving a pediatric study requirement in children under 6 years of age for the following reasons:

- We are waiving the pediatric study requirement for 0 to less than 4 weeks of age because with improvement in perinatal transmission prevention strategies there are insufficient numbers of neonatal subjects to be enrolled. Further, even when neonates are identified for enrollment, by the time enrollment is accomplished, dosing is initiated, and drug concentrations have reached steady state, the subjects are likely to be older than 4 weeks of age.

- We are waiving the pediatric study requirement in children 4 weeks of age to less than 6 years of age because the product fails to represent a meaningful therapeutic benefit over existing therapies, and is unlikely to be used in a substantial number of pediatric patients of this age.

In summary, a deferral to conduct a required pediatric study under PREA PMR in children 6 to 18 years of age will be granted to the Applicant because the product is ready for approval in adults. The required pediatric study under PREA PMR in children less than 6 years of age will be waived for reasons expressed above.

11. Other Relevant Regulatory Issues

No additional regulatory issues have been identified.

12. Labeling

• Physician Labeling

The following section highlights the changes to the sections 1, 2, 5, 6 and 14. These sections have been successfully negotiated with the Applicant during the review of this NDA. The PI will be reviewed by the SEALED team prior to finalization.

Section 1.0

CDER has initiated a Draft Guidance for Industry: Indication and Usage (I&U) Section of Labeling, which is currently an internal document. The purpose of the guidance is to improve the Indication and Usage section by making it more clear, concise, and consistent across FDA. In accordance with this plan, the language for the Indication and Usage section for Triumeq has been streamlined.

First, the indication statement has been simplified to “treatment of HIV-1 infection”. No additional wording is necessary as Triumeq can be used as a complete regimen to treat HIV infection or used in combination with other ARVs in treatment-experienced subjects providing subjects’ virus is susceptible to the components of the FDC.

Any limitations to the use of Triumeq are to be described under ‘Limitations of Use’. Of note, the Agency is moving away from using terms such as ‘points to consider’. Instead, any additional statements are to be captured under the subheading of ‘Limitation of Use’. For example, use of Triumeq (b) (4) is discussed under ‘Limitations of Use’ section. (b) (4) Triumeq alone is not recommended. (b) (4)

INDICATIONS AND USAGE:

1.0 TRIUMEQ is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults.

Limitations of Use:

- o TRIUMEQ alone (b) (4) in patients with current or past history of resistance to any components of TRIUMEQ [see Microbiology (12.4)]

(b) (4)

Section 2

In addition to providing the dosing recommendation for Triumeq in adults, this section also provides (b) (4) (b) (4)

In addition, dose recommendations are provided for patients who take certain ARVs which may decrease the exposure of DTG. Specifically, the dose required is 50mg DTG BID. This may be accomplished by taking an additional 50 mg DTG single tablet 12 hrs before or after taking Triumeq.

DOSAGE AND ADMINISTRATION

- o Screen for the HLA B*5701 allele prior to initiating therapy with TRIUMEQ. (b) (4)

(b) (4)

(u) (4)

The recommended dosage regimen of TRIUMEQ (b) (4) adults is one tablet daily orally with or without food. (b) (4)

(b) (4)

- 2.3 (b) (4) Recommendation With Certain Concomitant Medications
(u) (4) the dolutegravir (b) (4) (50 mg (b) (4) in TRIUMEQ is insufficient when co-administered with (b) (4) medications that may decrease dolutegravir concentrations, the following dolutegravir dosage regimen is recommended.

Coadministered Drug	Dosing Recommendation
Efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	The recommended dolutegravir dosage regimen is 50 mg twice daily. An additional dolutegravir 50-mg tablet, separated by 12 hours from TRIUMEQ, should be taken.

Section 5

Note: The Warnings and Precautions language specific for abacavir has been streamlined to keep the information relevant, upto date and concise. This recommendation was initiated by both the Division and by the Applicant. (b) (4), (b) (5)

(b) (4)

Section 6 and 14

The Clinical ADRs and Clinical Trials sections (6 and 14, respectively) primarily highlight results from the SINGLE trial. References to the DTG Prescribing Information are included for results from other Phase 3 trials.

- **Patient Labeling**

The Package Insert and Patient Labeling are currently being reviewed by the Patient Labeling team

13. Outstanding Issues

The following non-clinical item needs to be resolved prior to approval of this NDA:

- A recommendation from the Office of Compliance (Office of Scientific Investigations, OSI) is pending.

14. Recommendations/Risk Benefit Assessment

We recommend approval of this NDA, pending the resolution of all outstanding CMC issues and recommendation of acceptance from OSI. My recommendation is based on data from one pivotal phase 3 adult clinical trial in treatment-naïve subjects where the components of Triumeq (abacavir, dolutegravir and lamivudine) were studied, and an additional supportive Phase 3 trial in treatment-experienced INSTI-naïve adults.

Triumeq contains two NRTIs (ABC/3TC) which have well established safety and efficacy profile both from clinical trials and from post marketing use. The safety and efficacy of the third agent in Triumeq, DTG, has been described under NDA 204790. The bioequivalence trial (ING114580) contained in NDA 205551 demonstrated that the exposure from Triumeq is comparable to the exposures observed with the individual drug products. Therefore, data from the individual drugs can be used as sufficient evidence to recommend abacavir/dolutegravir/lamivudine fixed dose combination drug product for the treatment of HIV-1 infection.

The efficacy of DTG 50 mg once daily (QD) in combination with abacavir and lamivudine in treatment-naïve population was demonstrated in the SINGLE trial. Dolutegravir, in combination with other antiretroviral (ARV) agents, was also demonstrated in trials reviewed under NDA 204790. In SINGLE, DTG containing regimen arm was shown to be superior to an efavirenz containing regimen at both Week 48 and 96. Virologic response, defined as the proportion of subjects with HIV RNA < 50 copies/mL, was 80% for DTG and 72% for EFV at Week 96. Similarly, the efficacy of DTG containing regimen in the treatment-experienced, INI naïve population, as demonstrated in SAILING, was superior to raltegravir containing regimen, both at Week 24 and 48. The virologic response rate at Week 48 was 71% and 64% in the DTG and raltegravir arms, respectively. 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.

The primary safety concerns with DTG, as previously described under NDA 204790, include risk for hypersensitivity reactions including rash, elevation in liver chemistries, especially in the setting of hepatitis B and/or C co-infection. The prescribing information for DTG describes the hypersensitivity reactions and hepatic events observed during

clinical trials; both events are included and described in the Warnings and Precautions section of the DTG label. In addition to maintaining the above information, hypersensitivity due to ABC use has also been included in the proposed Triumeq label. Other ADRs identified with use of DTG include several neuropsychiatric events such as insomnia, dizziness, depression and headache. Laboratory toxicities, in addition to elevations in liver serum biochemistries include elevation in serum creatinine (due to blockage of OCT2 transporters) and CK elevation (primarily without clinical symptoms). These toxicities are described and included in the DTG label and proposed for the Triumeq label. Dolutegravir appears to have some advantage over Atripla in terms of rate of discontinuations - fewer subjects 14 (3%), discontinued DTG compared 52 subjects (12%) in the Atripla arm.

The availability of a FDC drug product containing ABC/DTG/3TC allows for potential use of Triumeq as a complete regimen, one pill once daily, for the treatment of HIV in patients with no resistance to the components of Triumeq. A one pill, once daily regimen could provide an adherence advantage for patients, which may reduce the development of resistance. Although NNRTI-based once pill once daily regimens are currently available, Triumeq provides an alternative, INSTI-based complete FDC drug regimen.

Recommendation for Postmarketing Risk Evaluation and Management strategies

No postmarketing risk management activities are required for this application.

Recommendation for other Postmarketing Requirements and Commitments

The following PMRs are recommended:

1. Deferred pediatric trial under PREA for the treatment of HIV-1 infection in pediatric subjects from 12 to <18 years of age. Evaluate the safety and antiviral activity of ABC/DTG/3TC FDC in pediatric subjects with safety and virologic response assessed over at least 24 weeks of dosing.
2. Deferred pediatric trial under PREA for the treatment of HIV-1 infection in pediatric subjects from 6 years of age to less than 12 years of age. Evaluate the safety and antiviral activity of ABC/DTG/3TC FDC in pediatric subjects with safety and virologic response assessed over at least 24 weeks of dosing.

Appendix 1

Clinical Investigator Financial Disclosure Review

Application Number: 204790

Submission Date: December 17, 2012

Applicant: GSK

Product: Dolutegravir

Reviewers: Charu Mullick, Yodit Belew, Wendy Carter

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

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>468</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
<p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>4 (honoraria payment)</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: n/a	Yes <input type="checkbox"/>	No <input type="checkbox"/> (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.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YODIT BELEW
07/14/2014

CHARU J MULLICK
07/14/2014

KIMBERLY A STRUBLE
07/14/2014

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 205551 Applicant: GSK Stamp Date: October 22, 2013

**Drug Name: dolutegravir (DTG) NDA/BLA Type: (Type 4, new combination)
Proposed Brand Name: TRIUMEQ**

On initial overview of the NDA/BLA application for filing:

Content parameter	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2. On it's face, is the clinical section of the application organized in a manner to allow substantive review to begin?	x			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5. Are all documents submitted in English, or are English translations provided when necessary?	x			
6. Is the clinical section legible so that substantive review can begin?	x			
LABELING				
7. Has the applicant submitted design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	x			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9. Has the applicant submitted the integrated summary of safety (ISS)?	x			Included in Module 5 (5.3.5.3) as Integrated Summary of Safety
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	x			Included in Module 5 (5.3.5.3) as Integrated Summary of Efficacy
11. Has the applicant submitted a benefit-risk analysis for the product?	x			Module 2, (2.5 Clinical Overview; Section 6(clinical-overview.pdf)
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug:	x			505(b)(1)
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	x			The dose finding studies and dose selection for DTG were conducted under IND (b) (4). DTG 50 mg QD was evaluated and approved under NDA 204790. The current NDA contains a fixed-dose combination drug product for DTG 50mg/ABC 600mg/3TC 300mg

EFFICACY			
14. Do there appear to be the requisite number of adequate and well controlled studies in the application? <i>Pivotal Studies:</i> <i>ING114467 (SINGLE):</i> 96-week data in treatment naïve adults <i>Supportive Studies:</i> <i>ING113086 (SPRING-2):</i> 96-week data in treatment naïve adults <i>ING114915 (FLAMINGO):</i> 48-week data in treatment naïve adults <i>ING111762 (SALING):</i> 48-week data in treatment experienced adults <i>Indication:</i> DTG/ABC/3TC is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults (b) (4)	x		
15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x		The indication proposes for use of the FDC product (b) (4) whether the indication will be extended (b) (4) is a review issue.
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x		
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. populations/practice of medicine in the submission?		x	The trials were conducted internationally with numerous sites within the U.S.
SAFETY			
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x		
19. Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	x		TQT studies were already conducted under NDA 204790
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?	x		DTG single agent was approved by FDA on August 12, 2013. The product was launched in the US on August 20, 2013 (pending in the rest of the world). In the time between launch in the US and writing of this FDC document, limited PM ADR cases were reported; thus, the primary PM

				information submitted to this NDA contains information related to ABC and 3TC. Additional DTG-related cases, if available, should be submitted to this NDA with the Safety-Update Report.
21. For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			Yes, based on adequate and well controlled trials, the individual drugs, DTG, ABC and 3TC are already approved for treatment of HIV infection.
22. For drugs not chronically administered (intermittent or short courses), have the requisite number of patients been exposed as requested by the Division?			x	
23. Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		x		
24. Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25. Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Case narratives were submitted for death, SAEs, pregnancies and hepatic events (ALT \geq 5x ULN).
OTHER STUDIES				
26. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	x			
27. For an Rx-to-OTC switch application, are the necessary special OTC studies included (e.g., labeling comprehension)?			x	
PEDIATRIC USE				
28. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			The applicant has submitted PSP and is requesting: -waiver for children less than 2 years of age. -deferral for children 2 to <18 years of age or children
ABUSE LIABILITY				
29. If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES				
30. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	Multiple U.S. sites were used in addition to the non-U.S. sites.
DATASETS				
31. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32. Has the applicant submitted datasets in the format agreed to previously by the Division?	x			Data for the Pivotal trial has been previously submitted and reviewed. No changes were made to the format. However, longer term data (48-96 weeks) are submitted in support of this NDA
33. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			The indication proposes for use of the FDC product (b) (4)

				(b) (4) Whether the indication will be extended (b) (4) is a review issue.
34. Are all datasets to support the critical safety analyses available and complete?	x			
35. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	x			
CASE REPORT FORMS				
36. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			Case narratives are included for SAEs, pregnancies and hepatic events
37. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?				CRFs are included as part of the NDA submission
FINANCIAL DISCLOSURE				
38. Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE				
39. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATIONS FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please submit the following:

- 1) Because the pivotal clinical trials have multinational sites, please provide a rationale for assuming the applicability of foreign data to U.S. populations/practice of medicine.
- 2) Please submit a Coding Dictionary used for mapping investigator verbatim terms to preferred terms.
- 3) Postmarketing safety reports (line listing and case narratives for serious events) should be submitted in the Safety Update Report.
- 4) Case narratives for adverse events leading to discontinuations may be requested during the review cycle if deemed necessary.
- 5) Please refer to sections 6 and 14 of your proposed labeling. The tables under these sections should reflect the longest use data for DTG and its comparator, even if the primary endpoint was defined as Week 48. Please revise the tables accordingly. We do not agree with (b) (4)

- 6) Safety and efficacy results displayed in the label should not include subjects who were enrolled from sites that were excluded during the original NDA review (e.g. Russian sites). Please revise the tables accordingly.

<u>Yodit Belew</u>	<u>12/30/13</u>
Reviewing Medical Officer	Date
<u>Kim Struble</u>	<u>12/30/13</u>
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YODIT BELEW
12/30/2013

KIMBERLY A STRUBLE
12/30/2013