Decisional Review for NDA 204790

Date	August 6, 2013
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA # Supp #	NDA 204790/Original Submission
Proprietary / Established (USAN) names	Tivicay™ Dolutegravir (DTG)
Dosage forms / strength	DTG 50 mg once daily in the following populations: • Treatment-naïve or treatment-experienced, integrase strand transfer inhibitor (INSTI)-naïve adults • Treatment-naïve or treatment-experienced, INSTI-naïve pediatric patients 12 years and older and weighing at least 40 kg DTG 50 mg twice daily in the following populations: • Treatment-naïve or treatment-experienced, INSTI-naïve adults and children 12 years and older and weighing at least 40 kg when co-administered with UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir or rifampin • INSTI-experienced adults with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance, noting that alternative combinations that do not include metabolic inducers should be considered where possible
Proposed Indication(s)	For use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg
Action	Approval

1. Introduction to Review: This Division Director's memorandum provides a topline summary of NDA 204790 for VIIV/GSK's New Drug Application (NDA) for Tivicay (dolutegravir, DTG), an integrase strand transfer inhibitor (INSTI) for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg. This decisional review summarizes pertinent multidisciplinary findings including clinical trial results from principal Phase 3 trials in adults in multiple populations including treatment-naïve, treatment-experienced, INSTI-naïve and INSTI-experienced with certain INSTI associated resistance substitutions, as well as

pediatric data to support an older pediatric population. Requested post-marketing studies and product labeling are also summarized throughout the document.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Division of Scientific Investigations (DSI) Status:

The NDA for DTG was submitted and received on December 17, 2012, and reviewed under the PDUFA V program. DTG is the third INSTI in the drug class. Overall, the dosage depends on the treatment history of the patient population and the use of concomitant medications. For example, DTG 50 mg once daily is recommended for use in the following populations:

- treatment naïve or treatment-experienced, INSTI-naïve adults
- treatment naïve or treatment-experienced, INSTI-naïve pediatric patients 12 years and older and weighing at least 40 kg

DTG 50 mg twice daily is the recommended dose in the following populations:

- treatment naïve or treatment-experienced, INSTI-naïve adults and children aged 12 years and older and weighing at least 40 kg when co-administered with potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranivir/ritonavir or rifampin

- INSTI-experienced adults with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance (alternative combinations that do not include co-administration of metabolic inducers should be considered where possible)

The safety and efficacy of DTG in pediatric patients younger than 12 years and or weighing less than 40 kg have not been established. In addition, DTG has not been studied in INSTI-experienced pediatric patients.

The application was granted a priority review because DTG provides a significant improvement in the treatment of HIV-infected adults and children including treatment-experienced adults who have failed an INSTI-containing antiretroviral regimen. Further, it is dosed once daily compared to the first approved INSTI, raltegravir (RAL), whereas elvitegravir, the second approved INSTI is only available as part of a fixed-dose combination, Stribild, that has a more limited indication for treatment naïve patients compared to DTG.

Five clinical trial sites were audited by the Division of Scientific Investigations (DSI). The trial sites were selected for review based on the numbers of patients enrolled per site. Per Dr. Antoine El-Hage, DSI, applicable statutory requirements and FDA regulations governing the conduct of clinical trials and the protection of human subjects were followed at these select sites. However, the Applicant closed two phase 3 trial sites. The Volvograd Regional Center in Russia was closed because GCP violations were found at the site pertaining to an unrelated

non-IND study of maraviroc. The safety and efficacy data from this site were excluded from analyses due to GCP violations. A U.S. site in Houston, Texas was also closed by the Applicant because the site's principal investigator did not comply with measures to address issues identified in an audit of the site. Since the Applicant was able to provide assurances of data integrity related to the 23 patients enrolled at that site and a recent DSI inspection found the site acceptable, the data were included in the analyses of safety and efficacy. In addition, GSK was asked about press reports of bribery concerns in China and to confirm that the Chinese government investigations do not involve any DTG trial site(s). The company responded by stating that the press reports about bribery concerned investigations of alleged improper sales/marketing practices in the People's Republic of China ("China"). The allegations do not concern the Republic of China ("Taiwan"). GSK further stated that the allegations have no bearing on the clinical development of DTG since there were no DTG clinical trial sites in China (or in Hong Kong). In Taiwan, one of the Phase 3 DTG trials (ING111762; SAILING) enrolled 11 patients across five sites, but again, the allegations and matters under investigation do not concern Taiwan.

3. Chemistry/Manufacturing/Controls (CMC): The CMC reviewers of the DTG NDA are: Drs. Lin Qi and Maotang Zhou. Dr. Deepika Lakhani is the Biopharmaceutics reviewer and Dr. Stephen Langille is the Product Microbiology reviewer. Dr. Rapti Madurawe supervised the CMC review with Dr. Stephen Miller serving as CMC-Lead. The CMC team reviewed data to assure the identity, strength, purity and quality of DTG 50 mg tablets. Further, the CMC review team reviewed data to support bridging between the tablets used in the phase 3 clinical trials and the commercial product.

The CMC reviewers concluded that the data contained in the NDA support an expiry date of 24 months.

The CMC reviewers, however, could not recommend approval because manufacturing site recommendations were pending as of the date of their reviews. An overall acceptable recommendation from the Office of Compliance was issued on 23-JUL-2013. Further, all CMC-related deficiencies have now been resolved for this application. There are no outstanding review deficiencies that would preclude a recommendation of approval from a CMC standpoint.

4. Pharmacology/Toxicology: Please see review of submitted nonclinical toxicology studies by Dr. Mark Seaton, supervised by Dr. Hanan Ghantous. Dr. Seaton's review states that gastrointestinal effects including inflammation and hemorrhage were the principal findings in short-term, subchronic and chronic repeat-dose studies across species. Effects were considered to be related to

local and not systemic exposure of DTG. Safety margins calculated based on systemic exposure were considered conservative and were adequate.

Hepatotoxicity was seen in an acute (2-week) study in monkeys. Findings included hepatocellular single cell necrosis and diffuse hepatocellular hypertrophy and/or vacuolation in male monkeys dosed 1000 mg/kg/day with corresponding systemic exposures of approximately 7X and 5X the expected human exposures for a 50 mg QD or BID dose, respectively. According to Dr. Seaton's review, there were no significant nonclinical hepatoxicity findings seen in longer term studies, nor were there other systemic effects related to DTG in subchronic or chronic nonclinical toxicology studies. Nonetheless, effects seen in nonclinical studies were examined in clinical trials.

DTG was neither genotoxic nor carcinogenic in nonclinical studies.

The conclusions of the Pharmacology/Toxicology review team are reflected in sections 8 and 13 of product labeling and are paraphrased below:

Animal Data

Reproduction studies have been performed in rats and rabbits at doses up to 27 times the human dose of 50 mg twice daily and have revealed no evidence of impaired fertility, teratogenicity or developmental delay. Specifically, oral administration of DTG to pregnant rats at doses up to 1,000 mg/kg daily, approximately 27 times the 50-mg twice-daily human clinical exposure based on AUC, from days 6 to 17 of gestation did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

Oral administration of dolutegravir to pregnant rabbits at doses up to 1,000 mg/kg daily, approximately 0.4 times the 50-mg twice-daily human clinical exposure based on AUC, from days 6 to 18 of gestation did not elicit developmental toxicity or teratogenicity. In rabbits, maternal toxicity (decreased food consumption, scant/no feces/urine, suppressed body weight gain) was observed at 1,000 mg/kg.

DTG is a pregnancy category B drug based on animal data as there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and DTG was shown to cross the placenta in animal studies, DTG should be used during pregnancy only if clearly needed. The labeling states that healthcare providers are encouraged to register patients in the Antiretroviral Pregnancy Registry and monitor maternal/fetal outcomes of HIV-infected pregnant women exposed to DTG and other antiretrovirals.

5. Clinical Pharmacology: The Office of Clinical Pharmacology reviewers were Drs. Su-Young Choi, Stanley Au, Assad Noory, Shirley Seo (Team Leader, Clinical Pharmacology), Jeffry Florian and Yaning Wang (Team Leader, Pharmacometrics), Jeffrey Kraft and Mike Pacanowski (Team Leader, Pharmacogenomics).

Twenty-nine in vitro studies evaluating metabolic pathways were submitted and reviewed. Ten phase 1 studies were reviewed and studies in special populations were reviewed including hepatic and renal impairment studies. A thorough QTc study was submitted for review as was a study investigating the effects of DTG on renal function. Seventeen drug-drug interaction studies were reviewed as well as the clinical studies supporting dose selection, safety and efficacy of DTG, including a pediatric study. The review team examined two population PK analysis reports and a meta-analysis of the effects of CYP/UGT polymorphisms on the PK of DTG.

Important findings from the review team are described thoroughly in their combined reviews and product labeling. Highlights include the following information:

- DTG can be taken without regard to food. Dosing separation is necessary when DTG is administered with polyvalent cation containing drugs.

- DTG is present in the CSF but the relevance of these findings is unknown at this time.

- Mass balance study revealed that 53% of the total daily dose is excreted as unchanged DTG in the feces; 31% of the total oral dose is excreted in the urine represented by three major metabolites and other minor metabolites.

- DTG is primarily metabolized and eliminated by the liver. DTG is primarily metabolized by UGT1A1 with CYP 3A4 as a secondary metabolic pathway.

- DTG has a terminal half-life of approximately 14 hours.

- Pop PK analyses did not reveal clinically significant covariates of DTG exposures. Extremely limited data were available from patients co-infected with hepatitis B and individuals older than 65 years of age.

- Exposure to DTG was generally similar between healthy adult subjects and HIV-infected patients.

DTG has a low potential to cause drug interactions as a perpetrator. However, significant drug interactions are expected with potent UGT1A and CYP3A inducers. In Dr. Kim Struble's CDTL memorandum, she expressed concerns with dosing DTG with potent inducers, e.g. efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir or rifampin in INSTI-experienced subjects. The lower DTG exposures observed in INSTI-experienced subjects with coadministration of potent inducers may result in loss of therapeutic effect and development of resistance to DTG or other co-administered ARVs. Alternative regimens that do not include metabolic inducers should be considered in this setting as outlined in product labeling. (b) (4) Labeling statements provide clinicians with information regarding the likelihood of reduced response rates for these combinations. In addition, labeling advises using DTG 50 mg BID in populations in whom QD dosing is recommended if they are also receiving ARVs that are potent inducers.

The effects of coadministered drugs on DTG and the effects of DTG on the exposure of coadministered drugs are shown in Table 5 of labeling. Of note, coadministration with dofetilide is contraindicated.

Dose selection was adequately explored for the various patient populations. Trials conducted by the Applicant in treatment naïve and treatment-experienced, INSTI-naïve subjects support the DTG dose 50 mg QD. In addition, the results of phase 2b and phase 3 trials in INSTI-experienced patients support use of 50 mg BID in these populations. The review team agreed with GSK's dose selection at the EOP2 meeting.

Use of DTG in special populations is described in labeling. In a trial comparing 8 subjects with severe renal impairment (CrCl <30 mL/min) with 8 matched healthy controls, AUC, C_{max}, and C_{24} of DTG were decreased by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. Further, population pk analysis using data from Phase 3 trials indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of DTG. However, caution is warranted for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with severe renal impairment, as some subjects will have decreases in DTG exposure that may compromise efficacy. Notably, DTG has not been studied in patients requiring dialysis. The review team further concluded that no dosage adjustment is necessary for treatment-naïve or treatment-experienced, INSTI-naïve patients with mild, moderate, or severe renal impairment.

Importantly, in a clinical trial, no clinically relevant differences in DTG pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. Therefore, dosage

adjustment of DTG is not necessary for subjects with mild-to-moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of DTG has not been studied. With regard to co-infected subjects, limited data from population pharmacokinetic analysis indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the pharmacokinetics of DTG.

The Applicant conducted a thorough QT study with DTG in 42 healthy subjects. This study was reviewed by the FDA's Interdisciplinary Review Team for QT Studies (IRT). The IRT concluded DTG's effect on QTc prolongation was below the threshold for regulatory concern and there appeared to be no clinically relevant effects on PR and QRS intervals.

6. Clinical Virology: Please see extensive review by Dr. Lisa Naeger with supervisory concurrence by Dr. Jules O'Rear. Resistance and cross-resistance wording appears in product labeling. HIV-1 variants harboring DTG resistance substitutions remained susceptible to other drug classes. DTG-resistant viruses were selected in cell culture. Substitutions in integrase (IN) that emerged in passaged virus included the following: E92Q, G118R, S153Y/T/F, G193E, and R263K. Passage of mutant viruses with the Q148R/H substitutions selected for additional substitutions in IN including L74M, E92Q, T97A, E138K, G140S, M154I, and N155H.

In phase 3 clinical trials of treatment naïve subjects (SPRING-2 and SINGLE), no subjects had viral isolates with a decrease in DTG susceptibility or emergent resistance substitutions to background NRTIs whereas in the comparator arms of these studies (raltegravir [RAL] or efavirenz [EFV] with two NRTIs), three subjects' isolates had emergent INSTI resistance substitutions to RAL and six subjects' isolates had emergent EFV substitutions; emergent substitutions were also seen to background NRTIs in the comparator arms. In treatment-experienced, INSTI-naïve subjects in the SAILING trial, there were 9% of subjects eligible for resistance testing in the DTG arm compared to 14% in the comparator RAL arm. As noted in product labeling, viruses from 5 of 15 subjects in the DTG arm with post-baseline resistance data had evidence of treatment-emergent integrase substitutions (1 subject each with L74M/I, Q95Q/L, or V151V/I, and 2 subjects with R263K) without detectable phenotypic decreases in susceptibility to either DTG or RAL. In the comparator RAL arm, 9 of 32 subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92E/Q, Q95Q/R, T97A, G140A/S, Y143C/R, Q148R/H, V151I, N155H, E157E/Q, and G163G/R) and RAL phenotypic resistance.

Table 10 that appears in product labeling was generated from the results of the VIKING-3 trial in INSTI experienced subjects with current or historical evidence of RAL and/or EVG resistance. Diminished virologic responses by week 24 were always seen in the presence of Q148 substitutions as highlighted below. Factors related to the anchor drug in the optimized regimen had an impact on response

rates. According to Dr. Naeger's review, overall response rates were lowest when enfuvirtide was used (50%) and highest when ritonavir boosted darunavir was used as part of the background regimen (80%). If RAL was part of the background drugs, the response rates were in between (~ 63%).

Table 10. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an INSTI in Study ING112574 (VIKING-3)

Baseline Genotype	Response at Week 24 (<50 copies/mL) Subset N = 124
Overall Response	64% (79/124)
N155H without a Q148 substitution	80% (16/20)
Y143R/C/H without a Q148 substitution	56% (10/18)
Q148H/R + G140A/S without additional INSTI-resistance substitutions	56% (10/18)
Q148H/R + ≥2 INSTI-resistance substitutions[a,b]	18% (3/17)

[a] INSTI-resistance substitutions include L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/R/Q/S, or G193E/R.

[b] The most common pathway with Q148H/R + ≥2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n = 12).

At failure, the median DTG fold-change from reference was 23-fold (range: 0.92 to 209) for isolates with emergent INSTI-resistance substitutions (n = 18). Further, resistance to one or more background drugs in the DTG twice-daily regimen also emerged in 30% (12/40) of the subjects in the Week 24 resistance analysis set of this advanced population**.** The most common treatment-emergent INSTI substitution was T97A (45%). Other frequently emergent (10-20%) substitutions included E138K/A, G140S/A, Y143H/C, Q148H/R/K and M154I. The emergence of T97A and E138 substitutions in the presence of G140S and Q148H resulted in > 25 fold reduced DTG susceptibility from baseline.

Regarding cross-resistance to other INSTIs, none of the FDA DTG resistance analysis subjects with post-baseline resistance data were resistant to RAL in the treatment-naïve trials. Similarly, in treatment-experienced, INSTI naive subjects with post-baseline data, none of the FDA DTG resistance analysis subjects were resistant to RAL. None of the subjects' isolates in the DTG arm with emergent INSTI resistance substitutions had phenotypic changes in susceptibility to either DTG or RAL whereas subjects' isolates in the RAL arm with emergent INSTI resistance substitutions all had RAL phenotypic resistance. However, in INSTI-experienced patients, all of the subjects' isolates in the week-24 FDA resistance subset with emergent INSTI resistance substitutions were cross-resistant to RAL. Dr. Naeger concluded that this was not an unexpected finding as Viking-3 was designed to enroll INSTI-experienced patients.

7. Efficacy and Safety: Clinical reviews were conducted by Drs. Charu Mullick, Wendy Carter and Yodit Belew with secondary review provided by Dr. Kim Struble. The Biometrics review was conducted by Dr. Tom Hammerstrom with secondary review provided by Dr. Greg Soon. The Phase 3 program encompasses multiple patient populations who enrolled in two treatment naïve trials – SPRING-2 and SINGLE (n=1461), a treatment-experienced, INSTI naïve trial – SAILING (n=715), an INSTI experienced trial – VIKING-3 (n=183) and a study in pediatric patients greater than 12 years old (n=23).

The efficacy of DTG in HIV-1–infected treatment-naïve adults is based on the analyses of 48-week data from two randomized, international, multicenter, double-blind, active-controlled trials, SPRING-2 and SINGLE. In SPRING-2, 822 subjects were randomized and received at least 1 dose of either DTG 50 mg once daily or RAL 400 mg twice daily, both in combination with either the FDC dual NRTI treatment of abacavir sulfate [ABC] and lamivudine [LAM] or emtricitabine/tenofovir [FTC]/TDF]; 808 subjects were included in the efficacy and safety analyses. Important baseline characteristics included the following: median age was 36 years, 13% female, 15% non-white, 11% had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA >100,000 copies/mL, 48% had CD4+ cell count <350 cells/mm^3, and 39% received ABC/LAM as their NRTI backbone.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either DTG 50 mg once daily with the FDC ABC/LAM or ATRIPLA (efavirenz/FTC/TDF). Baseline characteristics were comparable to SPRING-2 except for the following: 32% non-white, fewer were co-infected (7% had hepatitis C co-infection and hepatitis B virus co-infection was excluded).

Week 48 outcomes for SPRING-2 and SINGLE are provided in Table 12 in product labeling and below. In SPRING-2, an antiretroviral regimen containing DTG was non-inferior to a RAL-containing regimen based on the primary endpoint of HIV viral load < 50 copies/mL, 88% versus 86%, respectively (95% CI -1.9%, 7.2%). In SINGLE, DTG was superior to ATRIPLA for the same primary endpoint, 88% versus 81%, respectively (95% CI 2.5%, 12.3%) as more subjects discontinued for adverse events on the comparator arm.

Table 12. Virologic Outcomes of Randomized Treatment in SPRING-2 and SINGLE at Week 48 (Snapshot Algorithm)

	SPRING-2		SINGLE	
	DTG 50 mg Once Daily + 2 NRTIs (N = 403)	RAL 400 mg Twice Daily + 2 NRTIs (N = 405)	DTG 50 mg + ABC/FTC Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
HIV-1 RNA <50 copies/mL	88%	86%	88%	81%
Treatment difference[a]	2.6% (95% CI: -1.9%, 7.2%)		7.4% (95% CI: 2.5%, 12.3%)	
Virologic nonresponse[b]	5%	7%	5%	6%
No virologic data at Week 48 window	7%	7%	7%	13%
Reasons				
Discontinued study/study drug due to adverse event or death[c]	2%	1%	2%	10%
Discontinued study/study drug for other reasons[d]	5%	6%	5%	3%
Missing data during window but on study	0	0	0	<1%
Proportion (%) of Subjects With HIV-1 RNA <50 copies/mL at Week 48 by Baseline Category				
Plasma viral load (copies/mL)				
≤100,000	91%	90%	90%	83%
>100,000	82%	75%	83%	76%
Gender				
Male	89%	86%	88%	82%
Female	84%	82%	85%	75%
Race				
White	88%	86%	90%	84%
Non-white	85%	85%	84%	74%

[a] Adjusted for pre-specified stratification factors.

[b] Includes subjects who changed BR to new class or changed BR not permitted per protocol or due to lack of efficacy prior to Week 48 (for SPRING-2 only), subjects who discontinued prior to Week 48 for lack or loss of efficacy, and subjects who were HIV-1 RNA ≥50 copies/mL in the Week 48 window.

[c] Includes subjects who discontinued due to an adverse event or death at any time point from Day 1 through the Week 48 window if this resulted in no virologic data on treatment during the Week 48 window.

[d] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Immunologic benefits based on CD4 count were comparable between treatment arms in SPRING-2 where the median change in CD4 counts from baseline for both groups was 230 cells/mm^3 at 48 weeks. In SINGLE, median changes in CD4 counts from baseline for both groups were 267 cells/mm^3 for DTG and 208 cells/mm^3 for ATRIPLA at 48 weeks.

HIV-1 treatment-experienced, INSTI-naïve adult subjects in SAILING (n=719) were randomized and received either DTG 50 mg once daily or RAL 400 mg twice daily with investigator selected background regimen consisting of up to 2 agents, including at least 1 fully active agent; there were 715 subjects included in the efficacy and safety analyses. Baseline characteristics included the following: median age was 43 years, 32% were female, 49% non-white, 16% had hepatitis B and/or C virus co-infection, 46% were CDC Class C (AIDS), 20% had HIV-1 RNA >100,000 copies/mL, 72% had CD4+ cell count <350 cells/mm^3 and 49% of enrollees had at least 3-class antiretroviral treatment resistance. The primary endpoint was HIV RNA < 50 copies/mL at week 24 consistent with our guidance document for this population. Week 24 outcomes for SAILING are shown in Table 13 in product labeling and below. In this trial, DTG was superior to RAL for the same primary endpoint at week 24, 79% versus 70%, respectively (95% CI 3.4%, 15.9%).

Table 13. Virologic Outcomes of Randomized Treatment in SAILING at 24 Weeks (Snapshot Algorithm)

	DTG 50 mg Once Daily + BR[a] (N = 354)	RAL 400 mg Twice Daily + BR[a] (N = 361)
HIV-1 RNA <50 copies/mL	79%	70%
Adjusted[b] treatment difference	9.7% (95% CI: 3.4%, 15.9%)	
Virologic nonresponse	15%	24%
No virologic data at Week 24 window	6%	6%
Reasons		
Discontinued study/study drug due to adverse event or death	2%	2%
Discontinued study/study drug for other reasons[c]	3%	3%
Missing data during window but on study	<1%	<1%
Proportion (%) With HIV-1 RNA <50 copies/mL at Week 24 by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	83%	77%
>50,000 copies/mL	70%	53%
Background regimen		
No darunavir use or use of darunavir with primary PI substitutions	79%	67%
Use of darunavir without primary PI substitutions	80%	81%
Gender		
Male	78%	70%
Female	83%	69%
Race		
White	79%	69%
Non-white	80%	71%

[a] BR = Background regimen. Background regimen was restricted to ≤2 antiretroviral treatments with at least 1 fully active agent.

[b] Adjusted for pre-specified stratification factors.

[c] Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Mean changes in CD4 cell counts from baseline were 114 cells/mm^3 in the DTG group and 106 cells/mm^3 in the RAL group.

In HIV-1 infected INSTI experienced patients in VIKING-3, a multicenter, open-label, single-arm trial (n=183), adult patients with virological failure and current or historical evidence of RAL and/or EVG resistance received DTG 50 mg twice daily with their current failing background regimen for 7 days, then received DTG with a re-optimized background regimen from Day 8 onward. Baseline characteristics included: 133 subjects with INSTI resistance at screening and

50 subjects with only historical evidence of resistance (and not at screening), median age of subjects was 48 years; 23% were female, 29% non-white, and 20% had hepatitis B and/or C virus co-infection. This was an advanced patient population that had a median baseline CD4+ cell count of 140 cells/mm^3, median duration of prior antiretroviral treatment of 13 years, and more than half were CDC Class C. Subjects had multiple-class antiretroviral treatment resistance at baseline: 79% had ≥2 NRTI, 75% ≥1 NNRTI, and 71% ≥2 PI major substitutions; 62% had non-R5 virus.

The primary endpoint of this trial was a combination of a reduction from baseline in HIV-1 RNA at Day 8 and HIV-RNA < 50 copies/mL at Week 24 as outlined in the revised Draft Guidance for Industry for Developing Antiretroviral Drugs for Treatment of HIV-1 Infection. Response at Week 24 was affected by baseline INSTI substitutions as outlined in Dr. Naeger's virology review and the Microbiology section of labeling (12.4). Week 24 virologic outcomes for VIKING-3 are shown in Table 14 in product labeling and below.

Table 14. Virologic Outcomes of Treatment of VIKING-3 at 24 Weeks (Snapshot Algorithm)

	DTG 50 mg Twice Daily + Optimized Background Therapy (N = 114)
HIV-1 RNA <50 copies/mL	63%
Virologic nonresponse	32%
No virologic data at Week 24 Reasons Discontinued study/study drug due to adverse event or death	4%
Proportion (%) With HIV-1 RNA <50 copies/mL at Week 24 by Baseline Category	
Gender Male Female	 64% 60%
Race White Non-white	 67% 52%

The median change in CD4+ cell count from baseline was 65 cells/mm^3 at Week 24.

IMPAACT P1093 is a Phase 1/2, 48-week, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of DTG in combination treatment regimens in HIV-1 infected infants, children and adolescents. The data in adolescents (n=23) was submitted in the NDA and reviewed to support an indication in pediatric patients older than 12 years of age. Baseline characteristics of adolescents included the following: mean age of 14 years (range: 12 to 17), 78% female, 52% black, mean plasma HIV-1 RNA was 4.3 $\log_{10}$ copies/mL, median CD4+ cell count was 466 cells/mm^3 (range: 11

to 1,025), 17% had baseline plasma HIV-1 RNA >50,000 copies/mL and 39% were CDC class C. Most patients previously used at least 1 NNRTI (52%) or 1 PI (78%).

Results at 24 weeks were 70% of subjects treated with DTG once daily (35 mg: n = 4, 50 mg: n = 19) plus optimized background therapy achieved a viral load <50 copies/mL. The median CD4+ cell count increase from baseline to Week 24 was 63 cells/mm^3.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety database included more than the minimal requirements (500 patients for approximately 48 weeks) as outlined the Guidance for Industry. Overall a total of 2026 HIV-1 infected subjects received at least one dose of DTG, of which approximately 1400 were in Phase 2b/3 trials.

Rates of adverse events leading to discontinuation in ongoing treatment naïve trials were low. In SPRING-2, adverse events leading to discontinuation were 2% in both arms. In SINGLE, rates of adverse events leading to treatment discontinuation were lower in the DTG arm compared to the ATRIPLA arm, 2% versus 10%, respectively. Treatment-emergent adverse drug reactions of moderate-to-severe intensity were also low and described in patient labeling in Table 2. Grade 1 insomnia was less common in SPRING-2 (~ 1%) than SINGLE (7% for DTG compared to 3% for ATRIPLA).

Rates of adverse events leading to discontinuation in SAILING were low (2% DTG arm compared to 4% in RAL-based arm). The only treatment-emergent ADR of GRADE 2-4 intensity with a ≥2% frequency in either treatment group was diarrhea, 1% (5/354) in subjects receiving DTG 50 mg once daily plus a background regimen and 2% (6/361) in patients receiving RAL 400 mg twice daily plus a background regimen.

In VIKING-3, rates of adverse events leading to discontinuation were 4% at 24 weeks, comparable to rates seen in less advanced populations taking lower doses of DTG (50 mg QD).

Selected laboratory abnormalities at Week 48 in treatment-naïve subjects, Grades 2-4, appear in Table 3 in product labeling. Of note, rates in SAILING were overall similar to rates in SPRING-2 and SINGLE. See below.

Table 3. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 and SINGLE Trials (Week 48 Analysis)

Laboratory Parameter Preferred Term	SPRING-2		SINGLE	
	DTG 50 mg Once Daily + 2 NRTIs (N = 403)	RAL 400 mg Twice Daily + 2 NRTIs (N = 405)	DTG 50 mg + ABC/LAM Once Daily (N = 414)	ATRIPLA Once Daily (N = 419)
ALT				
Grade 2 (>2.5-5.0 x ULN)	2%	3%	2%	5%
Grade 3 to 4 (>5.1 x ULN)	2%	1%	<1%	<1%
AST				
Grade 2 (>2.5-5.0 x ULN)	3%	3%	2%	3%
Grade 3 to 4 (>5.1 x ULN)	2%	2%	0	2%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	2%	2%	<1%	0
Grade 3 to 4 (> 2.5 x ULN)	<1%	<1%	<1%	0
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	1%	3%	3%	1%
Grade 3 to 4 (>10.0 x ULN)	4%	3%	3%	4%
Hyperglycemia				
Grade 2 (126-250 mg/dL)	5%	5%	7%	4%
Grade 3 (>251 mg/dL)	<1%	1%	1%	<1%
Lipase				
Grade 2 (>1.5-3.0 x ULN)	5%	6%	8%	7%
Grade 3 to 4 (>3.1 ULN)	1%	3%	3%	2%
Total neutrophils				
Grade 2 (0.75-0.99 x 10^9)	3%	3%	2%	4%
Grade 3 to 4 (<0.74 x 10^9)	2%	1%	2%	3%

ULN = Upper limit of normal.

In VIKING-3, the most common treatment-emergent laboratory abnormalities (>5% for Grades 2 to 4 combined) were increased ALT (8%), AST (6%), cholesterol (8%), glucose (12%), and lipase (8%). Two percent (3/183) of subjects had Grade 3 to 4, treatment-emergent hematology laboratory abnormalities, with neutropenia (1% [2/183]) most frequently reported.

Other Safety Findings

Hypersensitivity and Rash

With regard to other safety findings, the clinical reviewers focused their assessment on nonclinical study findings as well as labeled events related to the other INSTIs. For example, GSK included a Warning and Precaution for hypersensitivity events in product labeling. Even though hypersensitivity was observed in less than 1% of subjects enrolled in phase 3 trials and the majority of cases were confounded, one case of a severe hypersensitivity reaction was observed in a subject with no known risk factors. Also another case of positive rechallenge of DTG provides additional basis for the Warning and Precaution. Hypersensitivity reactions were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury.

Additionally, rash was reported in 5-7% of subjects in phase 3. Rash occurred in fewer DTG subjects compared to efavirenz and in a similar proportion of patients as raltegravir. These events were predominately mild-to-moderate and did not result in discontinuation. There were no cases of SJS or TEN.

Hepatotoxicity and Gastrointestinal

Hepatotoxicity was seen in an acute (2-week) study in monkeys. In clinical trials, the rates of AST and ALT abnormalities were higher in subjects co-infected with hepatitis B and/or C virus for all treatment groups compared to HIV mono-infected subjects. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving DTG were observed in 16% vs. 2% with the 50-mg once-daily dose and 8% vs. 7% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution were also observed in some co-infected patients receiving DTG, particularly in those whose anti-hepatitis therapy was withdrawn. It was difficult to determine whether liver chemistry elevations were a result of hepatic flare secondary to withdrawal of anti-hepatitis therapy, immune reconstitution in the setting of a rising CD4 count or hepatoxicity. Product labeling includes the following wording related to the potential for immune reconstitution in the setting of co-infection under the Warnings and Precautions section:

Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY [see Adverse Reactions (6.1)]. In some cases the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Appropriate laboratory testing prior to initiating therapy and monitoring for hepatotoxicity during therapy with TIVICAY are recommended in patients with underlying hepatic disease such as hepatitis B or C.

Gastrointestinal (GI) mucosal inflammation and hemorrhage were observed in nonclinical studies, across different animal species. Overall, the GI profile was similar between DTG and controls. Dose-response increases in GI events were not seen with the DTG 50 mg twice daily compared to once daily. The most commonly observed drug-related GI events were nausea and diarrhea. Three cases of gastric or duodenal ulcer were seen with DTG, but all were confounded. Subclinical GI bleeding is unlikely because mean hemoglobin improved over 24-48 weeks. No additional labeling is needed for GI disorders.

Psychiatric disorders

The clinical team examined psychiatric disorders because events of suicidal ideation/behavior, particularly in subjects with a pre-existing history were seen during post-marketing with RAL. According to Dr. Struble's memorandum, psychiatric events with DTG occurred less frequently than with efavirenz and the DTG event rates were generally comparable to RAL. No marked differences were seen with DTG once daily compared to twice daily and no exposure-response was seen. One completed suicide did occur with DTG twice daily; however, the subject had pre-existing depression with co-existing social stressors and the event occurred seven months after entering the trial. Additionally, insomnia was frequently observed during phase 3 (3-11%). The rates were comparable to RAL but higher than EFV.

Renal

An increase in creatinine (Grade 1) was seen more frequently with DTG compared to EFV in a phase 2b trial. GSK evaluated this issue and concluded this was a result of DTG effects on the renal tubular transporter OCT2. DTG blocks OCT2 and affects creatinine secretion without affecting creatinine clearance or GFR. Iohexol and PAH evaluations also showed DTG did not affect GFR and renal plasma flow. Also see the pharmacometrics review for further details.

Deaths

Overall, 15 DTG treated adult subjects died in Phase 2b/3 trials and compassionate use program through the 60-day safety update report cut-off date. No deaths were reported in the pediatric trial. Causes of death and relatedness to study drugs were assessed by the clinical review team and described in the clinical review. Causes of death included PML, lymphoma, Kaposi's sarcoma, non-Hodgkin's lymphoma, myocardial infarction, cardiac death, suicide, homicide, motor vehicle accident, brain mass, pulmonary hemorrhage, fungal pneumonia and hemochromatosis and fibrosis secondary to HCV. After review of the narratives, the clinic team concurs with the investigators' assessments that none of the deaths was thought to be related to DTG.

8. Postmarketing Requirements (PMR):

1. Submit the final study report for 48 week data analyses from study ING111762 in treatment-experienced, integrase strand transfer inhibitor-naïve subjects.

2. Submit the final study report for 48 week data analyses from study ING112574 in treatment-experienced, integrase strand transfer inhibitor-experienced subjects.

   Required Pediatric Assessments:

3. Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected integrase strand transfer inhibitor-naïve, pediatric subjects 4 weeks to less than 12 years of age. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or substudy to allow dose selection. Using doses selected based on the pharmacokinetic study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of dolutegravir plus background regimen assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.

4. Conduct a trial to evaluate pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected treatment-experienced pediatric subjects with documented or clinically suspected integrase strand transfer inhibitor resistance, ages 2 years to less than 18 years. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or substudy to allow dose selection. Using doses selected based on the pharmacokinetic study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of dolutegravir plus background regimen assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.

Additionally, the following postmarketing commitments (PMCs) will be issued:

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

2. Conduct the requested (b) (4) testing for drug substance to target (b) (4) degradation, evaluate both drug substance and drug product impurities methods using these conditions, and submit the

data as a Changes Being Effected in 0 Days Supplement to be filed within 6 months from the date of NDA action.

9. Advisory Committee: This NDA was not presented before the Antiviral Products Advisory Committee. It was the third INSTI in the class. Notably, no issues were identified that required outside expertise.

Conclusions and Recommendations: Treatment of HIV-1 infected adults and children is complex. Suppression of viral load depends on many factors including potency of an antiretroviral regimen, viral characteristics such as presence of baseline or emergent resistance substitutions, along with patient adherence and tolerability of a regimen. DTG in combination with other antiretroviral agents addresses many of these issues. DTG is potent with superior efficacy compared to an EFV-containing regimen in the SINGLE trial in treatment-naïve subjects and to a RAL-containing regimen in SAILING in treatment-experienced, INSTI naïve subjects. In addition, DTG demonstrated potent activity in the VIKING-3 trial in INSTI-experienced subjects harboring RAL resistance substitutions, with an overall response rate of 63% in this advanced population with extremely limited treatment options. DTG can be dosed once daily in certain populations and was also well tolerated. Of note, drug-drug interactions were limited.

In sum, I am in agreement with the conclusions of the multidisciplinary review team that the risk-benefit assessment favors approval of DTG as part of a potent antiretroviral regimen in HIV-1 infected adults and children older than 12 years of age.

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/s/

DEBRA B BIRNKRANT
08/06/2013