Clinical and Cross Discipline Team Lead (CDTL) Review

Date	June 20, 2017
From	Yodit Belew, M.D.
Subject	Clinical Review
NDA/BLA # Supplement#	205551/S-11
Applicant	ViiV/GSK
Date of Submission	5/31/2017
PDUFA Goal Date	November 30, 2017
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 In adult and pediatric patients weighing at least 40kg
Recommended:	Approval

Table of Contents

1. Introduction

This combined Clinical and Cross Discipline Team Leader (CDTL) review provides an overview of the main findings for dolutegravir (DTG) abacavir (ABC) and lamivudine (3TC) as previously described in the respective NDAs. This review highlights the previously reviewed safety and efficacy, virology, clinical pharmacology data and overall risk/benefit assessments to support our recommendation for approval.

Triumeq contains abacavir (ABC) 600mg, dolutegravir (DTG) 50mg and lamivudine (3TC) 300mg. Hence, cross reference is made to NDAs 204790 for dolutegravir (Tivicay), 20977 and 20978 for abacavir (ABC, Ziagen), 20564 and 20596 for lamivudine (3TC, Epivir) and 21652 for ABC/3TC FDC (Epzicom).

Dolutegravir 50mg once daily is approved for the treatment of HIV infection in INSTI naïve adult and pediatric patients weighing at least 40kg. Abacavir and lamivudine administered twice-daily were approved over a decade ago for the treatment of HIV infection in pediatric patients, while once daily abacavir and lamivudine (Epzicom, ABC/3TC 600/300mg) were approved in 2015 for use in pediatric patients weighing at least 25kg.

Because once daily dosing regimen is now available for all the individual drug products (ABC, DTG and 3TC), the data that supported the approval of the individual drug products can be leveraged to support approval of Triumeq in pediatrics weighing at least 40kg without the need for additional or new clinical trial data. This supplemental NDA therefore cross-references the aforementioned NDAs in support of the indication sought for Triumeq in pediatric patients.

The current application partially fulfills the PREA PMR requirements for Triumeq:

> **2768-3:** Evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in HIV infected pediatric subjects 12 years to less than 18 years of age and weighing at least 40 kg. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 to less than 18 years of age and weighing at least 40 kg may not be required if dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products.

2. Background

Globally, approximately 37 million people were living with HIV in 2015, including 1.8 million children who are less than 15 years of age. The estimated incidence of HIV-1 diagnoses in the US in 2014 was 44,073 among adults and children, of which 174 were among children under the age of 13 years. The primary reasons for the dramatic decrease in diagnosis of pediatric HIV is the great progress made in preventing maternal-to-child transmission (MTCT) of HIV infection through early identification and treatment of the mother and providing prophylactic antiretroviral (ARV) treatment for the newborn. For example, per the CDC, the incidence of perinatal transmission in the US in 2014 was estimated to be 127 due to improved access to HIV therapy

in pregnant women. Treatment of HIV infection has also improved since the mid-1990s after the introduction of use of combination drug products (HAART). Effective treatment of HIV-1 infection comprises of combination antiretroviral therapy with at least 3 antiretroviral (ARV) medications.

Despite such progress, there is a continued need for development of new ARV drug products or improvement of the available drug products. The need for multiple drugs for effective treatment may lead to high pill burdens and complex dosing schedules, which may negatively affect patients' treatment adherence. The introduction of fixed-dose combination (FDC) drug products has allowed for simpler ARV regimens, increasing the likelihood of adherence and thereby improving treatment outcomes.

To date, six different antiretroviral drug classes are available comprising of over 38 single and fixed dose combinations for the treatment of HIV infection. The drug classes include: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, CCR5 co-receptor antagonists, and integrase strand transfer inhibitors.

DTG (Tivicay) is an integrase strand transfer inhibitor (INSTI) owned by ViiV Healthcare and developed by GlaxoSmithKline (GSK). DTG was approved on August 12, 2013 under NDA 204790 for the treatment of HIV-1 infection. GSK also co-formulated DTG with two non-nucleoside reverse transcriptase inhibitors (NRTIs) [ABC and 3TC] to create a fixed dose combination (FDC) drug product, Triumeq. Triumeq was approved on August 22, 2014 under NDA 205551. No new clinical safety and efficacy trials were conducted with Triumeq. Rather, in support of the approval of Triumeq, the following studies were utilized: a relative BA trial, Week 48 data from phase 3 trials from NDA 204790 -- SINGLE (ING114467) which evaluated the safety and efficacy of DTG when co-administered with ABC/3TC in treatment-naïve subjects; and SAILING (ING111762) which evaluated the safety and efficacy of DTG in treatment- experienced INSTI-naïve subjects.

ABC and 3TC, both a nucleoside reverse transcriptase inhibitors (NRTIs), are also owned by ViiV. NDA 20564 and NDA 20596 for Epivir (3TC) tablets and oral solution, respectively, were approved for twice-daily dosing on November 17, 1995 and on April 11, 1997, respectively. Twice daily-dosing for children was approved on March 23, 1999. Once-daily dosing administration for adult and pediatric use was approved on June 24, 2002 and March 23, 2015, respectively.

NDA 20977 and NDA 20978 for Ziagen (ABC) tablets and oral solution, respectively, were approved on December 17, 1998 and April 15, 2004, respectively. Twice-daily dosing for children was also approved on December 17, 1998. Once-daily dosing of ABC for adults was approved on August 2, 2004. On September 20, 2015, approval was granted for use of once daily Epzicom (ABC and 3TC) in pediatric patients weighing at least 25 kg.

This combined clinical and cross discipline team leader review therefore relies on previously reviewed data for DTG and ABC/3TC. The purpose of this combined Clinical and CDTL Review is to provide an overview and summary of the findings of the previously FDA reviewed NDAs and provide an overall risk-benefit assessment of Triumeq for use in pediatric patients.

DTG is among the listed preferred ARVs in the Department of Health and Human Services treatment guidelines for both treatment-naïve adults and pediatric patients with HIV-1 infection.

[1,2] ABC and 3TC are also included in the list of preferred NRTI "backbone" regimens. The availability of Triumeq will therefore provide a once-pill once daily regimen containing preferred ARVs for treatment of HIV in pediatric patients weighing at least 40kg.

3. CMC

There is no new CMC information for review. The same adult dosage form of Triumeq is proposed for use in pediatric patients weighing at least 40kg.

4. Nonclinical Pharmacology/Toxicology

Extensive programs of nonclinical studies with ABC, DTG, and 3TC have been previously conducted and deemed acceptable. Additional nonclinical data were not needed for this sNDA approval.

Please refer to the individual drug NDAs and prescribing information for further details.

5. Clinical Pharmacology/Biopharmaceutics

Refer to the individual drug NDAs and prescribing information for further details.
A brief summary is provided below.

Absorption, Food effects and Bioavailability- Triumeq

A relative BA study supported the approval of Triumeq. 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 Cmax and AUC[0-inf]); thus, Triumeq is bioequivalent to the individual drug products.

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

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.

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[1] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed June 20, 2017.

[2] Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. What to Start: Recommended Regimens for Initial Therapy of Antiretroviral-Naïve Children. Accessed June 20, 2017.

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.
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.

Drug-drug interactions (DDI)

In summary no new DDI studies were conducted using Triumeq. 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: Though no DDI trials were conducted using the FDC drug product, all the relevant DDI from the individual drug products are included in the Triumeq label. Specifically, based on DDI studies with DTG, the following recommendations are included in the label:

> Dosing Recommendation With Certain Concomitant Medications
> Because the dolutegravir dosage regimen (50 mg once daily) in TRIUMEQ is insufficient when co-administered with certain 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.

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 ABC or 3TC 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
A specific pattern of concern was not identified when safety was assessed 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.

Exposure-response and Exposure-safety analyses

No exposure-response and exposure-safety analyses were conducted for Triumeq. Previously conducted trials with the individual drug products were used to support the approval of Triumeq.

6. Clinical Microbiology

The label for Triumeq reflects all the pertinent microbiology findings from the individual drug products. Please refer to the respective NDAs and the prescribing information for details on the microbiology profile of abacavir, lamivudine and dolutegravir.

7. Clinical/Statistical- Efficacy

A separate efficacy trial evaluating the FDC Triumeq was not required for approval. Instead the efficacy of Triumeq was supported by the demonstration of bioequivalence between Triumeq and the individual components and the SINGLE trial which evaluated DTG plus ABC/3TC. Additional efficacy information supporting the efficacy of abacavir and lamivudine, in combination with other ARVs are also available. Please refer to the respective NDAs and prescribing information for additional details.

For ARV approvals in pediatric patients, typically we review the pharmacokinetic data in children to ensure similar exposures are achieved compared to adults. We do this because we presume

the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c). Thus, one can rely on the pharmacokinetics data to extrapolate efficacy; that is, the goal would be to target the exposure(s) (AUC) that are similar to the observed exposures (AUC) from the approved (or to-be marketed) adult dose(s). Although AUC is the primary pharmacokinetic parameter targeted when selecting pediatric dose(s), C_{24} may also be an important pharmacokinetic parameter for some antiretroviral drugs with regards to establishment of exposure-response relationship. The clinical efficacy (antiviral activity) data obtained from pediatric trials are also used as supportive data.

As part of the original NDA approval, dolutegravir 50mg once daily was also approved for use in pediatric patients weighing at least 40kg and without INSTI resistance. Trial P1093 provided safety, PK and antiviral activity (efficacy) in pediatric patients. Please refer to NDA 204790 for full details.

The efficacy of once daily ABC and 3TC in pediatric subjects is supported by the approvals of once-daily ABC and 3TC. The results from ARROW Randomization 3, demonstrated that once-daily dosing of ABC+3TC is non-inferior to twice-daily dosing of ABC+3TC in children who have received at least 36 weeks of ART on a twice-daily dosing schedule. Please refer to the reviews for NDA 20977 and NDA 20564 for details.

Therefore, highlighted in this section are the results from the pediatric trials P1093 for dolutegravir and ARROW Randomization 3 for ABC and 3TC once daily, supporting dosing recommendation for Triumeq in pediatric patients weighing at least 40kg.

Overview of the Trial Designs

P1093

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

The study is designed to have two stages. During Stage 1, intensive PK, tolerability and short term safety data were collected. Ten subjects were enrolled in Stage 1 of Cohort 1. These subjects continued treatment to allow evaluation of the long-term safety and efficacy of DTG. In stage 2, long-term (e.g. 48 weeks) safety and antiviral activity data are collected. A total of 23 adolescent subjects were enrolled in Cohort 1 to provide and antiviral activity of DTG in patients weighing at least 40kg.

ARROW

The ARROW trial enrolled HIV-1 infected, ARV-naive children ages 3 months to 17 years in Uganda and Zimbabwe who were eligible to initiate ARV. There were a total of four randomizations in the study: 2 primary and 2 secondary. All subjects underwent simultaneous

randomization into Randomizations 1 and 2 at study entry: Randomization 1 compared clinically driven monitoring (CDM) with laboratory plus clinical monitoring (LCM); Randomization 2 compared a 3-drug 2-class first line ARV regimen (2 NRTIs plus 1 NNRTI) with a 4-drug 2-class induction followed by maintenance with 3 drugs (1 or 2 classes). The secondary randomizations occurred after at least 36 and 96 weeks on ARV therapy (Randomization 3 and 4, respectively), to assess simplification strategies which could improve long-term ARV adherence: once versus twice daily ABC+3TC (Randomization 3) and stopping versus continuing daily cotrimoxazole prophylaxis (Randomization 4). A subset of subjects also participated in PK sub-studies.

Results Summary

- ***Disposition***

P1093

A total of 23 subjects were enrolled in Cohort 1 of P1093. Most subjects completed the trial and reached at least Week 48. Two subjects in Cohort I discontinued the study drug prior to the Week 48 Visit. Both withdrew at Week 40 due to non-adherence to treatment.

ARROW

A total of 1,206 subjects were enrolled in the ARROW trial, of which 669 participated in Randomization 3: 333 subjects in the BID arm and 336 subjects in the QD arm. All subjects completing the first 48 weeks (primary endpoint) and 664 (99%) completing 96 weeks. Reasons for discontinuation prior to Week 96 included 4 deaths (3 in the BID arm and 1 in the QD arm) and one subject in the QD arm who discontinued for other reasons.

- ***Summary of Pharmacokinetic***

P1093

In summary, DTG 50 mg QD achieved exposures in adolescents within the pre-defined targeted exposure range, as defined by the SPRING-1 data. The geometric mean for AUC_{24} and C_{24} were 46 mcg*h/mL and 0.9 mcg/mL, respectively. The %CV were 43.1 and 58.6, respectively. These exposures however were lower than what was observed in the adult Phase 3 data (adult Phase 3 data: AUC_{24} and C_{24} are 53.5 mcg/mL and 1.11 mcg/mL, respectively). Of note, one adolescent subject experienced a very low DTG exposure; no explanation was provided for the low exposure. When the exposure analysis is conducted after excluding this subject, the AUC_{24} and C_{24} are similar to what was observed in the Phase 3 adult trials (i.e. the exposures for AUC_{24} and C_{24} are 52.9 mcg/mL and 1.06 mcg/mL, respectively).

ARROW

Several pharmacokinetic (PK) studies have been reviewed in past, including 2 ARROW PK sub-studies, PENTA studies 13 and 15, and PACTG studies 1052 and 1018 in support of once-daily dosing of ABC and 3TC. Overall, the PK data demonstrate mean AUC0-24 values are comparable between QD and BID dosing for both ABC and 3TC. As expected, the C_{max} is higher and the C_{trough} is lower with QD dosing versus BID dosing. However, the observed values in the ARROW cohort exceeded the predicted pediatric values as well as historical adult reference values (study EPV10001). This is likely due to the slightly higher dosing recommended by the WHO in some pediatric weight bands compared to the US prescribing information.

- ***Summary of Baseline Demographic and Disease Characteristics***

P1093

Table 1 summarizes the baseline demographics and disease characteristics for Cohort I. All

subjects were treatment-experienced. All had previous NRTI use, 87% had previous PI use, and 48% had previous NNRTI use.

Table 1 P1093 Cohort 1 Baseline Demographic and Disease Characteristics

Demographics and Baseline Characteristics	Cohort I N=23
Sex, n (%)	
Male	5 (22)
Female	18 (78)
Age (years)	
Mean (SD)	14.8 (1.9)
Median	15.2
Min, max	12.2, 17.8
Weight Bands, n (%)	
≥40 kg	19 (83)
30 - <40 kg	4 (17)
Ethnicity, n (%)	
Hispanic or Latino	6 (26)
Not Hispanic/Latino	17 (74)
Unknown	0
Race, n (%)	
Black or African American	12 (52)
White	8 (35)
Asian	3 (13)
Other[a]	0
Baseline HIV-1 RNA (copies/mL)	
Mean (SD)	40,206 (59,167)
Median	17,996
Range	1,168-243,765
Baseline CD4 count (cells/mm^3) Mean (SD)	527 (285)
Median	466
Range	11-1,025
Baseline CD4 Count, n (%) <200	2 (9)
200 - <500	10 (43)
≥500	11 (48)

[a] Other includes the following races: Native Hawaiian/other Pacific Islander, More than one race, or Unknown.
Source: Adapted from clinical study report for P1093, Tables 7 and 8; P1093 Datasets.

ARROW

A total of 1,206 subjects were enrolled in the ARROW trial, of which 669 participated in Randomization 3 where 333 subjects were enrolled in the BID arm and 336 subjects were enrolled in the QD arm. Baseline demographic and disease characteristics were similar between the BID and QD groups (Table 2). Randomization between the two study groups was also well balanced by primary randomizations, study site, and drug formulation.

Table 2 ARROW Study Randomization 3 Baseline Demographic and Disease Characteristics

	BID Dosing (n=333)	QD Dosing (n=336)
Sex n (%)		
Male	161 (48)	163 (49)
Female	172 (52)	173 (51)
Median Age in Years (IQR)	5.1 (3.6 to 8.3)	5.9 (3.8 to 8.6)
Median Years Since ART Initiation (IQR)*	1.8 (1.4 to 2.3)	1.8 (1.4 to 2.1)
HIV-1 RNA PCR < 80 copies/ml	250 (76)	237 (71)
Median CD4 Percentage (IQR)	33 (27 to 39)	33 (28 to 39)
Median CD4 Count (IQR) (≥ 5 yrs)	836 (558 to 1,131)	760 (543 to 1,136)

*Reflective of time on BID ABC+3TC during the ARROW trial, prior to Randomization 3. All subjects were ART Naïve at ARROW baseline.
Source: Source: Clinical Review by Dr. Prabha Viswanathan for NDA 21652/S-019

- ***Summary of Efficacy***

P1093

Table 3 summarizes the results of the efficacy analysis of virologic outcomes at Week 24 and 48 for 23 subjects in Cohort I, 19 (83%) of whom weighed at least 40 kg. Per their weights, 4 subjects received 35 mg once daily and 19 subjects received 50 mg once daily.

The proportion of subjects in Cohort I with HIV-1 RNA <50 and <400 copies/mL at Week 48 were 61% (14/23) and 74% (17/23), respectively. Virologic outcomes were also evaluated based on body weight. At Week 48, 63% (12/19) of the subjects in Cohort 1 weighing at least 40 kg were virologically suppressed. None of the subjects in Cohorts I discontinued for lack of efficacy through Week 48; however, 2 subjects at Week 40 discontinued for other reasons (non-adherence to treatment) and both subjects had HIV-1 RNA ≥50 copies/mL. Out of the nine subjects who did not reach HIV RNA <50 copies/mL, 5 had HIV RNA ≥400 copies/mL. Resistance information was available for 2 subjects; neither of the 2 subjects developed INSTI associated resistance substitution.

Table 3 P1093 Cohort 1 Virologic Outcomes at Week 24 and 48 (Snapshot Algorithm)

Virologic Outcome, n(%)	Week 24 N=23	Week 48 N=23
HIV-1 RNA <50 copies/mL	16 (70)	14 (61)
HIV-1 RNA ≥50 copies/mL	7 (30)	9 (39)
Data in window not <50 copies/mL	7 (30)	7 (30)
Discontinued for other reasons while not <50 copies/mL	0	2 (9)

Source: Clinical study report and efficacy dataset for P1093; Clinical review by Dr Mark Needle for sNDA 204790/S-08

Although cross-trial comparisons should be viewed with caution, the response rate in adolescents appears to be numerically lower than the response rate observed in adults from the SAILING trial (Week 24: 70% vs. 79%; Week 48: 61% vs. 71%). Of note, 63% of the adolescent subjects from Cohort 1 weighing at least 40kg achieved HIV RNA <50 copies/mL. The efficacy outcome for pediatric subjects weighing at least 40kg further improves when the sample size is increased (i.e. when including subjects enrolled in Cohort IIA who weighed at least 40kg). At Week 48, 16/24 (67%) of pediatric subjects weighing at least 40kg achieved HIV RNA <50 copies/mL. This virologic outcome is comparable to the outcome observed in treatment-experienced, INSTI-naïve adults (i.e. 71%).

Table 4 Virologic Success (HIV-1 RNA <50 c/mL) at Week 48 Pediatric Subjects and Adults

Virologic Outcome	**Pediatric (weight band ≥ 40kg**			**Adult Treatment-experienced, INSTI-naïve (SAILING)**
HIV RNA <50 copies/mL	Cohort 1	Cohort 2A	Total	DTG+ BR* arm
Week 48	12/19 (63%)	4/5 (80%)	16/24 (67%)	71%

Source: Clinical reviews for the original and supplemental NDA 204790
*Background regimen

ARROW

Subjects in the QD group who weighed 25 kg at the start of Randomization 3 were treated with Epzicom tablets, whereas smaller children received the ABC and 3TC single entity products.

The primary efficacy endpoint for Randomization 3 was the percentage of subjects with virologic suppression at Week 48. The study was powered for a pre-specified non-inferiority margin of 12%. For FDA efficacy analysis, virologic suppression is defined as HIV-1 RNA < 50 copies/ml. However, due to the small sample volumes obtained during ARROW study, samples were diluted in order to perform the assay, requiring adjustment of the assay results. The definition of virologic suppression was hence defined as HIV-1 RNA PCR < 80 copies/ml. Table 4 summarizes the virologic outcome per FDA's snapshot algorithm. At Week 48, the proportion of subjects with HIV RNA <80 copies m/mL were 73% and 69% for the BID and QD arms, respectively, with treatment difference and 95% CI of -3.3% (-10% to +4%). At Week 96, the proportion of subjects with HIV RNA <80 copies m/mL were 73% and 69% for the BID and QD arms, respectively, with treatment difference and 95% CI of-2.4% (-9% to +5%). The virologic outcomes are summarized in Table 5.

Table 5 ARROW Study Virologic Outcomes at Randomization 3 Baseline, Week 48, and Week 96

	Baseline* N=669		Week 48* N=669		Week 96* N=669	
Virologic Outcome, n(%)	**BID Dosing** N=333	**QD Dosing** N=336	**BID Dosing** N=333	**QD Dosing** N=336	**BID Dosing** N=333	**QD Dosing** N=336
Virologic Success (≤80 copies/mL)	250 (76)	237 (71)	242 (73)	233 (69)	232 (70)	226 (67)
Virologic Failure (>80 copies/mL)	81 (24)	98 (29)	90 (27)	98 (29)	94 (28)	105 (31)
HIV RNA above threshold	81 (24)	98 (29)	90 (27)	95 (28)	90 (27)	100 (30)
Prior change in ART	N/A	N/A	0	3 (1)	4 (1)	5 (1)
No virologic data	2(<1)	1(<1)	1 (<1)	5 (1)	7 (2)	5 (1)
Missing data during window but on study	2 (<1)	1 (<1)	1 (<1)	5 (1)	4 (1)	3 (1)
Death	N/A	N/A	0	0	3 (1)	1 (<1)
D/C for other reasons	N/A	N/A	0	0	0	1 (<1)

Source: Clinical Review by Dr. Prabha Viswanathan for NDA 21652/S-019

8. Safety

Dolutegravir was approved in August 2013, for use in adults and pediatric patients weighing at least 40kg. The indication was extended in 2015 to include pediatric patients weighing 30 to 40kg (age range approximately 6-12 years old; Cohort IIA). Please refer to the original NDA 204790 and the subsequent sNDA containing longer-use safety data as well as pediatric safety data for extensive discussions on the safety and tolerability of dolutegravir in adult and pediatric patients.

Although Triumeq will be indicated only for pediatric patients weighing at least 40kg, safety review from all available pediatric age/weight group (i.e. Cohort I and IIA) is included to maximize the safety data and provide broader breadth of the safety profile of dolutegravir when administered to pediatric subjects.

The use and safety profiles for abacavir and lamivudine are extensive because the drugs have been marketed for over 15 years. Therefore, extensive review of the safety of ABC/3TC is not necessary. The ARROW trial provided large pediatric safety data to further evaluate the safety of ABC/3TC in children, in particular, to assess for differences in the overall safety of ABC/3TC when administered once daily, compared to twice daily. Because the ARROW study was conducted to inform best practices for treatment of HIV-1 infection in children in resource-poor settings, collection of adverse event (AE) data was limited to severe events (Grade 3 and 4). Collection of Serious Adverse Events (SAE) was also limited to those events not considered directly related to HIV disease. Additionally, only Grade 3 and 4 laboratory toxicities were collected.

Deaths and other SAEs

P1093

No deaths were reported in Cohort 1 and IIA. Table 6 summarizes the nonfatal serious adverse

events reported from Cohort I and Cohort IIA. Five subjects from Cohort I and 3 subjects from Cohort IIA experienced serious adverse events. Additional 2 subjects from Cohort I also experienced serious laboratory events. The most common SAE across both cohorts was deep vein thrombosis (4%), reported in 2 subjects from Cohort I. Both events occurred >48 weeks after starting DTG treatment. The other SAEs occurred in no more than one subject (2%) across both Cohorts. None of the SAEs were considered related to DTG treatment, resulted in permanent discontinuation or led to withdrawal from the trial. Note, HSV infection, lymphadenopathy, and B-cell lymphoma were all reported in 1 subject. Please refer to clinical review for NDA 204790 for narratives.

Table 6 Nonfatal Serious Adverse Events by Cohort

Preferred Term, n(%)	Cohort I N=23	Cohort IIA N=23	Cohorts I and IIA N=46
Clinical Serious Adverse Events			
Deep vein thrombosis	2 (9)	0	2 (4)
Abnormal behavior	0	1 (4)	1 (2)
Aggression	0	1 (4)	1 (2)
B-cell lymphoma	1 (4)	0	1 (2)
Depression/Suicide attempt	1 (4)	0	1 (2)
Gastritis/Abdominal pain	1 (4)	0	1 (2)
Herpes simplex/Oral herpes	1 (4)	0	1 (2)
Herpes zoster	1 (4)	0	1 (2)
Lymphadenopathy	1 (4)	0	1 (2)
Pelvic inflammatory disease/Pelvic pain	1 (4)	0	1 (2)
Pneumonia	0	1 (4)	1 (2)
Respiratory distress	0	1 (4)	1 (2)
Laboratory Serious Adverse Events			
Lipase increased	1 (4)	0	1 (2)
Neutrophils decreased	1 (4)	0	1 (2)

Source: Adapted from clinical study report for P1093 and Safety Dataset. Clinical review by Dr. Mark Needles for sNDA 204790/S-08

ARROW

Death was reported for 5 subjects during the 96-week study period: 4 in the BID arm and 1 in the QD arm. All deaths were in young children (5 to 9 years of age) and were deemed unrelated to the study or study medication. None of the deaths occurred among the 101 children who received Epzicom. Please refer to clinical review for NDA 20977/S-027 for brief narratives of each case.

The SAEs reported were primarily related to infection and included malaria (n=13, 4% and 13, 4%) in the QD and BID arms, respectively; measles (n=1, <1% and n=3, 1%) in the QD and BID arms, respectively; acute diarrhea (n=2, 1% and n=2, 1%) in the QD and BID arms, respectively. Anemia was also reported in 6 patients (2%) in the QD arm and 5(2%) in the BID arm.

Discontinuations due to AEs

P1093

No subject discontinued due to adverse events.

ARROW
As mentioned above, 4 deaths were reported (3 in the BID arm and 1 in the QD arm). Refer to clinical review for NDA 20977/S-027 for narratives.

Adverse Events of Interest

No such assessments were made during the ARROW trial. Therefore, no discussion is included in this section for ABC/3TC. Refer to the respective NDAs and prescribing information for further review of adverse events of interest in pediatrics patients when ABC/3TC is administered twice daily.

Based on signals from nonclinical toxicity studies or previously identified potential INSTI drug class effect, the adverse of events of interest for further safety evaluation for dolutegravir included hypersensitivity reactions and rash, neuropsychiatric events, hepatobiliary events, renal events, gastrointestinal events, and musculoskeletal events.

Rash

Hypersensitivity reaction is a well-established event for abacavir and the 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.

Rash was noted in 17 subjects (37%) across both Cohorts. All rashes were mild or moderate, most were self-limiting, and only one rash of Grade 2 or above considered possibly related to DTG treatment. Subject 690529 from Cohort I was noted to have a Grade 2 rash (face and legs) on Day 10 of treatment which was attributed as possibly related to DTG treatment. DTG treatment was continued and the event resolved after 18 days. There were no Grade 3 or Grade 4 rashes and no serious skin reactions such as Steven-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme reported.

Psychiatric Disorders

During the Phase 3 adult clinical trials, psychiatric disorders including suicide ideation and behaviors were reported. These events occurred primarily in subjects with pre-existing history of depression or other psychiatric illness. During P1093, 7 subjects (15%) across the two cohorts experienced psychiatric events.

Depressive Disorders: Depression, most frequently reported psychiatric event, was reported in 4 subjects and included 3 cases of depression and 2 cases of major depression. Three of the four subjects with depression had a medical history of depression or other relevant pre-existing risk factor.

Other psychiatric events: The other reported events were flat affect (1), initial insomnia (1) and ADHD (1).

No psychiatric event with severity greater than Grade 2 was considered related to DTG. Two subjects had Grade 3 or 4 SAE. One subject from Cohort I reported Grade 4 depression and suicide attempt. This subject had a long-standing history of mild intermittent situational depression. Another subject from Cohort IIA reported Grade 3 abnormal behavior and

aggression; this subject had a history of destructive behaviors since 3 years of age. Given the past medical histories in both subjects, it is difficult to assess causality of the events.

Hepatobiliary Disorders

No subject from Cohort I experienced a clinical event in the hepatobiliary system organ class. One subject from Cohort IIA experienced Grade 1 hepatomegaly starting 112 days after initiating the study drug. No elevation in ALT, AST, bilirubin, or alkaline phosphatase was reported. The event was considered not related to DTG. No cases fulfilled criteria for Hy's law of drug-induced liver injury. See laboratory section for discussion on serum liver biochemistries abnormalities.

Renal Disorders

No subjects in P1093 experienced renal failure. Refer to the laboratory section for discussion on serum creatinine and other parameters.

Gastrointestinal Disorders

Abdominal pain, diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events reported in the Phase 3 studies in adults.

Overall, 24 subjects (52%) across Cohorts I and IIA experienced gastrointestinal events during the trial. The most frequently reported gastrointestinal events (regardless of causality or severity) were diarrhea (28%), abdominal pain (20%), vomiting (13%), and nausea (7%). Abdominal pain was noted in 9 subjects, including 5 cases of abdominal pain, 3 cases of abdominal pain upper, 1 case abdominal discomfort, 1 case of epigastric discomfort, and 1 case of gastroesophageal reflux disease. Some subjects experienced more than one type of gastrointestinal event. Most events were mild or moderate, self-limiting and not considered to be related to DTG treatment. One subject from Cohort I reported Grade 3 gastritis and abdominal pain as serious gastrointestinal events. The events were self-limiting and not considered related to DTG treatment. No other serious or ≥Grade 3 gastrointestinal events were reported during P1093. No gastrointestinal erosion or ulceration was reported. There were 2 subjects who experienced ≥ Grade 2 gastrointestinal events that were considered possibly related to DTG treatment. One subject from Cohort I had Grade 2 abdominal pain and Grade 2 diarrhea possibly related to DTG treatment. Another subject from Cohort IIA had Grade 2 diarrhea considered possibly related to DTG treatment. None led to discontinuation of DTG.

Musculoskeletal Disorders

Adult subjects in the Phase 3 DTG clinical trials had few cases of myositis or CK elevations reported. During P1093 trial, 17 subjects (37%) across Cohorts I and IIA experienced musculoskeletal events during the trial. Most of the subjects (n=14) were from Cohort I. None of the events were reported as Grade 3 or Grade 4 and no musculoskeletal event of at least Grade 2 were considered related to DTG treatment. The most frequently reported musculoskeletal events across both Cohorts were muscular pain (20%) and pain in extremity (13%). Muscular pain was reported in 7 subjects, including 4 cases of back pain, 3 cases of musculoskeletal pain, and 2 cases of myalgia. There were no cases of rhabdomyolysis or myositis reported. Grade 1 creatinine phosphokinase elevation (CK) was noted in 1 subject from Cohort I. The event was not considered related to DTG treatment and the subject did not have any concomitant musculoskeletal events reported.

Common AEs

Because 'common AEs' were not collected during ARROW trial, this section only summarizes common AEs observed in P1093 for DTG.

All subjects (100%) in Cohort I and 22 subjects (96%) in Cohort IIA reported one or more treatment-emergent clinical adverse events. Cough was the most frequently reported clinical adverse event in both Cohort I and Cohort IIA, followed by oropharyngeal pain (39%), nasal congestion (35%), and diarrhea (35%) in Cohort I; and nasal congestion (30%), rash (30%), skin lesion (22%), and diarrhea (22%) in Cohort IIA. Table 7 summarizes the common clinical adverse events (all cause, all grade) reported in at least 4 subjects. All were reported as mild or moderate.

Table 7 Summary of Common Clinical Adverse Events by Cohort (Incidence ≥ 4 subjects)

Preferred Term	Cohort I N=23	Cohort IIA N=23	Cohorts I and IIA N=46
Clinical Adverse Events			
Cough	14 (61)	12 (52)	26 (57)
Nasal congestion	8 (35)	7 (30)	15 (33)
Diarrhea	8 (35)	5 (22)	13 (28)
Oropharyngeal pain	9 (39)	3 (13)	12 (26)
Lymphadenopathy	7 (30)	4 (17)	11 (24)
Pyrexia	7 (30)	4 (17)	11 (24)
Rhinorrhea	7 (30)	4 (17)	11 (24)
Headache	7 (30)	3 (13)	10 (22)
Rash	2 (9)	7 (30)	9 (20)
Decreased appetite	7 (30)	1 (4)	8 (17)
Pain in extremity	6 (26)	0	6 (13)
Skin lesion	1 (4)	5 (22)	6 (13)
Vomiting	4 (17)	2 (9)	6 (13)
Abdominal pain	5 (22)	0	5 (11)
Dermatitis atopic	1 (4)	4 (17)	5 (11)
Pruritus	1 (4)	4 (17)	5 (11)
Sinus congestion	4 (17)	1 (4)	5 (11)
Back pain	4 (17)	0	4 (9)
Dizziness	4 (17)	0	4 (9)
Fatigue	3 (13)	1 (4)	4 (9)
Papule	2 (9)	2 (9)	4 (9)
Tinea capitis	0	4 (17)	4 (9)
Wheezing	2 (9)	2 (9)	4 (9)

Source: Adapted from clinical study report and safety dataset for P1093. Clinical review by Dr. Mark Needles for sNDA 204790/S-08

Laboratory Toxicities for Selected Parameters

P1093

Serum liver biochemistries: 19 subjects (41%) across Cohorts I and IIA experienced hepatic-related laboratory toxicities (i.e., increased total bilirubin, ALT, AST, and/or alkaline phosphatase). There were no hepatic-related laboratory toxicities reported as SAEs and no

hepatic-related laboratory toxicities ≥ Grade 2 were considered related to DTG. Although no significant changes in liver transaminases were observed across Cohorts I and IIA, there were small increases observed in mean total bilirubin. Concomitant use of atazanavir was noted in 8 of the 9 subjects with hyperbiliruinemia, including the 3 subjects with Grade 3 events. These cases were not considered related to DTG treatment. One subject was noted to have Grade 1 hyperbilirubinemia associated with Grade 1 elevated AST, but no other subjects with hyperbilirubinemia had concomitant elevations in ALT, AST, and/or alkaline phosphatase. No cases fulfilled the laboratory criteria for Hy's law of drug-induced liver injury. Table 8 summarizes all hepatobiliary events by worst grade toxicities reported across Cohorts I and IIA.

Table 8 Hepatobiliary Events by Worst Grade Toxicities

Parameters, n(%)	Cohorts I and IIA N=46
ALT increased	
Grade 1	6 (13)
Grade 2	3 (7)
Grade 3	0
AST increased	
Grade 1	8 (17)
Grade 2	1(2)
Grade 3	0
Total Bilirubin increased	
Grade 1	3(7)
Grade 2	3(7)
Grade 3	3(7)
Alk Phos increased	
Grade 1	3(7)
Grade 2	1(2)
Grade 3	0

Source: Adapted from clinical study report and safety dataset for P1093. Clinical review by Dr. Mark Needles for sNDA 204790/S-08

Renal: One subject from Cohort I had multiple episodes of increased serum creatinine after initiating the study drug (baseline creatinine 0.68 mg/dL). This subject had Grade 1 serum creatinine elevations at Weeks 8, 12, and 24. The serum creatinine values were between 1.01 – 1.03 mg/dL (reference range upper limit 0.9 mg/dL). No associated proteinuria, hematuria, or abnormal urine albumin/creatinine ratio were noted and the events were not considered to be related to DTG treatment. This subject continued the study drug throughout and a normal creatinine level was noted at Week 48.

The mean and median serum creatinine levels are summarized in Table 9 by Cohort and Visit. Changes in the mean serum creatinine at Weeks 4, 24, and 48 compared to the mean baseline are also listed. Overtime, small non-progressive changes in serum creatinine were observed for Cohorts I and IIA. These changes were likely due to decreased tubular secretion of creatinine because the median urine albumin/creatinine ratios from Cohorts I and IIA remained stable over time. No subjects developed macroalbuminuria (ratio >300 µg/mg). Small non-progressive changes in serum creatinine were also observed in adults during the Phase 3 trials for DTG.

Table 9 Change in Serum Creatinine (mg/dL) Compared to Baseline

Cohort	Timepoint	N	Mean	Median	Min	Max
Cohort I	Baseline	23	0.58	0.58	0.40	0.90
	Week 4	22	0.65	0.60	0.40	0.95
	Change from Baseline		+0.07	+0.09	-0.10	+0.27
	Week 24	23	0.73	0.70	0.51	1.03
	Change from Baseline		+0.15	+0.16	-0.07	+0.35
	Week 48	22	0.68	0.69	0.46	1.00
	Change from Baseline		+0.12	+0.10	-0.10	+0.40
Cohort IIA	Baseline	21	0.42	0.44	0.17	0.78
	Week 4	20	0.49	0.51	0.21	0.70
	Change from Baseline		+0.06	+0.05	-0.26	+0.29
	Week 24	19	0.52	0.50	0.24	0.75
	Change from Baseline		+0.11	+0.10	-0.02	+0.27
	Week 48	14	0.53	0.52	0.41	0.72
	Change from Baseline		+0.09	+0.09	-0.03	+0.24
Cohorts I and IIA	Baseline	44	0.51	0.50	0.17	0.90
	Week 4	42	0.50	0.58	0.21	0.95
	Change from Baseline		+0.07	+0.08	-0.26	+0.35
	Week 24	42	0.63	0.63	0.24	1.03
	Change from Baseline		+0.13	+0.13	-0.07	+0.35
	Week 48	36	0.62	0.6	0.41	1.00
	Change from Baseline		+0.11	+0.10	-0.10	+0.40

Source: Adapted from clinical study report and safety dataset for P1093. Clinical review by Dr. Mark Needles for sNDA 204790/S-08

Other selected laboratory toxicities are summarized below in Table 10. Few Grade 3 or 4 toxicities were reported. For example, 2 subjects experienced ≥ Grade 3 or 4 neutropenia, where one event was considered SAE. A 12-year-old female enrolled into Cohort I had Grade 4 neutropenia on days 673, 755, and 1014 with one event (low WBC) being considered serious. No changes were made to the study drug and the decreased ANC and WBC were not considered related to the study drug as this subject had abnormal (Grade 1) baseline values. This subject was also taking trimethoprim/sulfamethoxazole and then dapsone which may have contributed to these events. A 16-year-old male subject enrolled into Cohort I experienced Grade 3 elevated lipase at day 344 (261 IU/L) and day 347 (268 IU/L). The subject was otherwise asymptomatic with no reports of clinical adverse events related to pancreatitis (i.e., abdominal pain, nausea, vomiting, etc). The study drug was temporarily held for 4 days and the event was considered not related to DTG treatment. Subsequent lipase level noted resolution of the event.

Table 10 Other Selected Laboratory Events by Worst Grade Toxicities

Laboratory toxicities, n(%)	Cohort 1 and II N=46
Hypoglycemia	
Grade 1	12 (26)
Grade 2	6 (13)
Neutrophils decreased	
Grade 1	5 (11)
Grade 2	3(7)
Grade 3	1(2)
Grade 4	1(2)
Hemoglobin decreased	
Grade 1	5 (11)
Grade 2	1(2)
Lipase increased	
Grade 1	2 (4)
Grade 2	0
Grade 3	1(2)
WBC decreased	0
Grade 1	0
Grade 2	1(2)
Grade 3	1(2)

Source: Adapted from clinical study report and safety dataset for P1093. Clinical review by Dr. Mark Needles for sNDA 204790/S-08

ARROW

As only Grade 3 or 4 events were collected, Table 11 is limited to selected laboratory parameters with Grade 3 or 4 toxicities. Overall the rate of Grade 3 or 4 laboratory abnormalities were low and 2% or less, with the exception of Grade 3 decrease in neutrophils. Please refer to clinical review for NDA 20977/S-027 for further details.

Table 11 ARROW Study Grade 3 and 4 Laboratory Abnormalities

Parameter and Toxicity Grade	QD Epzicom for any portion of study period n=101	QD ABC+3TC as single entities exclusively N=235	BID ABC +3TC as single entities n=333
Hemoglobin Decreased			
Grade 3	2 (2%)	3 (1%)	8 (2%)
Grade 4	2 (2%)	2 (1%)	3 (1%)
Neutrophils Decreased			
Grade 3	11 (11%)	9 (4%)	15 (5%)
Grade 4	2 (2%)	1 (<1%)	0 (0%)
Platelets Decreased			
Grade 3	3 (3%)	5 (2%)	4 (1%)
Grade 4	4 (4%)	3 (1%)	4 (1%)
AST Elevated			
Grade 3	1 (1%)	2 (1%)	5 (2%)
Grade 4	0	6 (3%)	2 (1%)
ALT Elevated			
Grade 3	2 (2%)	3 (1%)	7 (2%)
Grade 4	0	4 (2%)	4 (1%)

Source: Clinical Review by Dr. Prabha Viswanathan for NDA 21652/S-019

9. Advisory Committee Meeting

Not applicable.

10. Other Relevant Regulatory Issues

Hepatotoxicity

The Prescribing Information for DTG describes the observed increase in serum liver biochemistries in patients with co-infection with Hepatitis B or C during the registrational Phase 3 clinical trials. The Division of Antiviral Products (DAVP) consulted the Division of Pharmacovigilance (DVP) in the Office of Safety and Epidemiology (OSE) to review the postmarketing data to determine if there are cases of hepatotoxicity independent of hypersensitivity reaction or hepatitis B or C co-infection. Review of FDA Adverse Event Reporting System (FAERS) database and the published medical literature identified cases of hepatotoxicity, including a case of hepatic failure leading to liver transplant associated with use of DTG-containing regimens. DAVP, in consultation with OSE recommended that all DTG-containing labels be revised so that the Warnings and Precautions section reflects hepatotoxicity in patients without Hepatitis B or C co-infection. Therefore, Prescribing Information language for

Triumeq, under Warnings and Precautions, should be updated to reflect risk of hepatotoxicity in association with use of both DTG-containing regimen.

Anxiety

During the postmarketing review for Triumeq, in accordance with the requirement under section 505(r) [section 915 of FDAAA], anxiety was identified as an ADR associated with use of DTG-containing regimens. The Prescribing Information for all DTG-containing labels, including Triumeq, will therefore be updated to include anxiety as ADR.

11. Labeling

Labeling negotiation with the Applicant is currently ongoing for the safety-related labeling changes. Agreement has been reached for the pediatric-related labeling language.

Pediatric-related Labeling

Overall, the proposed language is generally acceptable. However, some revisions (new language **in red;** removed language ~~strikethrough~~) have been proposed by the review team. The major revisions are summarized below:

- Update the 'Indication' section to state the population: TRIUMEQ is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 40kg.
- Update the 'Dosage and Administration' section 2.2 to indicate the dosing recommendation is based on weight, not age and weight: TRIUMEQ is a fixed-dose combination product containing 600 mg of abacavir, 50 mg of dolutegravir, and 300 mg of lamivudine. The recommended dosage regimen of TRIUMEQ in adults and pediatric patients ~~aged at least 12 years and~~ weighing at least 40 kg is one tablet once daily orally with or without food.
- Update Table 7 to reflect dosing recommendation based on weight only.
- Update 'Clinical Trials' section 14.2.

Other Labeling Changes

- **1. Indication,** Limitations of Use
  The following statement has been removed because it is not a true limitation of use but is otherwise already covered in section 12.
  ~~Triumeq alone is not recommended for use in patients with current or past history of resistance to any components of TRIUMEQ *[see Microbiology (12.4)]*~~
- **5. Warnings and Precautions**
  Section 5.3 was updated to describe cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, acute liver failure and liver transplant that were reported with use of dolutegravir-containing regimen in patients without pre-existing hepatic disease or other identifiable risk factors. Please refer to reviews under NDA 204790 (S-14) and NDA 210192 for additional details.

'Posttreatment Exacerbations of 'Hepatitis' and 'Emergence of Lamivudine-Resistant HBV' were moved to a new subheading under Warnings and Precautions:

5.4 Patients with Hepatitis B Co-infection

- **6.2 Post-marketing Experience**
  During the 915 review for Triumeq, anxiety was identified as an adverse reaction associated with DTG. 'Anxiety' has been included in Triumeq and all DTG-containing products.

  Psychiatric
  Anxiety

12. Outstanding Issues

None.

13. Recommendations/Risk Benefit Assessment

Recommendation

We recommend approval of this supplemental NDA to expanding the population to include pediatric patients weighing at least 40kg. Our recommendation is based review of the totality of the information available, including use of DTG once-daily in pediatric patients weighing at least 30kg, as well as ABC/3TC administered once-daily in patients weighing at least 25kg.

Benefits/Risks

Triumeq contains two NRTIs (ABC/3TC) which have well established safety and efficacy profile both from clinical trials and from post marketing use, as described in NDAs 20977 and 20978 for ABC, 20564 and 20596 for 3TC and 21652 for Epzicom. 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 ABC/DTG/3TC fixed dose combination drug product for the treatment of HIV-1 infection.

Trial P1093 provided PK and antiviral activity (efficacy) of DTG 50 mg once daily in combination with NRTIs in pediatric subjects. The DTG exposures observed in pediatric patients weighing at least 40kg was similar to the observed exposures in adult patients receiving 50mg QD. Virologic response, defined as the proportion of subjects with HIV RNA < 50 copies/mL, was 70% and 61% at Week 24 and 48, respectively among subjects in Cohort I and 63% at Week 48 among subject weighing at least 40kg. The efficacy outcome further improved when the sample size was increased to include additional subjects from Cohort IIA who weighed at least 40kg. At week 48, 16/24 (67%) of subjects weighing at least 40kg achieved HIV RNA <50 copies/mL. This virologic outcome is comparable to the outcome observed in treatment-experienced (INSTI-naïve) adults (i.e. 71%).

ARROW trial provided robust clinical efficacy data demonstrating that the once daily ABC/3TC dosing regimen was not inferior to the approved twice daily dosing regimen. At Week 48, the proportion of subjects with HIV RNA <80 copies/mL were 73% and 69% for the twice- and once-

daily dosing arms, respectively, with treatment difference and 95% CI of -3.3% (-10% to +4%).

The primary safety concerns with DTG, as previously described under NDA 204790, include risk for hypersensitivity reactions including rash and elevation in liver chemistries, as described under Warnings and Precautions for DTG and Triumeq. Hepatotoxicity is also described with use of DTG-containing regimen. Other ADRs identified with use of DTG include several neuropsychiatric events such as insomnia, dizziness, depression and headache, as described in Section 6 of the label. 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).

ABC and 3TC, administered twice daily have been part of the standard of care in pediatric HIV treatment for many years. The primary safety concerns with use of ABC include hypersensitivity reaction, and myocardial infarction (MI). These risks are clearly outlined in all ABC-containing regimens. Risk of hypersensitivity is dramatically decreased by use of HLA screening prior to initiation of ABC. Risk of MI was described after a prospective observational epidemiological study while the pooled clinical trials did not demonstrate increased risk for MI. While the data are insufficient to make definitive conclusion, MI in general is not considered a likely risk for pediatric population. The safety concerns for the once-daily ABC/3TC were related to possibly increased toxicities due to higher peak concentrations or lower overall exposure due to wider dosing interval. Results from the ARROW study did not support these concerns, as evident by similar adverse events reporting and supportive pharmacokinetic data.

The availability of a FDC drug product containing ABC/DTG/3TC allows for 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.

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

None

14. Clinical Investigator Financial Disclosure Review

Reference is made to the original NDA review for dolutegravir (NDA 204790) and to the

supplemental NDA review for once daily dosing regimen in pediatric (NDA 21652/S-019). The financial disclosures for investigators were reviewed for the relevant trials. As no new clinical trial data were submitted for the current application, no new financial disclosure review is necessary. Please refer to the aforementioned NDA reviews for details.

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/s/

YODIT BELEW
11/06/2017

KIMBERLY A STRUBLE
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