CLINICAL REVIEW AND SUMMARY CDTL

Application Type	Original NDA and Supplemental NDA
Application Number(s)	NDA 213983 and NDA 204790/S-025
Priority or Standard	Priority
Submit Date(s)	December 12, 2019
Received Date(s)	December 12, 2019
PDUFA Goal Date	June 12, 2020
Division/Office	Division of Antivirals/Office of Infectious Diseases
Reviewer Name(s)	Gillian Taormina, DO – Primary Reviewer Peter Miele, MD – Cross-Discipline Team Leader (CDTL)
Review Completion Date	May 28, 2020
Established/Proper Name	Dolutegravir
(Proposed) Trade Name	TIVICAY® – film-coated tablets (FCT) TIVICAY PD – dispersible tablets (DT) for oral (b) (4)
Applicant	ViiV Healthcare Company
Dosage Form(s)	10-mg, 25-mg and 50-mg film-coated tablets (FCT); 5-mg dispersible tablets (DT) for oral suspension
Applicant Proposed Dosing Regimen(s)	Dose differs by weight band and formulation; see review and label for full details
Applicant Proposed Indication(s)/Population(s)	Treatment-naïve or treatment-experienced integrase strand transfer (INSTI)-naïve pediatric patients aged 4 weeks and older and weighing at least 3kg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	As proposed

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Glossary

AC	advisory committee
AE	adverse event
AESI	adverse event of special interest
AIDS	Acquired Immunodeficiency Syndrome
AR	adverse reaction
ARV	antiretroviral
ART	antiretroviral therapy
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DAIDS	Division of AIDS
DMC	data monitoring committee
DMEPA	Division of Medical Error Prevention and Analysis
ECG	electrocardiogram
eCTD	electronic common technical document
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GI	gastrointestinal
GRMP	good review management practice
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonization
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IND	Investigational New Drug Application
INSTI	integrase strand transfer inhibitor

IRIS	Immune Reconstitution Inflammatory Syndrome
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NME	new molecular entity
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OBT	optimized background therapy
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PENTA	Paediatric European Network for Treatment of AIDS
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Dolutegravir (TIVICAY®) is an HIV integrase strand transfer inhibitor (INSTI) that inhibits the catalytic activity of HIV integrase, an enzyme required for HIV-1 replication and integration into the host genome. Dolutegravir is currently approved in the U.S. for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 30 kg. The approved dose for treatment-naïve or treatment-experienced, INSTI-naïve adults and pediatric patients weighing ≥40 kg is 50 mg once daily. The approved dose for treatment-naïve or treatment-experienced INSTI-naïve pediatric patients weighing 30 kg to <40 kg is 35 mg once daily. Twice daily dosing is recommended in adults when co-administered with certain UGT1A/CYP3A inducers or in adults who are INSTI-experienced with suspected INSTI resistance. All currently approved dolutegravir dosing regimens use the marketed 10-mg, 25-mg or 50-mg film-coated tablet (FCT).

New Drug Application (NDA) 213983 proposes a new dosage form of dolutegravir as a 5-mg dispersible tablet (DT) for oral suspension for use in pediatric patients who are at least 4 weeks of age and weighing at least 3 kg. The proposed proprietary name for the new dispersible tablet is TIVICAY PD.

A new supplement (S-025) to NDA 204790 for TIVICAY proposes new dosing recommendations for the FCT in pediatric patients weighing 14 kg to <30 kg, and revised dosing recommendations for pediatric patients weighing 30 to <40 kg.

Dosing in pediatric patients is by weight. The DT and FCT formulations differ in bioavailability, so the proposed dose for each pediatric weight band differs by formulation. Table 1 provides a summary of the currently approved FCT doses and the new doses and formulations proposed for approval in pediatric patients who are least 4 weeks of age and weigh at least 3 kg.

Table 1: Approved and Proposed Dolutegravir Doses in Pediatric Patients

Weight band	Approved Doses for FCT (10-mg, 25-mg, 50-mg FCT)	Proposed Doses for DT (5-mg DT)	Proposed New Doses for FCT (10-mg, 50-mg FCT)
3 kg to <6 kg	N/A	5 mg once daily	N/A
6 kg to <10 kg	N/A	15 mg once daily	N/A
10 kg to <14 kg	N/A	20 mg once daily	N/A
14 kg to <20 kg	N/A	25 mg once daily	40 mg once daily
20 kg to <30 kg	N/A	30 mg once daily	50 mg once daily
30 to <40 kg	35 mg once daily		
≥40 kg	50 mg once daily		

Source: Reviewer-generated. Abbreviations: DT = dispersible tablet; FCT = film-coated tablet

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy of dolutegravir for a pediatric indication was based on demonstration of comparable pharmacokinetics (PK) between pediatric subjects receiving the proposed doses and formulations and adults treated with the approved 50 mg dose of dolutegravir once or twice daily in Phase 2 and 3 clinical trials. In the current submission, PK data from two pediatric trials demonstrated that the proposed doses provided comparable drug exposures to those demonstrated to be efficacious in the adult trials, as determined by PK parameters AUC_{0-24h} and C_{24h}. Importantly, the proposed doses achieved their adult PK targets in all pediatric weight bands, thereby supporting the extrapolation of adult efficacy to support approval. Virologic outcomes observed at Weeks 24 and 48 in the main pediatric trial (Study P1093) were acceptable and consistent with efficacy observed in clinical trials of treatment-experienced adults. Virologic failures observed in this pediatric trial were mainly associated with treatment noncompliance. In conclusion, the Applicant has provided substantial evidence of effectiveness, through matching adult PK targets, to support approval of dolutegravir in the pediatric populations of interest for the proposed indication.

Benefit-Risk Integrated Assessment

HIV-1 infection is a serious and life-threatening condition, for which there is no cure. The World Health Organization (WHO) estimates that 1.8 million children less than 14 years were living with HIV-1 infection globally as of 2017. In the U.S. and dependent areas, there were 2,238 children less than 13 years old living with HIV-1 as of 2016, per the Centers for Disease Control and Prevention (CDC). Early treatment with antiretroviral (ARV) drug therapy is recommended in all HIV-infected pediatric patients to support growth and immune function and reduce the risk of morbidity and mortality. There is a continued need for new ARV products, particularly for pediatric populations, that are safe and effective and can offer more convenient dosing, better tolerance, and higher barrier of drug resistance over existing therapies. Integrase strand transfer inhibitors (INSTIs), such as dolutegravir, have been effective and well tolerated as ARV therapy in HIV-infected adults, and dolutegravir is recommended as a first-line agent in adults by the Department of Health and Human Services (DHHS). Currently, dolutegravir is approved for pediatric patients weighing at least 30 kg. Given its safety profile, once-daily dosing, and high barrier of genetic resistance, expanding the dolutegravir indication to include younger children weighing less than 30 kg would be of great potential benefit to these patients.

This application proposes to expand the dolutegravir (TIVICAY®) indication to include pediatric patients who are at least 4 weeks of age, weigh at least 3 kg, and are INSTI-naive. A new dispersible tablet (DT) formulation for oral suspension (TIVICAY PD) has been developed for use in these patients, and dosing recommendations for the currently approved film-coated tablet (FCT) have been revised for patients weighing at least 14 kg. Data to support the approval were derived from an ongoing phase I/II multicenter, open label trial (Study P1093) designed to evaluate the pharmacokinetics (PK), safety, tolerability and antiviral activity of dolutegravir as part of a combination ARV regimen in HIV-1 infected infants, children and adolescents. In addition, two PK sub-studies that evaluated the DT and FCT formulations in HIV-1 infected children as part of a randomized, multicenter trial (ODYSSEY) provided further PK support for the proposed doses.

In brief, PK data from the P1093 and ODYSSEY trials demonstrated that the proposed doses provided comparable dolutegravir exposures (i.e., $AUC_{0\text{-}24h}$ and C_{24h}) to those observed to be efficacious in adult clinical trials of TIVICAY. Importantly, the proposed doses achieved their adult PK targets in all pediatric weight bands, thereby supporting extrapolation of adult efficacy to support the approval.

In Study P1093, either the existing FCT or the new DT formulation was used for once-daily dosing depending on the child's age and weight. The safety population consisted of 75 subjects who received the proposed doses and formulations. The majority of pediatric subjects were ARV treatment-experienced. There were 3 deaths in the entire study population, but none were considered related to dolutegravir. Through Week 24, there were no study drug discontinuations due to adverse events. Adverse reactions thought to be possibly related to study drug and that

occurred in more than one subject included immune reconstitution inflammatory syndrome (IRIS) (n=2), decreased hemoglobin (n=2), decreased neutrophil count (n=4) and blood bicarbonate decreased (n=3). Analyses of clinical adverse events and abnormal laboratory findings did not reveal any new safety concerns beyond those currently reported in TIVICAY labeling.

The effectiveness of dolutegravir in Study P1093 was evaluated based on virologic and immunologic outcomes. At Week 24, 62% (36/58) of treated subjects had HIV-1 RNA PCR <50 copies/mL; at Week 48, 69% (29/42) had HIV-1 RNA PCR <50 copies/mL. At Week 24 and Week 48, the median CD4 cell percentage increased by 5.1% and 6.6%, respectively.

In summary, dolutegravir, as part of a combination ARV regimen, demonstrated acceptable effectiveness in pediatric subjects at Weeks 24 and 48 in Study P1093. Safety results were similar to those seen in adult trials. While minor differences in safety and effectiveness were noted between the different pediatric weight bands, interpretation was limited by the small sample sizes in each weight band; these differences, however, did not affect the overall conclusions regarding dolutegravir safety and effectiveness. Importantly, the proposed dolutegravir doses achieved drug exposures in all the pediatric weight bands that matched the identified adult PK targets. Approval of the new dispersible tablet formulation and the proposed dosing recommendations would provide benefit to the HIV-1 infected pediatric population by expanding the armamentarium of safe, effective, and convenient treatment options.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HIV-1 infection is a life-long condition for which there is no cure. • If left untreated, HIV-1 infection can result in severe immune compromise, opportunistic infections, development of certain malignancies, and death. • In pediatric patients, early treatment of HIV-1 infection is associated with better growth, improved virologic control, preserved immune function, and decreased morbidity and mortality.[1]	HIV-1 infection is a serious, life-threatening condition. Early treatment is recommended in all HIV-infected pediatric patients to support growth and immune function and reduce the risk of morbidity and mortality.

[1] https://files.aidsinfo.nih.gov/contentfiles/lvguidelines/PediatricGuidelines.pdf

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The CDC estimates that over 2,000 children < 13 years old were living with HIV in the U.S. as of 2016. Globally, there are 1.8 million children < 14 years old living with HIV as of 2017, per WHO estimates.	
Current Treatment Options	• There are fewer treatment options for HIV-infected children compared to adults (See Table 2) • Current DHHS guidelines recommend 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and another drug, such as nevirapine, raltegravir, or a boosted protease inhibitor, depending on age and weight, as initial ARV regimens in pediatric patients. While these treatment options are safe and effective, their use can be limited by side effects (e.g., hepatotoxicity with nevirapine or gastrointestinal disturbance with raltegravir), drug interactions, tolerability (e.g., lopinavir/ritonavir has poor palatability), or low barrier to resistance (e.g., non-nucleoside reverse transcriptase inhibitors [NNRTIs]). • In addition to treatment-experienced patients, HIV-1 isolates from perinatally infected neonates have been found to harbor resistance mutations.[2] • Drugs in the INSTI class have a higher genetic barrier of resistance, few drug interactions, and a favorable efficacy and safety profile. • Within the INSTI drug class, only raltegravir and dolutegravir are approved for use in pediatric patients, and only raltegravir (usually dosed twice daily) is approved for children weighing less than 30 kg.	Although great advances have been made in HIV treatment and prevention, there is an unmet medical need for novel treatment options that are safe, effective, and convenient, particularly in pediatric patients for which there are fewer treatment options compared with adults. New drugs for treatment of HIV-1 infection in pediatric patients should provide potent and durable antiviral activity, be safe and well tolerated, provide easier dosing options with less pill burden, and have a high barrier to genetic resistance. New antiretroviral drugs that can be administered once daily and have an acceptable palatability profile may help improve adherence to HIV treatment regimens among pediatric patients.

[2] Karchava M, Pulver W, Smith L, et al. Prevalence of drug resistance mutations and non-subtype B strains among HIV-infected infants from New York state. J Acquir Immune Defic Syndr. 2006;42(5):614-61N9.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• High pill burden or need for frequent dosing may lead to poor drug adherence.	
Benefit	• Clinical trial data with oral dolutegravir, dosed once daily by weight, demonstrated good tolerance and adherence in pediatric subjects aged 4 weeks to 18 years. • The new dolutegravir dispersible tablet (DT) formulation was well tolerated in children aged 4 weeks to 5 years and resulted in comparable safety and effectiveness as the currently approved film-coated tablet, with drug exposures that matched those seen in adult efficacy trials. • In Study P1093, 62% of pediatric subjects achieved viral load suppression (HIV-1 RNA <50 copies/mL) at Week 24, whereas 69% were virologically suppressed at Week 48. • At Week 24, the median absolute CD4 count and CD4 percentage were increased by 105 cells/mm^3 and 5.1%, respectively; at Week 48, these were increased by 141 cells/mm^3 and 6.6%, respectively. • All evaluable treatment failures (n=11) occurred in the context of nonadherence; three of these subjects developed known integrase resistance-associated substitutions.	• The new dolutegravir dispersible tablet allows for easier dosing in younger children and demonstrated good tolerance and adherence. • The antiviral activity of dolutegravir in pediatric patients was potent and durable; rates of HIV suppression at Weeks 24 and 48 were comparable to those observed in treatment-experienced adults. • Low levels of emergent drug resistance were observed with dolutegravir in pediatric patients.
Risk and Risk Management	• The safety profile of dolutegravir in pediatric subjects was similar to that in adults based on review of clinical safety data in 75 pediatric subjects who received the proposed doses in Study P1093. • Three deaths occurred in Study P1093 due to reasons unlikely to be related to study drug (gastroenteritis, drowning, and unknown cause). • Serious adverse events were limited to immune reconstitution	No new safety signals were noted in the pediatric trials of dolutegravir. The safety profile in pediatrics is similar to that in adults. The identified safety risks can be managed through labeling and routine clinical monitoring. HIV care providers should

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	inflammatory syndrome (IRIS) and pediatric infections that are common in the regions where the trials were conducted. • No adverse events led to study drug discontinuation. • Adverse drug reactions that occurred in more than one subject were IRIS (n=2), decreased hemoglobin (n=2), decreased neutrophil count (n=4) and blood bicarbonate decreased (n=3). • The two oral tablet formulations are not bioequivalent, and therefore not substitutable on a milligram-to-milligram basis. These differences may lead to medication errors, which was reported in three subjects in Study P1093. • The new dispersible tablets can be easily dissolved in drinking water for administration as an oral solution or may be swallowed whole.	regularly monitor for adverse events, perform laboratory testing if indicated, and ensure adherence to the correct dose and dosage formulation. To avoid confusion between the two oral dosage forms, a new proprietary name (TIVICAY PD) is recommended for approval for the new DT formulation. In addition, a new warning is proposed for inclusion in the Prescribing Information (PI) to alert providers that the two formulations are not bioequivalent and not substitutable on a milligram-per-milligram basis. The Applicant intends to conduct outreach and educational campaigns for prescribers and pharmacists to mitigate the potential risk of medication error. A new Instructions for Use (IFU) and revised Patient Package Insert (PPI) are recommended for approval to ensure proper administration of the new DT formulation. The IFU and a measuring cup and syringe will be provided every time drug product is dispensed. Caregivers will be instructed to administer one DT at a time if the child prefers to swallow the tablets whole to reduce the risk of choking.

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☒	Clinician reported outcome (ClinRO)	Efficacy and Safety; See Sections 7 and 8
		☐	Performance outcome (PerfO)	
	☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		Human Factors study; See Section 4.3
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☒	Observational survey studies designed to capture patient experience data		Adherence questionnaires and palatability study; see Section 6.1.2
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The human immunodeficiency virus 1 (HIV-1) invades and destroys CD4 cells, leading to immune compromise, difficulty fighting certain infections and increased risk of other morbidities, such as certain cancers. The most advanced stage of HIV infection is the acquired immunodeficiency syndrome (AIDS), which is diagnosed when the CD4 count is <200 cells/mm^3, the CD4 percentage is less than 14% of total lymphocytes, or the patient develops an AIDS-defining opportunistic infection. According to the World Health Organization (WHO), an estimated 37.9 million people are living with HIV globally as of 2018.[3] As of 2017, they estimate that 1.8 million of these people are children less than 14 years old.[4] In the US, there are approximately 1.14 million people living with HIV as of the end of 2016.[5] According to the U.S. Centers for Disease Control and Prevention (CDC), there were 2,238 children less than 13 years old living with HIV in the U.S. and dependent areas as of the end of 2016, and 99 new HIV-1 infections were diagnosed in this age group in 2017.[6]

The goal of HIV treatment is to suppress HIV viral load, restore immune function, and reduce HIV-associated morbidity and mortality. Recent developments in antiretroviral therapy (ART) have provided HIV-infected patients with improved long-term survival. Effectively suppressing HIV replication also has the public health benefit of decreasing HIV transmission. Treatment regimens for HIV-1 infection are generally comprised of a combination of least 3 antiretroviral (ARV) medications, two of which typically belong to the nucleoside/nucleotide reverse transcriptase (NRTI) class. The third agent is selected from one of the following drug classes: non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), or integrase strand transfer inhibitors (INSTI).

Despite the great progress made since ART was first introduced in the 1990s, due to the ongoing worldwide HIV epidemic, there is a continued need for new ARV products, including fixed-dose combination products and new dosing regimens. More options are needed to individually tailor ART regimens to overcome limitations associated with existing therapies, such as poor tolerance due to unfavorable side effects, development of drug resistance, drug interactions, or difficulty adhering to multiple-drug regimens with high pill burdens. In pediatric

[3] https://www.who.int/hiv/data/en/; accessed January 9, 2020
[4] https://www.who.int/data/maternal-newborn-child-adolescent/indicator-explorer-new/mca/number-of-0-14-year-olds-living-with-hiv#indicators-display; accessed January 9, 2020
[5] https://www.cdc.gov/hiv/statistics/overview/ataglance.html; accessed January 9, 2020
[6] https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-2017-vol-29.pdf; accessed January 9, 2020

patients, formulation issues such as palatability and ease of administration are also of critical importance, as young children often cannot take pills. The current treatment options for HIV-1 infection are summarized in Table 2, including products with an FDA approved pediatric indication.

2.2. Analysis of Current Treatment Options

Table 2 summarizes the currently approved treatment options for HIV-1 infection by drug class.

Table 2: Treatment Armamentarium for HIV-1 Infection as of April 2020

Drug Class	Generic Name	Trade Name	Pediatric Approval
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Abacavir (ABC)	Ziagen®	≥ 14 kg, ≥ 3 months
	Didanosine (ddI)	Videx®	≥ 2 weeks *
	Emtricitabine (FTC)	Emtriva®	Birth
	Lamivudine (3TC)	Epivir®	≥ 14 kg, ≥ 3 months
	Stavudine (d4T)	Zerit®	Birth *
	Tenofovir alafenamide (TAF)	See fixed-dose combinations	
	Tenofovir disoproxil fumarate (TDF)	Viread®	≥ 10kg, ≥ 2 years
	Zidovudine (ZDV)	Retrovir®	Birth
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz (EFV)	Sustiva®	≥ 3.5kg, ≥ 3 months
	Etravirine (ETR)	Intelence®	≥ 10kg, ≥ 2 years
	Nevirapine (NVP)	Viramune®	≥ 15 days
	Rilpivirine (RPV)	Edurant®	≥ 35kg, ≥ 12 years
	Doravirine (DOR)	Pifeltro®	
Protease Inhibitors (PIs)	Darunavir (DRV)	Prezista®	≥ 10kg, ≥ 3 years
	Fosamprenavir (FPV)	Lexiva®	≥ 4 weeks*
	Indinavir (IDV)	Crixivan®	N/A*
	Lopinavir (LPV)	See fixed-dose combinations	
	Nelfinavir (NFV)	Viracept®	≥ 10kg, ≥ 2 years*
	Saquinavir (SQV)	Invirase®	≥ 16 years*
	Tipranavir (TPV)	Aptivus®	≥ 2 years*
	Atazanavir (ATV)	Reyataz®	≥ 5kg, ≥ 3 months
Fusion/Entry Inhibitors	Enfuvirtide (T-20)	Fuzeon®	≥ 11kg*
	Ibalizumab	Trogarzo®	
CCR5 receptor antagonist	Maraviroc (MVC)	Selzentry®	≥ 10kg, ≥ 2 years
Integrase Inhibitor	Dolutegravir (DTG)	Tivicay®	≥ 30kg
	Elvitegravir (EVG)	Vitekta®	
	Raltegravir (RAL)	Isentress®	≥ 2kg
	Bictegravir (BIC)	See fixed-dose combinations	

Drug Class	Generic Name	Trade Name	Pediatric Approval
Pharmacokinetic Enhancers	Ritonavir (RTV)	Norvir®	≥ post-menstrual age (PMA) 44 weeks
	Cobicistat (COBI)	Tybost®	≥ 35kg
Fixed-Dose Combinations	ABC and 3TC	Epzicom®	≥ 25kg
	Lopinavir/Ritonavir (LPV/RTV)	Kaletra®	≥ 14 days, ≥ PMA 42 weeks
	ABC, 3TC, and ZDV	Trizivir®	≥ 40kg
	ABC, 3TC, and DTG	Triumeq®	≥ 40kg
	EVG, COBI, FTC, and TAF	Genvoya®	≥ 25kg
	EVG, COBI, FTC, and TDF	Stribild®	≥ 35kg, ≥ 12 years
	FTC and TAF	Descovy®	≥ 25kg**
	FTC, RPV, and TAF	Odefsey®	≥ 35kg
	FTC, RPV, and TDF	Complera®	≥ 35kg
	FTC and TDF	Truvada®	≥ 17kg
	EFV, FTC, and TDF	Atripla®	≥ 40kg
	3TC and ZDV	Combivir®	≥ 30kg
	3TC and TDF	Temixys®	≥ 35kg
	3TC and RAL	Dutrebis®	
	ATV and COBI	Evotaz®	
	DRV and COBI	Prezcobix®	
	DTG and 3TC	Dovato®	
	DTG and RPV	Juluca®	
	BIC, FTC and TAF	Biktarvy®	≥ 25kg
	3TC and TDF	Cimduo®	≥ 35kg
	DOR, 3TC and TDF	Delstrigo®	
	EFV, 3TC and TDF	Symfi®; Symfi Lo®	≥ 40kg; ≥ 35kg
	DRV, COBI, FTC, and TAF	Symtuza®	≥ 40kg

Source: Adapted from Table 2.2-1 in sNDA 204790 S-008 by M. Needles, MD; updated based on review of current drug labels
*No longer recommended by DHHS Pediatric HIV Guidelines Panel[7]
**No dosing available for <35 kg when co-administered with an HIV-1 protease inhibitor with ritonavir or cobicistat

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

[7] https://files.aidsinfo.nih.gov/contentfiles/lvguidelines/PediatricGuidelines.pdf; accessed April 15, 2020

Dolutegravir is currently approved for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 30 kg. The original NDA was approved on August 12, 2013 for treatment of adult patients.

The first pediatric supplement (S-008) was submitted in December 2015 to partially fulfill postmarketing requirement (PMR) 2078-1, issued under the Pediatric Research Equity Act (PREA), as described in the approval letter of August 12, 2013. The submission was (b) (4) S-008 for pediatric patients weighing 30 to <40 kg (b) (4) . Supplement-008 was approved on June 9, 2016, (b) (4) .

Risk of Neural-Tube Defects

On March 27, 2019, the Applicant submitted a Periodic Benefit Risk Evaluation Report (PBRER) for the reporting period January 17, 2018 to January 16, 2019, which included new safety information from the ongoing Tsepamo Study in Botswana. The Tsepamo Study is a surveillance study initiated in 2014 to confirm the safety of efavirenz exposure at conception, particularly as it pertains to the risk of neural-tube defects; however, the surveillance system captures all ARV exposures, including dolutegravir exposure.[8] In May 2018, an interim review of data from the Tsepamo Study in Botswana showed a higher than expected number of neural-tube defects in infants of mothers who were exposed to dolutegravir at the time of conception. TIVICAY labeling was updated in September 2018 to include a warning about embryo-fetal toxicity and to recommend consideration of alternative treatment during conception and first trimester.

Other Postmarketing Safety Signals

Acute hepatic failure was added to the prescribing information in 2017 as a rare adverse reaction. (b) (4) weight gain, (b) (4) was added to Section 6.2 Postmarketing Experience in 2018. Lastly, updates were added to the prescribing information in 2020 regarding the potential risk of seizure when taking TIVICAY with dalfampridine.

3.2. Summary of Presubmission/Submission Regulatory Activity

[8] Zash, R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. N Engl J Med 2019;381:827-840.

Summary of Pediatric Postmarketing Requirements

- PMR 3091-1: Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected INSTI-naïve pediatric participants weighing less than 15 kg and at least 4 weeks in age
- PMR 3091-2: Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected INSTI-naïve pediatric participants weighing 15 kg to less than 30 kg
- PMR 3091-3: Conduct a trial to evaluate pediatric pharmacokinetics, safety and anti-viral activity of dolutegravir in HIV-1 infected INSTI-naïve pediatric participants less than 12 years of age weighing 30 kg to less than 40 kg. (*NB: This PMR was fulfilled in 2016.*)
- PMR 3091-4: Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected pediatric subjects weighing 20 kg to less than 40 kg who are INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance
- PMR 3091-5: Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity of dolutegravir in HIV-1 infected pediatric subjects ages 12 to less than 18 years and weighing at least 40 kg who are INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance

(b) (4)

(b) (4)

Summary of Regulatory Activities Related to Current Submission

(b) (4) it was agreed that the Applicant would submit separate applications to provide data supporting the use of TIVICAY in pediatric patients weighing less than 30 kg. In April 2019, the decision was made to submit an original NDA for a new 5-mg dispersible tablet (DT) formulation in addition to a supplemental NDA supporting new dosing recommendations in patients <30 kg for the currently approved film-coated tablet (FCT). In September 2019, a Type B pre-sNDA meeting was held to discuss the structure and content of the submissions, including PK data from two trials, P1093 and ODYSSEY, and Week 24 and Week 48 efficacy outcomes from Study P1093.

The current submissions were submitted on December 12, 2019 and seek to fulfill PMR 3091-1 (<15 kg) and PMR 3091-2 (15 to <30 kg), (b) (4) .

3.3. Foreign Regulatory Actions and Marketing History

As of December 2019, TIVICAY is approved in over 100 countries for treatment of adults,[9] and in at least 20 countries for pediatric patients, with multiple marketing applications pending.[10]

Foreign regulatory authorities took similar steps as FDA regarding the risk of neural-tube defects based on reports from the Tsepamo study, as well as regarding hepatoxicity and concern about interactions with dalfampridine (see Section 3.1). (b) (4)

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

- A consult request was submitted to the Office of Study Integrity and Surveillance (OSIS) for biopharmaceutical inspections of two analytical sites, (b) (4) (Study P1093) and (b) (4) (ODYSSEY).
- After inspection of the (b) (4) site, OSIS determined no action was indicated. They did not observe any objectionable conditions and considered the drug concentration data from Study P1093 reliable to support a regulatory decision.
- OSIS was unable to perform an in-person bioequivalence analytical review of the (b) (4) due to the outbreak of the COVID-19 pandemic, but their conclusion, based on review of the site's responses to information requests and the ODYSSEY method validation and bioanalytical reports, was that the analytical data were acceptable.
- Inspections of an analytical site in (b) (4) and a clinical site in Austin, TX were requested in reference to the submitted bioavailability Study 205893. OSIS determined

[9] https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_GB/files/Tivicay_adult_wwrs_03Dec2019-for_external_use.pdf; Accessed January 10, 2020
[10] https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_GB/files/Tivicay_paed_wwrs_03Dec2019-for_external_use.pdf; Accessed January 10, 2020

that inspection was not warranted due to recent inspections at these sites.

For further details, refer to the OSIS reviews by Drs. Stanley Au and Yiyue Zhang. Clinical site inspections were not requested as the basis of approval was the demonstration of matching PK and most clinical sites only enrolled a small number of subjects.

4.2. Product Quality

The film-coated tablet used in the pediatric trials is the same as the currently marketed product. No new chemistry or manufacturing information was submitted for the FCT formulation. The FCT is available as 10-mg, 25-mg and 50-mg tablets.

The new dispersible tablet for oral suspension is a 5-mg, white, round, strawberry cream flavored, film-coated, biconvex tablet. Each bottle of 60 tablets has a child-resistant closure and is packaged with one 30-mL dosing cup and one 10-mL oral dosing syringe with 1-mL gradations. The DT formulation used in the pediatric trials is the same as the product proposed for approval. The DT can be swallowed whole or dispersed in drinking water; the tablet dissolves well in water. The DT is not meant to be chewed, cut or crushed. Refer to the Integrated Product Quality review from the Office of Pharmaceutical Quality (OPQ) under NDA 213983 for full CMC details.

4.3. Clinical Microbiology

The FDA Virology review team identified 11 evaluable virologic failures among the 58 subjects in the Proposed Dose (PD) Efficacy Population of Study P1093. Three of these subjects developed known integrase resistance-associated substitutions (G118R E138T, S147S/G, S153S/A/F/V, R263K). Baseline genotypes were not provided for all subjects, making the total number of existing and developing substitutions difficult to ascertain. The Applicant verified that all subjects were INSTI-naïve.

All 11 failures were reported to be noncompliant with study drug by the Applicant. A PK analysis of the 11 failures showed that 2 subjects had low exposures during intensive PK sampling and 7 had low exposures during sparse PK sampling, consistent with noncompliance. The failures without known integrase resistance-associated substitutions may have also been related to noncompliance, but the precise mechanism of failure in each case is not known.

Refer to the full Clinical Virology review by Dr. Anamaris Colberg-Poley for full details.

4.4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology information was submitted with these applications. Nonclinical studies were submitted with the original NDA 204790 and reviewed for the initial

adult approval. The main preclinical finding was gastrointestinal toxicity. Juvenile toxicity studies were significant for decreased food consumption and decreased body weight in female rats and two deaths in male rats. There were no concerns raised by the carcinogenicity, mutagenicity, reproductive or developmental toxicity studies. Refer to the original Pharmacology/Toxicology review by Dr. Mark Seaton under NDA 204790 for further details.

4.5. Clinical Pharmacology

In order to extrapolate adult efficacy to support a pediatric indication, it is necessary to demonstrate matching drug exposures between adult and pediatric study populations. In the ongoing pediatric trials, the identified PK targets were plasma dolutegravir geometric mean (range) values of 995 (697-2260) ng/mL for C_{24h} (primary PK endpoint) and 46 (37-134) µg*h/mL for AUC_{0-24h} (secondary PK endpoint) based on exposure in adults after 50 mg once daily or twice daily in the Phase 2 and 3 clinical trials. (b) (4) , the exposures observed with the currently proposed doses achieved their adult PK targets for all weight bands, thereby justifying the extrapolation of adult efficacy to support regulatory approval. Data from both Study P1093 and ODYSSEY contributed to this conclusion.

Of note, the Applicant initially proposed (b) (4) for use in children weighing 6 to <10 kg (b) (4) The review team, however, recommended that consideration be given to (b) (4) to simplify dosing recommendations. (b) (4) A 15 mg dose was then considered. As there were no subjects <6 months of age who were exposed to a 15 mg dose in the submitted pediatric trials, exposure-response analyses were conducted by the Applicant and FDA using observed and model-derived exposures to assess the relationship between drug exposures and safety. These analyses did not reveal any concerning relationships between C_{max} or AUC parameters and adverse events or laboratory toxicities. It was further noted that the proposed dosing recommendations for the other weight bands resulted in higher C_{max} levels across weight bands in children <12 years of age compared to historical adult data, yet no new safety signals emerged in the pediatric trials. Lastly, it was noted that the WHO intends to recommend a 15 mg daily dose for this weight band.[11] Given the above, the FDA proposed simplifying the dosing recommendation to 15 mg once daily for all patients weighing 6 to <10 kg (b) (4), which was accepted by the Applicant.

[11] https://www.who.int/hiv/pub/meetingreports/pado3-review/en/index4.html; Accessed May 7, 2020

The proposal to extend the FTC 50 mg dose down to children weighing at least 20 kg was supported by the observation of similar plasma dolutegravir C_{24h} levels among three weight bands (20 -<25 kg, 25-<30 g, and 30-<40 kg) in the ODYSSEY PK sub-studies compared to data in children weighing ≥40 kg in Study P1093 and historical data in adults.

Importantly, a relative bioanalytical study (Study 205983) showed that the DT and FCT formulations are not bioequivalent. Compared with one 25-mg FCT, administration of a 25 mg dose of DT (5 x 5-mg DTs) resulted in geometric mean plasma C_{max} and AUC levels that were 1.5 to 1.8-fold higher. Therefore, the two formulations are not substitutable on a milligram-by-milligram basis. For this reason, the two formulations have different dosing recommendations for each weight band (see Table 1).

For further details, refer to the FDA Clinical Pharmacology Review by Drs. Qin Sun, Ruojing Li, Justin Earp, and Su-Young Choi.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Results of a human factors study were submitted. The study examined the ability of caregivers (n=31) to use the Instructions for Use (IFU) to simulate the preparation and administration of a dose of dolutegravir to children 4 weeks to 12 years of age using the 5-mg DT formulation. All critical tasks were completed with a 94-100% error-free rate. When asked about their experience, 92% gave positive feedback about the clarity and ease of use of the IFU, and 91% gave positive feedback about the supplies (bottle of tablets, dosing cup and syringe). Some parts of the IFU led to comprehension errors, such as the option to swallow the DT whole if the patient preferred, as well as instructions to give a rinse dose if any product remained in the cup/syringe, which were then clarified in the IFU. Review of the study by the Division of Medication Error Prevention and Analysis (DMEPA) did not identify any major concerns with the study design or results.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3 summarizes the two pediatric trials used in this review, which will be referred to as P1093 and ODYSSEY.

Table 3: Efficacy and Safety Trials

Study Name	Study Objectives	Study Design	Treatment Details	Number of Subjects	Centers
P1093 (IMPAACT)	To select a DTG dose for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG once daily adult dose. To determine the safety and tolerability of DTG in HIV-1 infected infants, children, and adolescents at 24 and 48 weeks. To evaluate steady-state PK of DTG in combination with other ARVs that achieves a targeted C24h and AUC0-24h in this population.	Phase I/II, multi-center, open-label, non-comparative intensive PK and safety study	DTG; target dose (~1 mg/kg to ~1.25 mg/kg) up to a maximum dose of 50 mg FCT or 30mg DT, or granules for oral suspension; once daily; 48 weeks	Safety population: 159 subjects PD population by Enrollment Weight Band: 3 to <6 kg: 15 enrolled 6 to <10 kg: 20 enrolled 10 to <14 kg: 10 enrolled 14 to <20 kg: 6 enrolled ≥35 kg: 24 enrolled	Botswana (2 centers) Brazil (5 centers) Kenya (1 center) South Africa (3 centers) Tanzania (1 center) Thailand (3 centers) U.S. (17 centers) Uganda (1 center) Zimbabwe (1 center)
ODYSSEY (PENTA 20)	WB-PK sub-studies; To provide PK data for participants in the first 3 WHO weight bands (Lower WB-PK1, ongoing) To provide PK data with DTG 25 mg FCTs in participants from 14 to <25kg (WB-PK1, Part I, completed) To provide PK data in participants from 14 to <20 kg on DTG administered as DTs and in participants from 20 to <25 kg on DTG	The main study is a Phase I/II, multi- center open-label, randomized (1:1), non-inferiority, 2-arm clinical trial comparing DTG+2NRTIs with SOC. The study has integrated PK sub-studies: WB-PK1 Parts I and II, WB-PK2 and Lower WB- PK1.	WB- PK sub-study dosing; DTG; once daily; dosed according to weight band: 3 to <6kg: one or two 5 mg DT 6 to <10kg: three 5 mg DT 10 to <14kg: four 5 mg DT 14 to <20kg: five 5 mg DT	Safety Population: 99 subjects Enrollment Weight Band 3 to <6 kg: 1 enrolled 6 to <10 kg: 10 enrolled 10 to <14 kg: 5 enrolled 14 to <20 kg: 33 enrolled	PK sub-study centers: South Africa (1 center) Uganda (3 centers) Zimbabwe (1 center)

	administered as DTs or 50 mg FCTs once daily (WB-PK1 Part II, completed) To provide PK data with DTG 50 mg in participants from 25 to <40 kg (WB-PK2, completed) To provide safety data for new dosing		20 to <25: one 50 mg FCT or six 5mg DT 25 to <35: one 50 mg FCT ≥35 kg: one 50 mg FCT	20 to <25 kg: 28 enrolled 25 to <30 kg: 16 enrolled 30 to <40 kg: 6 enrolled	

Source: Reviewer-generated using modules 5.2 and 5.3.5.
Abbreviations: PK = pharmacokinetic; WB = weight band; DTG = dolutegravir; DT = dispersible tablet; FCT = film-coated tablet; SOC = standard of care; NRT = nucleoside reverse transcriptase inhibitor; ARV = antiretroviral; WHO = World Health Organization

5.2. Review Strategy

Gillian Taormina, DO was the primary clinical reviewer and conducted the safety and efficacy analyses. Peter Miele, MD was the secondary clinical reviewer and cross-discipline team leader (CDTL). The primary reviewer for Clinical Virology was Anamaris Colberg-Poley, PhD. The primary reviewer for Clinical Pharmacology was Qin Sun, PhD. The proposed proprietary name, IFU, draft Prescribing Information (PI) and Patient Package Insert (PPI) were reviewed by DMEPA and the Patient Labeling team.

The clinical review was conducted using datasets, study reports, case narratives and other documents as submitted by the Applicant. Data were analyzed using the JMP® statistical software (Version 13).

Study P1093 was the primary trial used for the safety review. This is an ongoing trial, a collaboration between the Applicant and the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), Division of DAIDS (DAIDS), of the National Institutes of Health (NIH).

- Safety in subjects who received the proposed dose (PD safety population) was analyzed through Week 24 as this was the pre-specified primary safety endpoint and represented the larger sample size based on the data cut-off date of April 30, 2019 (95% of subjects had reached Week 24 versus 75% who had reached Week 48); the full Week 48 safety data are expected to be submitted in a future supplement. Study P1093 was not powered for efficacy; however, virologic and immunologic responses at Week 24 and Week 48 were reviewed (see Section 7).

- Initially, efficacy data for Week 24 subjects only plus 1 additional subject at Week 48 (b) (4). Upon review of the submitted datasets, an additional 17 subjects with Week 48 viral load and CD4 data were identified. The Applicant agreed to include the additional subjects in the Week 48 efficacy descriptions.

ODYSSEY is an ongoing, randomized controlled trial to evaluate the efficacy and safety of DTG plus 2 NRTIs versus standard of care in HIV-infected children aged <18 years who are starting first-line ART or switching to second-line ART. The trial is sponsored by the Paediatric European Network for Treatment of AIDS (PENTA) Network and the Medical Research Council. Efficacy data are not available (b) (4). Two PK sub-studies in the ODYSSEY trial were used to provide supportive PK data for the proposed pediatric doses (see Section 4.5). Summary safety data from ODYSSEY were reviewed but the trial was not used for the main analysis of safety because of suboptimal data collection (see Section 8).

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study P1093

6.1.1. Study Design

Overview and Objectives

The primary objectives for P1093 are as follows:

- To select a dose for each formulation of dolutegravir (DTG) for chronic dosing in infants, children and adolescents that achieves similar exposure to the DTG 50 mg once daily adult dose
- To determine the safety and tolerability of DTG in HIV-1 infected infants, children and adolescents at 24 and 48 weeks
- To evaluate the steady state PK of DTG in combination with optimized background therapy (OBT) in treatment-experienced and treatment-naïve HIV-1 infected infants, children and adolescents and to determine the dose of DTG that achieves the targeted C_{24h} (primary PK endpoint) and $AUC_{0\text{-}24h}$ (secondary) PK parameters in this population

The secondary objectives are as follows:

- To evaluate the antiviral activity of DTG in combination with an OBT by measuring virologic response in infants, children and adolescents at 24 and 48 weeks
- To evaluate the effect on immunologic response from baseline to 24 and 48 weeks
- To assess changes in HIV-1 genotype and phenotype to DTG and other components of the OBT in participants experiencing virologic failure

- To determine DTG exposure, its variability and clinical covariates that impact DTG disposition using intensive and sparse sampling and population PK (Pop PK) analysis
- To determine the extended long term (≥ 48 weeks) safety, tolerability and efficacy of DTG in HIV-1 infected infants, children and adolescents
- To explore the relationship between DTG exposure and the antiviral activity
- To evaluate the PK, safety and tolerability profiles of DTG when dosed by weight bands

Trial Design

- *Study design:* Phase I/II multi-center, open-label, noncomparative trial in pediatric populations. Early in the trial, subjects were enrolled based on age (Table 4).

Table 4: Enrollment Cohorts for Study P1093

Cohort	DTG Formulation	Age Range
Cohort I	FCT	≥ 12 to < 18 years
Cohort II	FCT	≥ 6 to < 12 years
Cohort III-DT	DT	≥ 2 to < 6 years
Cohort IV-DT	DT	≥ 6 months to < 2 years
Cohort V-DT	DT	≥ 4 weeks to < 6 months

Reviewer-generated
Abbreviations: DT = dispersible tablet; DTG = dolutegravir; FCT = film-coated tablet

Due to increasing international recommendations for pediatric dosing according to weight, independent of age, enrollment of sufficient participants to analyze by weight was incorporated into the protocol (version 5.0) as shown below:

- 3 to <6 kg
- 6 to <10 kg
- 10 to <14 kg
- 14 to <20 kg

Participants were enrolled first into Stage 1, during which intensive PK samples were collected at steady state. Target enrollment for Stage 1 was 10 evaluable participants for each age cohort, after which exposure and 4-week safety data were reviewed by the protocol team. Within each age cohort participants were dosed by weight. Enrollment into Stage 1 continued until at least 8 evaluable participants were enrolled into each of the WHO-defined weight bands. Stage 2 opened to enrollment if data from Stage 1 were considered acceptable. Target enrollment for Stage 2, during which only sparse PK samples were collected, was 12 participants per cohort. Participants were then to be followed through Week 48 and for another 3 years as part of long-term safety follow-up.

- *Trial locations:* 34 sites in 9 countries in North America, South America, Africa and Asia

- *Diagnostic criteria*: Confirmed HIV-1 infection with age-appropriate tests on two different blood samples at different time points

- *Key inclusion/exclusion criteria*: There was a need to enroll pediatric patients in lower weight bands to collect more data with the new DT dosage form. The goal was to enroll at least 10 subjects each in Cohorts III-DT, IV-DT and V-DT, while also enrolling at least 8 subjects each in the 3-<6 kg, 6-<10 kg, 10-<14 kg and 14-<20 kg weight bands.

    - Inclusion

        - Age ≥ 4 weeks to < 18 years
        - HIV-1 diagnosis with HIV RNA viral load > 1,000 copies/mL at screening
        - ARV treatment-naïve or ARV treatment-experienced (previously treated and off ARV for at least 4 weeks OR on a currently failing regimen) but INSTI-naïve
        - Female participants of reproductive potential must agree to use two methods of contraception

    - Exclusion

        - Weight less than 3 kg
        - History of exposure to integrase inhibitors as treatment, or in utero or breastmilk if mother was taking an integrase inhibitor
        - Known INSTI resistance
        - Use of disallowed medications per study protocol
        - Certain pre-existing Grade 3 laboratory toxicities (neutrophil count, hemoglobin, platelets, AST, ALT, lipase, creatinine, total bilirubin) or a Grade 4 laboratory toxicity
        - Patients with malignancy, pregnancy or breastfeeding, pancreatitis, AIDS-defining opportunistic infection, active tuberculosis or other clinically significant condition judged by the investigator to place participant at unacceptable risk or have potential to compromise study outcome

- *Dose selection:* As this was a dose-finding trial, not all participants received the DTG doses ultimately proposed for licensure. Initial dose ranges were identified for each formulation by weight band and changed as necessary based on interim PK results.

- *Study treatments:* Participants were stratified into cohorts and weight bands. Depending on their weight band and ability to take each oral formulation, subjects were given either granules for suspension ((b) (4)), dispersible tablets or film-coated

tablets. Doses were given once daily unless otherwise indicated based on certain concomitant medications. DTG was to be given as part of an OBT regimen consisting of one ARV with predicted antiviral activity and at least one other ARV. The OBT regimens were approved by the protocol team.

- *Dose modification, dose discontinuation:* Subjects were given the initial selected dose for their weight band. If a subject grew into the next weight band, the dose was adjusted accordingly. In Stage 1, doses within a cohort were adjusted based on PK until an appropriate dose for the cohort was identified. In Stage 2, subjects were continued at that same dose. Subjects receiving DTs were to continue the same formulation through Week 48, after which they could switch to the FCT dosage form if approved by the protocol team. Patients receiving oral granules were switched to DTs.

- *Procedures and schedule:* Through Week 48, study visits were conducted at entry (Day 0), Days 5-10, and Weeks 4, 8, 12, 16, 24, 32, 40 and 48. Each visit consisted of history and physical and laboratory testing; see Section 8.3.3.

- *Treatment compliance:* Adherence questionnaires were administered at every clinic visit. The questionnaire asked about missed doses in the past 72 hours and any barriers to adherence. Drug dosing was directly observed by clinic staff for the intensive PK visit. Increases in viral load prompted further investigation into potential non-adherence.

- *Subject completion, discontinuation, or withdrawal*: Patients could be discontinued from the trial if they were noncompliant (with treatment, study evaluations or study requirements), if they required a disallowed medication, or had virologic failure and did not meet criteria for continuation. Study drug was discontinued in cases of pregnancy, drug toxicities such as liver toxicity, or if continued participation was thought to be detrimental to the participant's well-being. Participants also discontinued if they did not have a feasible OBT.

Study Endpoints

The key efficacy endpoint was virologic outcome through Week 24 and Week 48 based on HIV-1 RNA viral load (<400 copies/mL and <50 copies/mL) using the FDA snapshot algorithm. Safety through Week 24 was a primary endpoint; safety through Week 48 and beyond was a secondary endpoint. Assessment of safety included all adverse events (AEs), laboratory toxicities of ≥ Grade 3 severity, and any AEs or ≥ Grade 3 laboratory toxicities, discontinuations or deaths thought to be possibly related to study drug. Primary and secondary PK endpoints were C_{24h} and $AUC_{0\text{-}24h}$, respectively. Other secondary endpoints were CD4 and CD8 count/percent, genotypic and phenotypic measures of resistance, and disease progression.

Statistical Analysis Plan

A sample size of 10 subjects per age cohort was considered adequate based on power calculations. Dose selection was based on descriptive statistics of safety and PK by age cohort and weight band.

The safety population included all participants who had taken at least 1 dose of dolutegravir, but did not include Stage 1 participants who required dose adjustments for inadequate PK. The All Treated (AT) population included all participants who had taken at least 1 dose of dolutegravir. The final dose population included all participants who received the final selected dose for their cohort throughout the study. The Proposed Dose (PD) population included all subjects who received the doses proposed for approval and labeling.

Reviewer comment: The submitted clinical study report for P1093 primarily reported safety findings in the AT population. As noted in Section 5.2, this clinical reviewer conducted safety analyses on the PD population as these represented the doses proposed for marketing. The study report indicates that safety results between the AT and PD populations were similar.

The highest grade reported for a given event during the first 24 weeks of exposure to optimal dose was used for the analysis of AEs. The frequencies of AEs and laboratory toxicities were reported by cohort. HIV-1 RNA viral load and CD4/8 counts at Week 24 and Week 48 were collected and virologic outcome was calculated according to the FDA snapshot algorithm. Incidence of drug resistance was presented descriptively at baseline and at virologic failure.

Protocol Amendments

The protocol for Study P1093 is currently in its 5th version. Major changes included the addition of more age cohorts, changes in formulation to exclude oral granules in favor of the DT and FCT forms, dose analysis by WHO weight bands, change of primary PK endpoint to C_{24h}, revision of PK targets, and updated toxicity management guidelines.

6.1.2. Study Results

Compliance with Good Clinical Practices

The clinical study report provides attestation that the trial was conducted in accordance with good clinical practices.

Financial Disclosure

There were no investigators with disclosable financial interests or arrangements (see Section 13.2). There were 18 investigators from 11 sites for whom information could not be obtained.

Reviewer comment: The latter did not impact the review conclusions given the standardized method of collecting safety information and the objective PK and virologic endpoints.

Patient Disposition

The AT population consisted of participants who took at least 1 dose of DTG, which includes any dose or formulation (FCT, DT, or granules). The PD population consisted of participants who received the currently proposed dose for their weight band with either the FCT or 5-mg DT. Efficacy analyses included participants who completed Week 24 or Week 48 by the efficacy cut-off date (February 14, 2019) and safety analyses included participants who completed Week 24 through the safety cut-off date (April 30, 2019).

Table 5: Study Subject Populations (P1093)

Population	Total (N)
AT Population	159
AT Safety Population	159
AT Efficacy Population	142
PD Population	75
PD Safety Population	75
PD Efficacy Population	58
Intensive PK Population	114
Sparse PK Population	146

Source: Adapted from Table 10 in P1093 Clinical Study Report, Module 5.3.5.2
Abbreviations: AT = All Treated; PD = Proposed Dose

Subject dispositions for the AT and PD populations are described in Table 6.

Table 6: Subject Disposition (P1093)

Disposition	AT Population (N=159) n (%)	PD Population (N=75) n (%)
Ongoing	84 (53)	48 (64)
Completed Week 24	147 (93)	64* (85)
Completed Week 48	124 (78)	47 (63)
Completed Week 96	91 (57)	22 (29)
Completed Week 192	44 (28)	11 (15)
Off Study	75 (47)	27 (36)
Completed protocol	42 (26)	12 (16)
Pregnancy	2 (1)	2 (1)
Virologic failure	7 (4)	1 (1)
Disallowed medication	1 (1)	0
Unable to get to clinic	2 (1)	1 (1)

Site closure	4 (3)	1 (1)
Withdrawal of consent	3 (2)	2 (3)
Not willing to adhere	6 (4)	4 (5)
Unable to contact	5 (3)	2 (3)

Source: adapted from P1093 Clinical Study Report, Module 5.3.5.2
*As of the safety cut-off date (April 30, 2019), 64 subjects had completed Week 24, but 6 had not reached Week 24 by the efficacy cut-off date (February 14, 2019), thus only 58 subjects are included in the PD Efficacy Population

Protocol Violations/Deviations

The most common protocol deviations were based on eligibility criteria, such as a subject with no viral load obtained in the last 8-12 weeks. Another common deviation was incorrect timing of OBT initiation. Some subjects signed the incorrect consent form for an outdated study protocol and were reconsented. The eligibility violations were reviewed and not judged to have impacted the primary outcomes.

There were several subjects with dosing errors. Three subjects (Subjects (b) (6) and (b) (6)) at a single site were given the incorrect formulation in an attempt to reduce pill burden. All 3 subjects were supposed to receive a 15 mg dose using 3 x 5-mg DTs but were instead administered 1 x 5-mg DT and 1 x 10-mg FCT for about 5-9 months. They were considered evaluable for safety but not included in the PD population.

Reviewer comment: Use of the incorrect formulation in these three subjects resulted in chronic underdosing. This is concerning because underdosing of ARVs can lead to loss of therapeutic effect and development of resistance. Subject (b) (6) and (b) (6) had viral loads >50 copies/mL at Weeks 24 and 48; Subject (b) (6) had <50 copies/mL starting at Week 24.

These occurrences highlight the potential for medication errors in the post-marketing setting given that the DT and FCT are not bioequivalent. This concern is further heightened by the continued availability of the 10-mg and 25-mg FCTs. In response to an FDA query, the Applicant reported that they intend to continue production of the 10-mg and 25-mg FCT but will provide clear dosing instructions and education to prescribers. They intend to periodically reassess the demand and need for these lower strength FCTs.

Table of Demographic Characteristics

The demographics for the PD Efficacy population are provided in Table 7. The majority of subjects were female, Black or African-American, and from the U.S. or Africa. The mean age was 6 years (range 2 months to 17 years).

Table 7: Demographics for Week 24 PD Efficacy Population (P1093)

Demographic Parameters	Total (N=58) n (%)
Sex	
Male	26 (45)
Female	32 (55)
Age	
Mean ± SD (years)	6.3 ± 6.4
Median (years)	2.5
Range (years)	0.17-17
Cohort (Age Range)	
Cohort I-FCT (≥12-<18 years)	19 (33)
Cohort IIA-FCT (≥6-<12 years)	5 (9)
Cohort III-DT (≥2-<6 years)	8 (14)
Cohort IV-DT (≥6 months-<2 years)	9 (15)
Cohort V-DT (≥4 weeks-<6 months)	17 (29)
Baseline Weight Band	
3-<6kg	10 (17)
6-<10kg	17 (29)
10-<14kg	3 (5)
14-<20kg	4 (7)
≥35kg	24 (41)
Race	
White	10 (17)
Black or African American	39 (67)
Asian	4 (7)
Multiple, Other or Unknown	5 (9)
Ethnicity	
Hispanic or Latino	12 (21)
Not Hispanic or Latino	45 (77)
Unknown	1 (2)
Region	
United States	25 (43)
South America (Brazil)	3 (5)
Asia (Thailand)	4 (7)
Africa (Botswana, Kenya, Uganda, South Africa, Zimbabwe)	26 (45)

Source: Reviewer-generated using ADSL dataset
Abbreviations: DT = dispersible tablet; FCT = film-coated tablet

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Relevant baseline disease characteristics are provided in Table 8. Most subjects (78%) had baseline HIV-1 RNA viral loads < 100,000 copies/mL and 74% of subjects had CD4 counts ≥ 500 cells/mm^3. The majority (88%) of subjects were treatment-experienced; the most commonly used drugs included lamivudine (3TC), lopinavir/ritonavir (LPV/RTV), zidovudine (ZDV), nevirapine (NVP) and abacavir (ABC). As per the protocol, there were no subjects with previous INSTI treatment.

Table 8: Baseline HIV Disease Characteristics for Week 24 PD Efficacy Population (P1093)

Baseline Disease Characteristic	Total N=58 n (%)
Baseline Viral Load (copies/mL)	
≤100,000	45 (78)
>100,000-≤500,000	4 (7)
>500,000	9 (15)
Baseline CD4 Count (cells/mm^3)	
<50	2 (4)
50-<200	1 (2)
200-<350	6 (10)
350-<500	6 (10)
≥500	43 (74)
Treatment History	
Treatment-naive	7 (12)
Treatment-experienced	51 (88)

Source: Reviewer-generated using ADSL dataset

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance and Palatability

Subjects were asked about adherence to the medication at each study visit using an adherence questionnaire. In the PD population (n=75), 65 (87%) subjects reported at least 90% adherence with study drug.

Palatability and acceptability were assessed for 3 age cohorts receiving the DT formulation (Cohorts III-DT [n=26], IV-DT [n=25] and V-DT [n=23]) at Day 10, Week 4 and Week 24. The majority of subjects in each cohort reported the taste to be “good” and there were only 3 subjects with preparation and administration problems (1 subject with problems fully dispersing tablets, 1 subject with problems cleaning and drying the cup, and 1 subject with vomiting).

Concomitant Medications

Various study-approved OBT regimens were used in combination with dolutegravir. The OBT regimens for the PD Safety Population are shown in Table 9.

Table 9: Optimized Background Treatment Regimens for PD Population (P1093)

Regimen	Total N=75 n (%)
2 NRTIs	37 (49)
ZDV/3TC	10 (13)
ABC/3TC	22 (29)
PI-based	27 (36)
LPV/RTV	9 (12)
DRV	12 (16)

Source: Adapted from sponsor table 20 in CSR, module 5.3.5.2
Abbreviations: ABC = abacavir; DRV = darunavir; LPV = lopinavir; NRT = nucleoside reverse-transcriptase inhibitor; PI = protease inhibitor; RTV = ritonavir; 3TC = lamivudine; ZDV = zidovudine

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was virologic success using the FDA snapshot algorithm. (b) (4) 17 additional subjects with Week 48 efficacy data were identified and added to the analysis. Table 10 and Table 11 provide the Week 24 and Week 48 virologic outcomes, respectively.

Table 10: Virologic Outcomes at Week 24 (P1093 - PD Efficacy Population)

HIV-1 RNA PCR Outcome at Week 24	3-<6kg n=10 (%)	6-<10kg n=17 (%)	10-<14kg n=3 (%)	14-<20kg n=4 (%)	**≥35kg** n=24 (%)	Total n=58 (%)
Successes (<50 copies/mL)	3 (30)	10 (59)	3 (100)	2 (50)	18 (75)	36 (62)
Treatment-experienced	2/3 (67)	8/10 (80)	3/3 (100)	2/2 (100)	18/18 (100)	33/36 (92)
Treatment-naïve	1/3 (33)	2/10 (20)	0 (0)	0 (0)	0 (0)	3/36 (9)
Failures (≥50 copies/mL)	7 (70)	7 (41)	0 (0)	2 (50)	6 (25)	22 (38)
Treatment-experienced	3/7 (43)	7/7 (100	0 (0)	2/2 (100)	6/6 (100)	18/22 (82)
Treatment-naïve	4/7 (57)	0 (0)	0 (0)	0 (0)	0 (0)	4/22 (18)

Source: Reviewer-generated using ADEFF dataset

At Week 24, subjects in the 10-<14 kg (n=3) and ≥35 kg (n=24) weight bands had the highest success rates at 100% and 75%, respectively. The 3-<6 kg weight band (n=10) had the lowest success rate at 30%. Other than viral load being above the threshold, however, no other

reasons were reported for virologic failure (i.e., there were no missing values in the window).

Table 11: Virologic Outcomes at Week 48 (P1093 - PD Efficacy Population)

HIV-1 RNA PCR Outcome at Week 48	3-<6kg n=6 (%)	6-<10kg n=9 (%)	10-<14kg n=2 (%)	14-<20kg n=1 (%)	>=35kg n=24 (%)	Total n=42 (%)
Successes (<50 copies/mL)	3 (50)	8 (89)	2 (100)	0 (0)	16 (67)	29 (69)
Treatment-experienced	2/3 (67)	6/8 (75)	2/2 (100)	0 (0)	16/16 (100)	26/29 (90)
Treatment-naïve	1/3 (33)	2 (25)	0 (0)	0 (0)	0 (0)	3/29 (10)
Failures (≥50 copies/mL)	3 (50)	1 (11)	0 (0)	1 (100)	8 (33)	13 (31)
Treatment-experienced	1/3 (33)	1/1 (100)	0 (0)	1/1 (100)	8/8 (100)	11/13 (85)
Treatment-naïve	2/3 (67)	0 (0)	0 (0)	0 (0)	0 (0)	2/13 (15)

Source: Reviewer-generated using ADEFF dataset

At Week 48, subjects in the 6-<10 kg (n=9) and 10-<14 kg (n=2) weight bands had the highest success rates at 89% and 100%, respectively. One subject in the 3-<6 kg weight band was considered a failure due to continued viremia in the setting of noncompliance. Two subjects in the ≥35 kg weight band were considered failures due to discontinuing study drug while their viral load was not below the threshold (one was unwilling to maintain adherence and the other could not be reached by the study site).

Reviewer comment: Most of the weight bands had very small sample sizes, precluding robust conclusions regarding the relationship between baseline weight and virologic outcome. Virologic success rates, however, were higher using a cut-off of <400 copies/mL at Week 48, suggesting that dolutegravir is successful at suppressing viral replication, but may take longer to reach the lower cut-off of <50 copies/mL in children. As discussed in the Virology review, all 11 of the evaluable virologic failures were noncompliant with treatment.

Table 12 and Table 13 present the change in absolute CD4 count and CD4 percentage at Week 24 and Week 48, respectively. Mean and median CD4 percentage were increased from baseline at both time points, with more robust response seen at Week 48.

Table 12: Immunologic Outcomes at Week 24 (P1093 - PD Efficacy Population)

	Baseline n=58	Week 24 n=57	Change from Baseline n=57
CD4 count (cells/μL)			
Mean	1556	1541	+31.16
Median	1125	1021	+105
CD4/lymphocytes %			
Mean	24.9	29.8	+5.2
Median	24	30	+5.1

Source: Reviewer-generated using ADLB dataset

Table 13: Immunologic Outcome at Week 48 (P1093 - PD Efficacy Population)

	Baseline n=58	Week 48 n=40	Change from Baseline n=40
CD4 count mean (cells/μL)			
Mean	1556	1394	+106.8
Median	1125	918	+140.5
CD4/lymphocytes %			
Mean	24.9	31.2	+6.9
Median	24	32.2	+6.6

Source: Reviewer-generated using ADLB dataset

Reviewer comment: There is a natural decrease in CD4 cell count observed from birth to 6 years, but CD4 percentage remains consistent with growth. Therefore, increase in CD4 percentage is a more accurate predictor of immunologic response in young children.

Data Quality and Integrity

The quality and integrity of the submitted datasets were adequate. The datasets were reviewed, and the Applicant's analyses verified, by the primary reviewer. As previously mentioned, 17 subjects with Week 48 efficacy data were not included in the Applicant's analysis, although their data were provided in the datasets and included in the FDA analyses.

Efficacy Results – Secondary and other relevant endpoints

Virologic outcomes were also analyzed by DTG formulation (Table 14). At Week 24, subjects receiving the FCT had a higher success rate (75%) than those receiving the DT formulation (53%); however, at Week 48, based on a smaller DT sample size, success rates were similar.

Table 14: Virologic Outcome by Oral Formulation (P1093 - PD Efficacy Population)

HIV-1 RNA PCR Outcome at Week 24	Dispersible Tablet (n=34) N (%)	Film-Coated Tablet (n=24) N (%)	Total (n=58) N (%)
Virologic successes (<50 copies/mL)	18/34 (53)	18/24 (75)	36/58 (62)
Virologic failures (≥50 copies/mL)	16/34 (47)	6/24 (25)	22/58 (38)
HIV-1 RNA PCR Outcome at Week 48	Dispersible Tablet (n=18) N (%)	Film-Coated Tablet (n=24) N (%)	Total (n=42) N (%)
Virologic successes (<50 copies/mL)	13/18 (72)	16/24 (67)	29/42 (69)
Virologic failures (≥50 copies/mL)	5/18 (28)	8/24 (33)	13/42 (31)

Source: Reviewer-generated using ADEFF dataset

Reviewer comment: The small sample sizes precluded robust efficacy analyses by formulation. Of note, AE rates of vomiting and diarrhea were moderately higher in the DT groups compared with the FCT groups (see Section 8.5.5), raising concerns that subjects receiving the DT formulation might be at risk for decreased absorption. However, the drug exposure analyses showed adequate exposures across all weight bands and dosage forms.

At Weeks 24 and 48, subjects with lower baseline viral loads (≤100,000 copies/mL) had higher success rates than those with higher baseline viral loads (Table 15). At Week 48, however, the majority of subjects in the >500,000 copies/mL baseline group had achieved virologic success.

Table 15: Virologic Outcome by Baseline Viral Load (P1093 - PD Efficacy Population)

HIV-1 RNA PCR Outcome at Week 24	≤ 100, 000 (n=45) N (%)	> 100,000 - ≤ 500,000 (n=4) N (%)	> 500,000 (n=9) N (%)	Total (n=58) N (%)
Virologic successes (<50 copies/mL)	32/45 (71)	1/4 (25)	3/9 (33)	36/58 (62)
Virologic failures (≥50 copies/mL)	13/45 (29)	3/4 (75)	6/9 (67)	22/58 (38)
HIV-1 RNA PCR Outcome at Week 48	≤ 100, 000 (n=31) N (%)	> 100,000 - ≤ 500,000 (n=4) N (%)	> 500,000 (n=7) N (%)	Total (n=42) N (%)
Virologic successes (<50 copies/mL)	24/31 (77)	1/4 (25)	4/7 (57)	29/42 (69)
Virologic failures (≥50 copies/mL)	7/31 (23)	3/4 (75)	3/7 (43)	13/42 (31)

Source: Reviewer-generated using ADEFF dataset

Reviewer comment: Subjects with lower baseline viral loads may be reasonably expected to have higher success rates. The number of subjects with higher viral loads at baseline, however, was very small, thus any differences in virologic success by baseline viral load should be interpreted with caution.

Dose/Dose Response

As noted, robust conclusions regarding dose response could not be made because of the small sample sizes for each weight band. The basis of approval, however, is the demonstration of drug exposures comparable with adult exposures, which was achieved in this submission (see the FDA Clinical Pharmacology review for details). Extrapolation of adult efficacy to a pediatric population is therefore appropriate.

Durability of Response

Virologic and immunologic effects are durable as long as the patient remains adherent to ARV therapy. Durability of response was noted through Week 48 in Study P1093.

Persistence of Effect

Antiretroviral therapy is expected to have a beneficial effect as long as the patient remains adherent but is not expected to persist after treatment is stopped; therefore, this section is not applicable.

Additional Analyses Conducted on the Individual Trial

Subgroup analyses of virologic outcomes at Week 24 were conducted by sex, race, and country of origin. Male and female subjects had similar virologic success rates, as expected (Table 16).

Table 16: Efficacy by Sex at Week 24 (PD Efficacy Population)

	Females (n=32) N (%)	Males (n=26) N (%)
Virologic successes (<50 copies/mL)	21 (66)	15 (58)
Virologic failures (≥50 copies/mL)	11 (34)	11 (42)

Reviewer-generated using ADEFF dataset

White and Asian subjects had the highest success rates numerically, but their sample sizes were small (Table 17). Of the 39 Black or African-American subjects, 13 were from the U.S.; these subjects had a 62% success rate. Black subjects from African sites (n=26), however, had lower success rate at 50%.

Table 17: Efficacy by Race at Week 24 (PD Efficacy Population)

	Black/ African-American (n=39) N (%)	Asian (n=4) N (%)	White (n=10) N (%)	Other (n=5) N(%)
Virologic successes (<50 copies/mL)	21 (54)	3 (75)	9 (90)	3 (60)
Virologic failures (≥50 copies/mL)	18 (46)	1 (25)	1 (10)	2 (40)

Reviewer-generated using ADEFF dataset

Reviewer comment: Overall, Black or African-American subjects had lower virologic success rates, but this was driven by subjects at African sites (see Table 18) as African-American subjects at U.S. sites had higher rates, comparable to the larger study population. This suggests that external factors, such as differences in resources or adherence, rather than racial differences likely accounted for the lower virologic success rates at the African sites.

The United States, Thailand and Brazil had the highest rates of virologic success (Table 18). Botswana, Kenya, Uganda, South Africa and Zimbabwe all had lower rates of success.

Table 18: Efficacy by Country at Week 24 (PD Efficacy Population)

Country	Virologic successes (<50 copies/mL) N (%)	Virologic failures **(≥50** copies/mL) N (%)
Brazil (n=3)	2 (66)	1 (33)
Botswana (n=2)	1 (50)	1 (50)
Kenya (n=7)	3 (43)	4 (57)
Thailand (n=4)	3 (75)	1 (25)
Uganda (n=2)	1 (50)	1 (50)
United States (n=25)	18 (72)	7 (28)
South Africa (n=3)	1 (33)	2 (66)
Zimbabwe (n=12)	7 (58)	5 (42)

Reviewer-generated using ADEFF dataset

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Only Study P1093 trial provided efficacy data, thus this section is not applicable.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The data submitted demonstrate that the proposed doses of dolutegravir achieved their pre-specified exposure targets; therefore, extrapolation of adult efficacy in support of these pediatric dose regimens is appropriate. Moreover, based on Study P1093, treatment with dolutegravir at the proposed doses and oral formulations, in combination with optimized background therapy, resulted in acceptable rates of virologic suppression at Weeks 24 and 48 in HIV-1 infected children. These rates are comparable to those reported in the treatment-experienced adult trials. Study P1093 also showed that U.S. subjects achieved among the highest rates of virologic suppression (HIV-1 RNA < 50 copies/mm^3). Taken together, it is reasonable to expect that clinical benefit will be similar in the postmarket setting.

The Division of Medication Error Prevention and Analysis (DMEPA) raised concerns about the risk of underdosing or overdosing should prescribers or caregivers/patients inadvertently substitute one oral tablet formulation for the other without adjusting the dose, since the two forms are not bioequivalent and have distinct dosing recommendations. This concern is further heightened by the continued presence of the 10-mg and 25-mg film-coated tablets on the market. The latter FCTs were used to accomplish pediatric dosing under the old dosing recommendations, but with the introduction of the new DT formulation and revised dosing recommendations for the FCT formulation, their ongoing role is uncertain. Underdosing could have implications on efficacy by increasing the risk of virologic failure and development of drug resistance. Overdosing could potentially pose a safety concern, although data regarding the effects of dolutegravir overdosage are limited. This concern led DMEPA to recommend that the two dosage forms have different proprietary names to help differentiate them to prescribers and consumers. In response, the Applicant proposed a modifier for the DT formulation name, TIVICAY PD (Pediatric Dosing), which was accepted by DMEPA and the review team.

With regards to the 10-mg and 25-mg FCTs, the Applicant has indicated plans to continue production of these two lower dose-strength tablets. They assert that some patients might prefer to take two 25-mg FCTs instead of one 50-mg FCT. They also intend to keep the 10-mg FCT tablet to support pediatric dosing for the 14 to <20 kg weight band (i.e., 40 mg QD using 4 x 10-mg FCTs), although the Prescribing Information will recommend that children in this weight band use the DT formulation if possible.

7.2.2. Other Relevant Benefits

The availability of an additional formulation that can be swallowed or dispersed in drinking water is a benefit for younger patients as it gives prescribers another safe, effective and convenient treatment option for the pediatric HIV population. The DT formulation was found to be tolerable and easy to administer based on palatability and human factors studies, which is expected to continue in the postmarket setting.

7.3. Integrated Assessment of Effectiveness

Pediatric HIV trials are not powered to demonstrate efficacy. The basis of approval for a new pediatric ARV drug is matching PK in pediatric subjects to exposures demonstrated to be effective in adult trials. Adult efficacy can then be extrapolated to pediatrics because the disease process, and the drug's effect on the disease, is similar between adult and pediatric populations.

The dolutegravir doses proposed in this application achieved the prespecified PK targets with acceptable virologic success rates at Week 24 and Week 48 as demonstrated in the PD Efficacy Population of Study P1093. While there were some differences between weight bands in virologic outcomes, these are difficult to interpret because of the small sample sizes. It is reassuring to note that all the evaluable virologic failures reported in P1093 were associated with treatment noncompliance. Dolutegravir also had a favorable immunologic effect based on the change from baseline in CD4 percentage at Weeks 24 and 48.

The efficacy outcomes were similar to those seen in SAILING, a trial of DTG in treatment-experienced adults. At Week 24, 62% of the P1093 PD Efficacy population (n=58) had viral load <50 copies/mL compared with 79% of the adult population in SAILING (n=354). At Week 48, 69% of the P1093 PD Efficacy population (n=42) had viral load <50 copies/mL compared with 71% of the adult population (n=354).

There were some racial and region-specific disparities in terms of efficacy in Study P1093, but these appeared to be related to differences between higher- and lower-income countries.

Proposed labeling will include efficacy results from Study P1093 in terms of the virologic success (<400 copies/mL and <50 copies/mL) as well as the median increases in absolute CD4 cell count and CD4 percentage from baseline at Week 24 and 48.

8. Review of Safety

8.1. Safety Review Approach

Safety data from Study P1093 provided the basis for this review; safety from the ODYSSEY trial was supportive. Although the two trials had many similarities (similar populations, both open-label, and both adapted to introduce new weight-based dosing during the course of the study), data from the two trials were not pooled together due to key differences in study design. Most notably, the collection of AEs differed between the trials; AEs of all grades were collected in Study P1093 while in the ODYSSEY PK sub-studies, Grade 1 and 2 AEs were only collected if they resulted in a dose modification or DTG discontinuation. In addition, the severity grading tables used in each trial were different. Lastly, the ODYSSEY trial included more treatment-naïve

subjects and the weight bands for participants ≥ 25 kg were defined differently.

Safety events through Week 24 were analyzed in Study P1093 as this was the primary endpoint; toxicity through Week 48 and beyond was a secondary endpoint. As part of this review, safety data from Week 24 through Week 48 were analyzed for any new safety signals. (The Applicant intends to submit complete safety data through Week 48 in a future supplement once all subjects have completed Week 48 follow-up.)

Study P1093

The safety review focused on safety in 75 subjects who received the proposed dose (PD population). The Applicant conducted analyses on the "All Treated" population (AT population) and compared these to the PD population.

ODYSSEY

The safety review focused on the Intended DTG Dose Population, which consisted of 97 participants who received at least 1 dose of the intended DTG formulations and doses according to weight band.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Study P1093

Table 19: P1093 Drug Exposure as of April 30, 2019

Duration of Exposure (days)	PD Population (n=75)
Range	15-1525
Median	350
Mean ± SD	547 ± 459

Source: Reviewer-generated using P1093 ADEX dataset

ODYSSEY

Table 20: ODYSSEY Drug Exposure as of February 28, 2019

Duration of Exposure (days)	Intended DTG Dose Population (n=97)
Range	26-842
Median	466
Mean ± SD	457 ± 216

Source: Reviewer-generated using ODYSSEY ADEX dataset

8.2.2. Relevant Characteristics of the Safety Population

Study P1093

The PD safety population (n=75) was larger than the PD efficacy population (n=58) (see Table 7), but there were no clinically significant differences between the two populations with respect to demographics or baseline characteristics. There was good distribution of enrollment across the weight bands. However, there are some key differences in some baseline factors that may help explain some of the differences observed in the safety findings. For example, enrollment was initially sequential by descending age cohort, and thus older participants were on study for longer duration than those in the younger cohorts. Older children were mostly from the U.S., Thailand, and South Africa, as these sites were the first with regulatory approval. In addition, older participants were primarily taking the FCT formulation, whereas younger children were more often from low and middle-income locations and were mostly on DTs. It is also important to note that there were no subjects in the 20-<35 kg weight bands in the PD population.

Table 21: Demographics for PD Safety Population (P1093)

Demographic Parameters	PD Safety (N=75) n (%)
Sex	
Male	44 (59)
Female	31 (41)
Age	
Mean ± SD (years)	5.2 ± 6
Median (years)	2
Range	1 month-17 years
Cohort (Age Range)	
Cohort I-FCT (≥12-<18 years)	19 (25)
Cohort IIA-FCT (≥6-<12 years)	5 (7)
Cohort III-DT (≥2-<6 years)	16 (21)
Cohort IV-DT (≥6 months-<2 years)	12 (16)
Cohort V-DT (≥4 weeks-<6 months	23 (31)
Baseline Weight Band	
3-<6kg	15 (20)
6-<10kg	20 (27)
10-<14kg	10 (13)
14-<20kg	6 (8)
≥35kg	24 (32)
DTG Formulation	
DT	51 (68)

FCT	24 (32)
Race	
White	10 (13)
Black or African American	51 (68)
Asian	7 (9)
Multiple, Other or Unknown	7 (9)
Ethnicity	
Hispanic or Latino	15 (20)
Not Hispanic or Latino	59 (79)
Unknown	1 (1)
Region	
United States	25 (33)
South America (Brazil)	7 (9)
Asia (Thailand)	7 (9)
Africa (Botswana, Kenya, Uganda, South Africa, Tanzania, Zimbabwe)	36 (48)

Source: Reviewer-generated using P1093 ADSL dataset

ODYSSEY

The demographics in the ODYSSEY Intended DTG Dose Population were similar to those in the P1093 PD Safety population but included all weight bands.

Table 22: Demographics for Intended DTG Dose Population (ODYSSEY)

Demographic Parameters	Total N=97 n (%)
Sex	
Male	47 (48)
Female	50 (52)
Age	
Mean ± SD (years)	7.5 ± 3.6
Median (years)	7.6
Range (years)	0.34-17.5
Age Range	
≥12-<18 years	8 (8)
≥6-<12 years	59 (61)
≥2-<6 years	19 (20)
≥6 months-<2 years	10 (10)
≥4 weeks-<6 months	1 (1)
Baseline Weight Band	
3-<6kg	1 (1)
6-<10kg	10 (10)

10-<14kg	5 (5)
14-<20kg	31 (32)
20-<25kg	28 (29)
25-<30kg	16 (17)
30-<40kg	6 (6)
DTG Formulation	
DT	16 (17)
FCT	81 (83)
Race	
Black or African American	97 (100)
Country	
South Africa	3 (3)
Uganda	57 (59)
Zimbabwe	37 (38)

Source: Reviewer-generated using ODYSSEY ADSL dataset

8.2.3. Adequacy of the safety database

The safety database was considered adequate. The safety population of Study P1093 was lacking participants in 20-<35kg weight bands, but all age cohorts were represented. The ODYSSEY trial had representation in all weight and age cohorts. The duration of exposure was adequate. Participants from the U.S. made up a third of the P1093 safety population, thus the baseline demographics are considered relevant to a U.S. pediatric HIV-1 population.

Reviewer comment: The proportion of U.S. subjects in these trials was overall small (n=25), and white, Asian and Hispanic subjects were underrepresented. Nonetheless, based on adult data, there is no reason to suspect that the safety of dolutegravir in pediatric patients should differ by race, ethnicity, or country of origin. Therefore, these demographic limitations should not affect the ability to draw generalizable safety conclusions from the available data.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant conducted appropriate safety analyses for studies P1093 and ODYSSEY. The submitted datasets were reviewed by the primary reviewer and the Applicant's analyses were verified. Narratives were provided for deaths, serious adverse events (SAEs), other significant events, and pregnancies. An Integrated Summary of Safety (ISS) was provided.

Collection of adverse events was less complete in the ODYSSEY trial compared to P1093, which precluded pooling of data across trials; however, both trials collected ≥ Grade 3 AEs and SAEs, which allowed for some direct comparison.

8.3.2. Categorization of Adverse Events

Study P1093

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22. While there was some splitting of preferred terms, similar events were combined in the FDA analyses as noted.

Adverse events were considered serious based on the definition found in the ICH E2A guidelines. Causality for AEs was assessed by the investigators. Severity of AEs was graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version I, December 2004, Clarification 2009). Treatment-emergent AEs were defined as events that started after Day 0 (or for laboratory AEs, events where the toxicity grade increased compared to baseline).

Adverse events of special interest (AESIs) were determined based on non-clinical and clinical safety data with DTG and other INSTIs. In this trial, the identified AESIs included immune reconstitution inflammatory syndrome (IRIS), hypersensitivity and rash, hepatobiliary disorders, psychiatric disorders including suicidality, GI disorders, musculoskeletal disorders and renal disorders.

ODYSSEY

Adverse events were summarized using an in-house coding system. Subjects or their caregivers were prompted at each visit for "symptoms relating to possible drug toxicities." Severity of AEs was graded using the 2014 DAIDS toxicity grading scale. Grade 1 and 2 clinical events were not reported unless they resulted in a dose modification or DTG discontinuation. The list of AESIs was the same as in Study P1093.

Reviewer comment: The lack of standardized coding of adverse events, in addition to the incomplete collection of AEs, precludes robust safety conclusions based on the ODYSSEY trial.

8.3.3. Routine Clinical Tests

Study P1093

Through Week 48, study visits were conducted at entry (Day 0), Days 5-10, and Weeks 4, 8, 12, 16, 24, 32, 40 and 48. Routine laboratory tests included hematology, fasting lipid profile, blood chemistry, and urinalysis. The collection of samples varied slightly depending on cohort, formulation and PK stage. Fasting was not required for the laboratory analyses; however, if triglycerides were Grade 2 or higher (using DAIDS toxicity table for fasting triglycerides), a complete fasting lipid profile (triglycerides, cholesterol, HDL, and LDL) was drawn. Laboratory

samples were analyzed using certified local laboratories.

Reviewer comment: The evaluations and schedule of assessments in P1093 are appropriate for the population, disease and indications being investigated.

ODYSSEY

The schedule of assessments for ODYSSEY is shown below.

Table 23: Schedule of Assessments (ODYSSEY)

WEEK	Screening	Randomization 0[a]	(2)	4	12	24	36	48	60	72	84	96	Further follow-up	End of study
Patient information sheet and consent for screening	X													
Informed consent for trial enrolment		X												
History and clinical assessment	X	X	(X)[t]	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Tanner scale [c]		X				X		X		X		X	Every 24 weeks	X
Lipodystrophy assessment [p]		X						X				X	Every 48 weeks	X
Drug supply to next visit		X	(X)	X	X	X	X	X	X	X	X	X	Every 12 weeks	
HIV-1 RNA viral load [d]	X[d]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	As per local practice	X[d]
T cell lymphocyte subsets [e]	X	X		X	X	X	(X)	X	(X)	X	(X)	X	As per local practice	X
Biochemistry [f]	X	(X)	(X)[t]	X	(X)	X	(X)	X	(X)	X	(X)	X	As per local practice	X
Hematology [g]	X	X	(X)[t]	X	(X)	X	(X)	X	(X)	X	(X)	X	As per local practice	X
Lipids/glucose [h]		X[o]				(X)		X				X	Every 48 weeks	X
Bone profile [i]		(X)						(X)				(X)	(Every 48 weeks)	(X)
Urine dipstick [j]		X						X				X	Every 48 weeks	X
Quality of Life questionnaire [c]		X			X	X		X				X	Every 48 weeks	X
Pregnancy test [k]	X	X[k]	X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Plasma storage [l, q]	X	X	(X)	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Red blood cell folate (RBC)/RBC storage and B12/serum storage												X	(At next clinic visit if the 96 week sample is not	
PBMC (Cell) storage [m]		X[m]			X[m]			X[m]				X[m]		
Adherence questionnaire [q, r]	X[n]			X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Acceptability, sleep & mood questionnaire [q, r]		X[s]		X	X	X		X		X		X	Every 24 weeks	X

Source: Protocol Version 5, Module 5.3.5.2

Notes:
( ) Optional, not mandatory.
Darker shaded boxes indicate visits where overnight fasting is required for blood lipids/glucose.
Up to 12 mls of blood may be collected at each visit for routine assays and tests plus an additional 8-18 mls blood may be collected for storage (plasma and when requested, PBMCs). Total amounts drawn will depend upon the size of the child and their health.

a. Randomization visit should take place within 4 weeks after the screening visit, ideally within 2 weeks
b. Clinical assessment: including height, weight (and adjustment of drug doses accordingly) and mid upper arm circumference (MUAC), change in HIV disease stage, clinical events and presence of adverse events
c. In children aged 8 or over
d. Real-time viral loads will be measured on all children in ODYSSEY B at the screening visit, unless a viral load result of ≥500 c/ml dated within four weeks of the screening visit is available. If such a result is not available, it is mandatory that this test is done in ODYSSEY B participants. For children recruited in ODYSSEY A, this is not mandatory. Thereafter in both ODYSSEY A and B, viral loads should be measured locally at sites according to the routine frequency, where viral loads are not measured in real time, they will be run retrospectively in batches on stored plasma

e. CD4 and CD8 percentage and absolute, total lymphocyte count. In addition, immunophenotyping (IPT) on the same blood draw will be done at the sites participating in the immunology/virology substudy, and where IPT tests are available. At the other sites IPT will be done on the cell storage samples.
f. Biochemistry: mandatory: creatinine, bilirubin, ALT; optional (if results are available or routinely done): AST
g. Hematology: Hgb, MCV, WBC, lymphocytes, neutrophils, platelets
h. Lipids/Glucose: triglycerides, cholesterol (total, HDL, LDL), glucose (overnight fasting required at randomization and weeks 24 and 48, and then every 48 weeks)
i. Bone profile (optional): calcium, phosphate, alkaline phosphatase
j. Urine dipstick: for protein and glucose, performed at randomization and then every 48 weeks and at end of study visit
k. Pregnancy test: urine sample; the test should be performed for all females of childbearing potential at screening, randomization and all trial follow-up visits and at other time-points if required.
l. Plasma storage: for retrospective HIV-1 RNA viral load, resistance testing where not routinely available locally, sparse PK sampling, folate substudy and immunology/virology substudy. Samples may be assayed locally or moved to another country.
m. Peripheral blood mononuclear cells (PBMCs) will be stored at selected sites only, for use in the immunology/virology substudy.
n. Baseline adherence questionnaire for patients screened for ODYSSEY B and currently taking their first-line treatment
o. The glucose test at the randomization visit may be omitted if there is a medical justification (e.g. anaemia) to limit the total volume of blood drawn.
p. At selected sites bioelectrical impedance analysis (BIA) measurements will be done.
q. In case of attendance at an unscheduled visit at the point of treatment failure, plasma storage and adherence and acceptability questionnaires should be done. (The acceptability questionnaire should also be done if treatment failure occurs at a scheduled visit where it is not normally done, e.g. week 36).
r. Adherence and acceptability questionnaires should also be completed if ART regimen is changed.
s. The mood and sleep section of the acceptability questionnaire should be completed at the enrolment visit.
t. Clinical assessment, hematology and biochemistry tests at week 2 are required for all children 3-<14kg and optional for children ≥14kg.
u. (b) (4)

8.4. Safety Results

8.4.1. Deaths

Study P1093

There were 3 deaths reported. Narratives are summarized and discussed below.

1. Subject (b) (6): This subject was a 15-year-old male from Thailand who was taking dolutegravir 50 mg FCT once daily. He was also taking lamivudine, tenofovir disoproxil fumarate, and ritonavir-boosted atazanavir. He had Grade 3 increases in ALT at the Week 2, 4, and 16 visits and Grade 1 increases in bilirubin between Week 8 and Week 156. He also had a foot abscess at Week 156 treated with surgical drainage and antibiotics. He was reported to have died from a drowning accident after 1,459 days on dolutegravir.

Reviewer comment: No details were provided regarding the drowning accident. The subject's death was unlikely to be related to dolutegravir. Drowning can be a result of a clinical event such as loss of consciousness due to seizure or arrhythmia, but such information is lacking in this case.

2. Subject (b) (6): This subject was an 8-month-old female from Zimbabwe who was

taking 10 mg DT once daily; at baseline she was 6 months old and in the 3-<6 kg weight band (baseline weight 5.6 kg), so her initial dose should have been 5 mg per the proposed dosing recommendations; if she crossed into the 6-<10 kg weight band she should have switched to 15 mg once daily (b) (4). She was also taking LPV/RTV and ABC/3TC as ART and trimethoprim-sulfamethoxazole as prophylaxis. Her clinical course was unremarkable except for poor weight gain (only 0.2 kg in 8 weeks) and an upper respiratory tract infection at Week 4, which was treated with amoxicillin. On Day 57, shortly after the Week 8 visit, she presented to the hospital with fever, diarrhea, dehydration and lethargy and was reported to have repeated episodes of tonic-clonic seizures and shortness of breath. She was diagnosed with acute infective gastroenteritis with severe dehydration and encephalitis as well as severe acute malnutrition; no causative pathogen was identified, although blood culture, lumbar puncture or head imaging were not done. She was treated with fluids, sedatives and anticonvulsive medications (diazepam, phenobarbital and phenytoin), ceftriaxone, and empiric tuberculosis treatment (rifampin, isoniazid, pyrazinamide, and ethambutol). The subject's condition reportedly deteriorated despite supportive measures, and she died after 2 days of hospitalization; dolutegravir was discontinued one day prior to death.

Reviewer comment: In all likelihood, this subject had gastroenteritis with an infectious etiology based on the presence of fever, although no causative pathogen was reported. The seizures may have been febrile seizures, related to infection if there was central nervous system involvement, or due to electrolyte abnormalities from dehydration. It is unlikely that dolutegravir contributed to the illness causing her death, although it cannot be ruled out. The finding that her DTG dose was 10 mg daily when it should have been either 5 or 15 mg daily, (b) (4), was likely not a factor. At her final study visit at Week 8, her HIV-1 RNA viral load was 47 copies/mL, suggesting that lack of efficacy did not play a role.

3. Subject (b) (6): This subject was a 2-year-old male from Brazil who was taking 10 mg DT once daily. The proposed dose for his age and weight band is 15 mg once daily, but he was not in the PD population. He was also taking 3TC and LPV/r, multivitamin and iron supplements. At Week 2, he had a Grade 1 increase in bicarbonate and sodium. At Week 8, he had a Grade 1 decrease in non-fasting glucose. At Day 91, he had a Grade 2 increase in AST and ALT. On Day 130, he was reported to have had generalized convulsions and was found unconscious at home, but reportedly there were no witnesses, so the convulsions were not confirmed. Emergency services reported fixed and dilated pupils and asystole; attempts to resuscitate at the hospital were unsuccessful. There were some initial concerns about malnutrition and skin lesions being possibly related to neglect, but the autopsy report described good nutrition status and overall appearance inconsistent with neglect. A formal investigation did not reveal a cause of death, leaving the cause of death as "unknown."

Reviewer comment: This subject may have had an event leading to his death that may not have been detected on autopsy, such as seizure or arrhythmia. As the cause of death is unclear, and there is limited information about his health in the days and weeks immediately preceding death, the relationship to dolutegravir cannot be determined.

ODYSSEY

There were no deaths reported among subjects enrolled in the PK sub-studies.

8.4.2. Serious Adverse Events

Study P1093

Serious adverse events (SAEs) reported through Week 24 in the PD population (n=75) are discussed here. There were 5 subjects (7%) who experienced SAEs, 2 of whom had multiple SAEs. The following table summarizes the individual SAEs and provides the reviewer's assessment of relationship to study drug.

Table 24: Summary of Individual Serious Adverse Events (P1093)

Subject ID	Age	Sex	Baseline Weight Band (kg)	Dose/ Formulation	Preferred Term	Study Day	Action Taken on Study Drug	Outcome	Relation to Study Drug
(b) (6)	2 mo	M	3-<6	10 mg DT	Gastroenteritis	36	None	Resolved	Unlikely
	6 mo	F	3-<6	10 mg DT	Gastroenteritis	57	Withdrawn	Fatal	Unlikely
	5 y	M	6-<10	15 mg DT	Pneumonia respiratory syncytial viral	2	None	Resolved	Unlikely
	5 y	M	6-<10	15 mg DT	Pneumonia parainfluenzae viral	2	None	Resolved	Unlikely
	5 y	M	6-<10	30 mg DT	Diarrhea	23	Interrupted	Resolved	Unlikely
	5 y	M	6-<10	30 mg DT	IRIS	34	None	Resolved	Likely
	5 y	M	6-<10	30 mg DT	Mycobacterium avium complex infection	34	None	Resolved	Unlikely
	5 y	M	6-<10	30 mg DT	Atypical mycobacterial lymphadenitis	85	None	Resolved	Unlikely
	5 y	M	6-<10	40 mg DT	Pneumonia adenoviral	177	None	Resolving	Unlikely
	1 y	F	6-<10	15 mg DT	Herpes zoster	36	None	Resolved	Unlikely
	1 y	F	6-<10	15 mg DT	IRIS	36	None	Resolved	Likely
	5 mo	M	6-<10	10 mg DT	Pneumonia	29	None	Resolved	Unlikely

Source: Reviewer-generated from subject narratives and ADAE dataset

Many of the SAEs had an infectious etiology, making relationship to study drug unlikely. While the cases of IRIS were considered generally related to ART, they were not considered specific to dolutegravir. The fatal case of gastroenteritis (Subject (b) (6)) is discussed in Section 8.4.1. The other case of gastroenteritis in Subject (b) (6) was associated with vomiting, diarrhea and fever and was treated with antibiotics and oral rehydration solution; this event was likely infectious in nature and unlikely to be related to study drug. The case of diarrhea in Subject (b) (6) was associated with fever and cold symptoms, and also unlikely related to study drug; study drug was temporarily held but no further details were provided.

After Week 24, two additional SAEs were reported through Week 48, both in Subject (b) (6), with pneumonia on Days 235 and 281. These were unlikely to be related to study drug.

ODYSSEY

Three subjects (3%) had SAEs reported through Week 24 in the Intended DTG Safety Population (n=97). They each experienced multiple SAEs. Narratives are summarized below.

1. Subject (b) (6) was a 2-year-old Ugandan female in the 6-<10 kg weight band who was receiving DTG 15 mg DT. On Day 62, she developed an SAE of lower respiratory infection and was hospitalized. She was treated with 5 days of ceftriaxone and meropenem and improved. She was also diagnosed with SAEs of measles, severe malnutrition, and iron deficiency anemia during this hospitalization. Anemia was managed with ferrous sulphate and malnutrition was managed with nutritional feeds. Measles was diagnosed presumptively. No action was taken on study drug.

Reviewer comment: It is unlikely that any of these SAEs were related to study drug. They were more likely related to underlying disease.

2. Subject (b) (6) was a 12-year-old Ugandan male in the 30-<40 kg weight band who was receiving DTG 50 mg FCT. On Day 152, he was diagnosed with cryptococcal meningitis. He had previously been diagnosed with non-meningeal cryptococcal disease about 4 months prior based on positive serum cryptococcal antigen. No action was taken on study drug. This episode of meningitis resolved but recurred about 8 months later.

Reviewer comment: Cryptococcal meningitis is likely associated with the subject's underlying disease and immunocompromised status, and unlikely related to study drug.

3. Subject (b) (6) was a 1-year-old Ugandan female in the 6-<10 kg weight band who was receiving DTG 15 mg DT. On Day 16, she was admitted with a 7-day history of fever, cough, rash and ear discharge. She was diagnosed with SAEs of pneumonia and otitis media. She improved on unspecified treatment. No action was taken on study drug.

Reviewer comment: These infections are common in this age group and unlikely to be related to study drug.

In conclusion, the rates of SAEs reported in the P1093 and ODYSSEY trials were low. Most SAEs were reported in the Infections and Infestations MedDRA System Organ Class and were not considered related to dolutegravir.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study P1093

There were no reported AEs resulting in discontinuation of study drug or dropout from the trial.

ODYSSEY

Two subjects discontinued study drug due to an AE. Their narratives are summarized below.

1. Subject (b) (6) was a 6-year-old male from Uganda. His weight band at baseline was 14-<20 kg and he was started on dolutegravir 25 mg FCT once daily; his weight band at onset of AE was 20-<25 kg but his dose had not been changed. He was also on abacavir, lamivudine, trimethoprim-sulfamethoxazole prophylaxis, and tuberculosis treatment with isoniazid and pyridoxine. On Day 252, he developed ALT of 7700 U/L (Grade 4) and AST of 1094 U/L (Grade 4), and total bilirubin of 28.7 micromol/L (Grade 2). Antiretrovirals were held. The subject reportedly had "flu" for 3 days prior to this visit and was also noted to have jaundice and dark yellow urine. He was diagnosed with acute hepatitis A based on positive IgM. His liver enzymes were improved 8 days later (ALT 589 U/L, AST 211 U/L, and total bilirubin 19.8 micromol/L). The next day, he developed fever and diarrhea which resolved, and liver enzymes continued to improve. He developed fever again 48 days after initial presentation and was diagnosed with bacteremia. At this time, his AST and ALT were 3.5 x ULN. One week later his ALT was 70 U/L (1.7 x ULN) and AST was 88 U/L (2.2 x ULN). Transaminases continued to improve but dolutegravir was not restarted.

Reviewer comment: The subject's transaminases gradually improved following hepatitis A diagnosis, which would be expected given the typical self-resolving nature of this infection. Although the role of dolutegravir cannot be excluded given the improvement noted following cessation of study drug, it is likelier that the subject's transaminitis and hyperbilirubinemia were secondary to acute hepatitis A infection.

2. Subject (b) (6) was a 5-year-old female from Uganda. Her weight band at baseline was 14-<20 kg and she was started on dolutegravir 25 mg FCT once daily; based on the

proposed doses for her weight band, she should have initiated dolutegravir 40 mg FCT or 25 mg DT once daily. Weight band at AE onset was still 14-<20 kg. She was also on ABC and 3TC. On Day 161, routine labs showed elevated ALT (Grade 4, value not provided) and AST (Grade 4, value not provided) and normal bilirubin. She was asymptomatic with a normal physical exam, but evaluation revealed cholecystitis on abdominal ultrasound, positive hepatitis A IgM, and CMV viral load of 428. She was switched to dolutegravir 25 mg DT once daily on Day 162 (correct per proposed dosing recommendations) but stopped her current ARV regimen, including study drug, on Day 165. Hepatitis was reported as resolved after 16 days, and a new ARV regimen not containing dolutegravir was started.

Reviewer comment: It is likely that the subject's transaminitis was secondary to acute hepatitis A infection, but the role of dolutegravir cannot be excluded. She was also found to have cholecystitis on imaging, which can cause transaminitis, but she had no complaints or findings on physical exam which makes this less likely. She was on a lower-than-proposed dose of DTG until the last several days of study drug, but she was reportedly responding to the ARV regimen. It is unclear why a new regimen was started if she was responding and the investigators attributed her transaminitis to hepatitis A infection.

8.4.4. Significant Adverse Events

Study P1093

Severe or life-threatening (≥ Grade 3) AEs occurred in 26 subjects in the PD Safety Population through Week 24 (Table 25). The most common MedDRA System Organ Class was Investigations (21/26, 81%), followed by Infections and Infestations (5/26, 19%). The most common Grade 3 AEs were neutropenia (12%) and anemia (5%); the most common Grade 4 AE was neutropenia (2%). Importantly, none of the ≥ Grade 3 events were considered related to study drug by the investigators.

Table 25: **≥** Grade 3 Adverse Events in the PD Population through Week 24 (P1093)

Toxicity Grade	System Organ Class	Preferred Term	Baseline Weight Band*				Total (n=75) N (%)
			3-<6kg (n=15)	6-<10kg (n=20)	10-<14kg (n=10)	**≥35kg** (n=24)	
Total with Grade 3 or 4			10 (67)	11 (55)	4 (40)	1 (4)	26 (35)
Total with Grade 3			10 (67)	8 (40)	3 (30)	1 (4)	22 (29)
Total with Grade 4			3 (20)	3 (15)	1 (10)	0	7 (9)
3	Blood and lymphatic system disorders	Anaemia[1]	3	0	1	0	4 (5)
	Gastrointestinal disorders	Diarrhoea	1	1	0	0	2 (3)

	General disorders and administration site conditions	Pyrexia	1	1	0	0	2 (3)
	Infections and infestations	Atypical mycobacterial lymphadenitis	0	1	0	0	1 (1)
		Gastroenteritis	1	0	0	0	1 (1)
		Herpes zoster	0	1	0	0	1 (1)
		Mycobacterium avium complex infection	0	1	0	0	1 (1)
		Pneumonia	0	1	0	0	1 (1)
		Pneumonia adenoviral	0	1	0	0	1 (1)
		Pneumonia parainfluenzae viral	0	1	0	0	1 (1)
		Pneumonia respiratory syncytial viral	0	1	0	0	1 (1)
	Investigations	Blood alkaline phosphatase increased	0	1	0	0	1 (1)
		Blood bicarbonate decreased	0	1	2	0	3 (4)
		Blood bilirubin increased	0	0	0	1	1 (1)
		Blood glucose decreased	1	0	0	0	1 (1)
		Blood phosphorus decreased	1	0	0	0	1 (1)
		Blood potassium increased	0	1	0	0	1 (1)
		Blood sodium increased	1	0	0	0	1 (1)
		Lipase increased	0	0	1	0	1 (1)
		Neutrophil count decreased	6	3	0	0	9 (12)
		Platelet count decreased	1	0	0	0	1 (1)
	Metabolism and nutrition disorders	Dehydration	1	0	0	0	1 (1)
	Nervous system disorders	Lethargy	1	0	0	0	1 (1)
	Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	0	0	0	1 (1)

4	Investigations	Blood bicarbonate decreased	1	0	0	0	1 (1)
		Blood creatinine increased	1	0	0	0	1 (1)
		Blood potassium increased	0	1	0	0	1 (1)
		Lipase increased	0	1	0	0	1 (1)
		Neutrophil count decreased	0	1	1	0	2 (2)
	Nervous system disorders	Seizure	1	0	0	0	1 (1)

Source: Reviewer-generated using ADAE dataset
* There were no Grade 3 or 4 adverse events in the 14 to <20 kg weight band (n=6)
**Three subjects in the 3-<6 kg weight band had both Grade 3 and Grade 4 events
1. Combines "anaemia" and "haemoglobin decreased"

Neutropenia was the most common Grade 3-4 AE reported in Study P1093, occurring in 11 subjects (15%). Only 3 subjects had neutropenia at baseline, but zidovudine was listed as a concomitant medication in 5 (45%) of the 11 subjects and may have played a role.

Anemia was also commonly reported at 5%, with all 3 cases occurring in the 3-<6 kg weight band. All three subjects were anemic at baseline, but their hemoglobin levels continued to decline during the trial, thus a causative role of study drug cannot be excluded. However, these infants may have been anemic for a variety of other reasons including nutritional status, other medications or concomitant illnesses.

Reviewer comment: Decreases in neutrophil count and hemoglobin are discussed further in Section 8.4.6.

As can be seen in Table 25, there was a higher proportion of ≥ Grade 3 AEs in the lower weight bands; however, many of these events were in the Investigations or Infections System Organ Class and there was no clustering of MedDRA Preferred Terms within each weight band to suggest a causative relationship with study drug. The Applicant attributes these findings to background factors including use of multiple concomitant medications and higher rates of infections among younger children in the countries where these participants lived. Subgroup analyses by weight/age are discussed in further detail in Section 8.6.

No new signals were identified in reviewing events after Week 24 and through Week 48.

ODYSSEY

Grade 3 or greater AEs through Week 24 in the Safety Intended DTG population (n=97) were analyzed. Anemia was the most common Grade 3 AE occurring in 2 subjects (3%). The following

Grade 3 AEs occurred in 1 subject each: diarrhea, lower respiratory tract infection, otitis media, pneumonia, and dehydration. All Grade 4 AEs occurred in 1 subject each: neutropenia, hepatitis A, meningitis cryptococcal, and malnutrition.

Reviewer comment: There were fewer ≥ Grade 3 AEs in the ODYSSEY trial possibly due to differences in AE collecting, coding or grading of events.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Study P1093

There were 1,052 total treatment-emergent adverse events (TEAEs) reported in 73/75 (97%) subjects in the PD population through Week 24. TEAEs occurring at a rate ≥ 5% are displayed in Table 26. Similar MedDRA Preferred Terms were combined as described in footnotes.

Table 26: Treatment-emergent Adverse Events in At Least 5% of Subjects (P1093)

System Organ Class	Preferred Term	Baseline Weight Band					Total N=75 (n %)
		3-<6kg (N=15)	6-<10kg (N=20)	10-<14kg (N=10)	14-<20kg (N=6)	**≥35kg** (N=24)	
Blood and lymphatic system disorders	Lymphadenopathy	1	1	0	0	4	6 (8)
Gastrointestinal disorders	Diarrhoea	3	5	0	1	2	11 (15)
	Vomiting[1]	4	7	1	1	1	14 (19)
	Abdominal pain[2]	0	0	0	0	4	4 (5)
General disorders and administration site conditions	Pyrexia[3]	3	7	1	0	3	14 (19)
Infections and infestations	Gastroenteritis	3	2	0	0	1	6 (8)
	Oral candidiasis	0	4	0	0	0	4 (5)
	Otitis media	0	3	0	0	2	5 (7)
	Rash pustular	1	2	0	0	1	4 (5)
	Upper respiratory tract infection	0	4	0	1	0	5 (7)
Investigations	Alanine aminotransferase increased	3	0	0	2	4	9 (12)
	Aspartate aminotransferase increased	1	1	1	1	3	7 (9)
	Blood albumin decreased	8	6	1	1	2	18 (24)
	Blood alkaline phosphatase increased	1	2	5	0	1	9 (12)

	Blood bicarbonate decreased	11	19	7	4	7	48 (64)
	Blood bilirubin increased	0	0	0	0	5	5 (7)
	Blood glucose decreased	1	2	0	1	6	10 (13)
	Blood glucose increased	3	4	1	2	2	12 (16)
	Blood phosphorus decreased	4	2	0	1	3	10 (13)
	Blood potassium increased	6	6	1	3	0	16 (21)
	Blood sodium decreased	9	12	6	4	4	35 (47)
	Blood sodium increased	1	1	0	1	1	4 (5)
	Haemoglobin decreased	13	12	3	2	0	30 (40)
	Lipase increased	3	6	1	0	0	10 (13)
	Neutrophil count decreased	11	9	3	3	4	30 (40)
Metabolism and nutrition disorders	Decreased appetite[4]	2	3	0	0	3	9 (12)
Nervous system disorders	Headache	0	0	1	0	4	5 (7)
Respiratory, thoracic and mediastinal disorders	Cough[5]	3	14	0	5	5	27 (36)
	Dyspnoea	1	2	0	0	1	4 (5)
	Nasal congestion	2	4	0	1	2	9 (12)
	Pharyngeal inflammation	1	4	0	1	0	6 (8)
	Rhinorrhoea	1	7	0	1	2	11 (15)
Skin and subcutaneous tissue disorders	Rash[6]	6	2	0	2	3	13 (17)

Source: Reviewer-generated in JMP using ADAE dataset

1) combines "vomiting" and "infantile vomiting"
2) combines “abdominal pain” and “abdominal pain upper”
3) combines "pyrexia" and "feeling hot"
4) combines “decreased appetite” and “poor feeding infant”
5) combines "cough" and "productive cough" and "upper airway cough syndrome"
6) combines "rash," "rash generalised," "rash maculopapular," "rash papular," and "rash vesicular"

Cough, pyrexia, vomiting, diarrhea, rash, and rhinorrhea were the most common clinical TEAEs reported. The majority of these AEs are expected for this population since childhood infections are common, and frequently include respiratory infections and diarrheal illness for children < 5 years in low to middle-income countries. Many of the abnormal investigations, such as electrolyte abnormalities and low albumin, may have been related to poor nutritional status.

Rash occurred at a rate of 17%, but this included many different types of rash, without a clear pattern to suggest causality. Only two rash events (both in the same subject) were considered possibly related to study drug by the investigator (see Section 8.5.2).

The most common laboratory TEAEs thought to be clinically significant were decreased hemoglobin and decreased neutrophils, both at 40%. The rate of reported decreased bicarbonate (64%) was unusual and unexpected, but there were no reports of clinically significant acidosis. These 3 laboratory TEAEs were also seen more frequently in the lower weight bands. Objective laboratory findings are analyzed in Section 8.4.6.

Reviewer comment: The finding of decreased bicarbonate was unexpected, especially in the absence of associated symptoms or other laboratory abnormalities. While acidosis has been described with other classes of ARV drugs, it has not been described with dolutegravir or INSTIs in general. The finding was further investigated by the protocol team, including consultation with an NIH nephrologist, and determined to be possibly artifact or laboratory error.

In reviewing the events in the PD population after Week 24 through Week 48, 55 subjects experienced TEAEs but no new safety signals were identified.

Adverse Drug Reactions

Adverse drug reactions (assessed by the investigator as being possibly, probably or definitely related to study drug) through Week 24 in the PD population are displayed in Table 27.

Table 27: Adverse Drug Reactions through Week 24 (P1093)

Relationship	Toxicity Grade	Preferred Term	Baseline Weight Band*				Total N=75
			3-<6kg (N=15)	6-<10kg (N=20)	14-<20kg (N=6)	**≥35kg** (N=24)	
POSSIBLY RELATED	1	Alanine aminotransferase increased	1	0	0	0	1
		Blood bicarbonate decreased	1	1	0	1	3
		Blood cholesterol increased	0	0	1	0	1
		Dizziness	0	0	0	1	1
		Haemoglobin decreased	0	1	0	0	1
		Headache	0	0	0	1	1
		Low density lipoprotein increased	0	0	1	0	1

		Muscle spasms	0	0	0	1	1
		Neutrophil count decreased	1	0	0	1	2
		Proteinuria	0	0	0	1	1
	2	Abdominal pain	0	0	0	1	1
		Blood glucose decreased	0	0	0	1	1
		Blood glucose increased	0	1	0	0	1
		Diarrhoea	0	0	0	1	1
		Haemoglobin decreased	1	0	0	0	1
		Neutrophil count decreased	0	0	0	2	2
		Rash	0	0	0	1	1
		Rash pustular	0	1	0	0	1
PROBABLY RELATED	1	Decreased appetite	0	0	0	1	1
		Nausea	0	0	0	1	1
DEFINITELY RELATED	2	Immune reconstitution inflammatory syndrome	0	2	0	0	2

Reviewer generated using ADAE dataset
*There were no drug-related AEs in the 10 to <14 kg weight band (n=10)

Overall, 13 subjects (17%) experienced adverse drug reactions; all were Grade 1 or Grade 2. Adverse drug reactions reported in more than 1 subject were decreased blood bicarbonate (n=3), decreased hemoglobin (n=2), decreased neutrophil count (n=4), and IRIS (n=2).

ODYSSEY

Treatment-emergent AEs occurred in 7 subjects (7%) in the Safety Intended DTG population (n=97) through Week 24. The only TEAE reported in more than 1 subject was anemia in 3 subjects (3%). The following TEAEs occurred in only one subject each: neutropenia, diarrhea, hepatitis A, lower respiratory tract infection, measles, meningitis cryptococcal, otitis media, pneumonia, dehydration, and malnutrition. None of these AEs were thought to be related to study drug by the investigators.

8.4.6. Laboratory Findings

Study P1093

Post-baseline laboratory toxicities were analyzed in the PD population through Week 24. Maximum grade abnormalities were identified for each subject for each parameter. Table 28 displays the ≥ Grade 2 laboratory abnormalities.

Table 28: **≥** Grade 2 Laboratory Toxicities Through Week 24 (P1093)

Parameter		Toxicity Grade	3-<6kg (N=15)	6-<10kg (N=20)	10-<14kg (N=10)	14-<20kg (N=6)	**≥35kg** (N=24)	Total n=75 (N%)
Hematology	Hemoglobin (g/dL)	2	0	4	0	0	0	4 (5)
		3	2	0	1	0	0	3 (4)
	Neutrophils (cells/uL)	2	2	2	2	0	2	8 (11)
		3	6	3	0	0	0	9 (12)
		4	0	1	1	0	0	2 (3)
	Platelets (uL)	2	0	1	0	0	0	1 (1)
		3	1	0	0	0	0	1 (1)
Chemistry	Alanine Aminotransferase (IU/L)	2	2	0	0	0	1	3 (4)
	Aspartate Aminotransferase (IU/L)	2	0	0	0	0	1	1 (1)
	Alkaline Phosphatase (IU/L)	2	0	0	1	0	0	1 (1)
		3	0	1	0	0	0	1 (1)
	Bilirubin (mg/dL)	2	0	0	0	0	2	2 (3)
		3	0	0	0	0	1	1 (1)
	Albumin (g/dL)	2	1	0	0	0	0	1 (1)
	Bicarbonate (mEq/L)	2	6	10	4	2	0	22 (29)
		3	0	1	2	0	0	3 (4)
		4	1	0	0	0	0	1 (1)
	Creatinine (mg/dL)	4	1	0	0	0	0	1 (1)
	Fasting Glucose (mg/dL)	2	0	0	0	1	0	1 (1)
	Glucose (mg/dL)	2	0	2	0	0	3	5 (7)
		3	1	0	0	0	0	1 (1)
	Lipase (IU/L)	2	2	3	0	0	0	5 (7)
		3	0	0	1	0	0	1 (1)
		4	0	1	0	0	0	1 (1)
	Phosphate (mg/dL)	2	0	0	0	0	1	1 (1)
		3	1	0	0	0	0	1 (1)
	Potassium (mEq/L)	2	1	0	0	0	0	1 (1)

		3	0	1	0	0	0	1 (1)
		4	0	1	0	0	0	1 (1)
	Sodium (mEq/L)	2	1	1	1	0	0	3 (4)
		3	1	0	0	0	0	1 (1)
Urine	Protein	2	1	0	0	0	0	1 (1)
	Erythrocytes	2	0	0	1	0	2	3 (4)

Reviewer generated using ADLB dataset

The most commonly observed laboratory toxicity was decreased bicarbonate, reported in 35% of subjects overall. Most reports of decreased bicarbonate were Grade 2 and seen more frequently in the lower weight bands (see Figure 1 and discussion below). Decreased neutrophil count was also common at 25%, with higher rates in the lower weight bands.

Grade 3-4 laboratory toxicities that occurred in more than 1 participant were decreased neutrophils (n=11), decreased bicarbonate (n=4), decreased hemoglobin (n=3), increased lipase (n=2), and increased potassium (n=2). There was one case of a Grade 4 increase in serum creatinine in a 5-month-old male infant in the 3-<6 kg weight band, but there were no associated signs or symptoms and creatinine returned to baseline within 6 days without intervention; the increase in serum creatinine was not thought to be related to study drug.

Reviewer comment: Many of the observed laboratory toxicities could have been related to underlying disease, concomitant medication, or nutritional status. The decreased bicarbonate was likely artifact or laboratory error, as previously noted. The Applicant states that subjects with ≥ Grade 3 decreased neutrophils all had risk factors including Black/African-American race and location in sub-Saharan Africa (higher risk of poor nutrition and infections). There was also a higher use of lopinavir/ritonavir, trimethoprim-sulfamethoxazole and zidovudine in the lower weight bands, all of which could lead to neutropenia. The three subjects with Grade 3 decreased hemoglobin all had low hemoglobin levels at baseline and were taking trimethoprim-sulfamethoxazole; their anemia was not attributed to study drug.

The following laboratory parameters were further analyzed through Week 24 in the PD population: hemoglobin (Hb), white blood cell count (WBC), neutrophil count, platelets, AST, ALT, albumin, total bilirubin, bicarbonate, potassium, creatinine, lipase, and amylase. Median values were compared at baseline and Week 24. These analyses were limited by the varying and often small sample sizes at each time point, precluding meaningful interpretation.

Hematology

There were no clinically meaningful trends in leukocyte or neutrophil counts over time through Week 24 (data not shown). There were no outliers with a low WBC or neutrophil count. The median WBC count was 8.8 $x10^9$/L at baseline and 7.7 $x10^9$/L at Week 24; the median

neutrophil count was 2602 cells/µL at baseline and 2230 cells/µL at Week 24.

Similarly, hemoglobin and platelet counts remained stable through Week 24 (data not shown), with no outliers or significant changes in median values from baseline to Week 24.

In conclusion, hematology parameters remained stable in the PD Safety Population as whole over the first 24 weeks, despite commonly reported laboratory-related AEs of neutropenia and anemia.

Chemistry

Although decreased sodium was a commonly reported TEAE (47%), these appear to have been isolated events as sodium values overall remained stable through Week 24 (data not shown). The median sodium level was 138 mEq/L at both baseline and Week 24. There were 2 outlier subjects with values as low as 129 mEq/L. One of these subjects (Subject (b) (6)), who represented 3 of the 4 outlier values, had multiple SAEs involving viral illnesses and was likely dehydrated during these episodes.

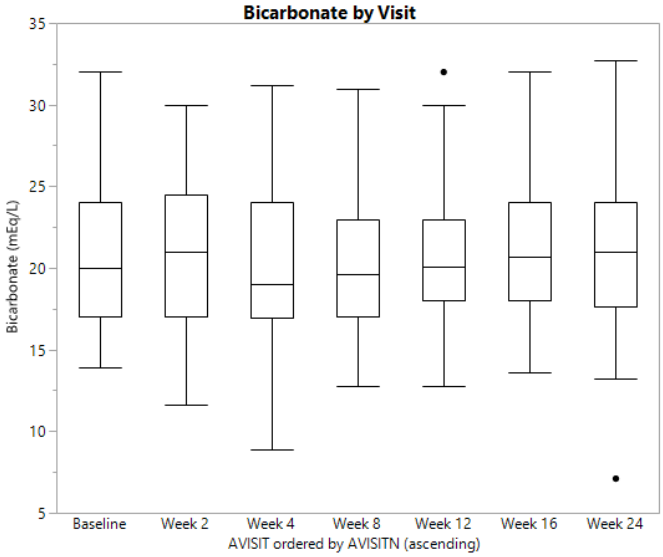
Potassium levels also remained stable over time (data not shown), with baseline and Week 24 median values of 4.6 mEq/L and 4.5 mEq/L, respectively. There were 2 outliers with high potassium values (range 6-7 mEq/L), one at Week 4 and one at Week 16, but these were isolated findings not associated with clinical events and may have represented hemolyzed samples.

Serum Bicarbonate

Median serum bicarbonate levels remained stable through Week 24 (see Figure 1). The median serum bicarbonate level was 21 mEq/L at both baseline and Week 24. There was one outlier with a low bicarbonate at Week 24. Subject (b) (6), a 3-month-old female in the 3-<6 kg weight band, had a Grade 4 bicarbonate level of 7.1mEq/L on Day 173; however, a repeat level on Day 183 was 16.7 mEq/L. There was no blood gas done on this subject and no narrative provided.

Low bicarbonate was a commonly reported laboratory-related AE, but the overall trend in objective laboratory values was stable over the first 24 weeks. The Applicant reported that decreased bicarbonate was an unexpected finding, especially without trends in associated symptoms or other laboratory abnormalities. It was assessed by the protocol team and a nephrologist from NIH as possibly being artifact or laboratory error, which is a reasonable explanation.

Figure 1: Serum Bicarbonate Values Over Time (P1093)



Source: Reviewer-generated using ADLB dataset

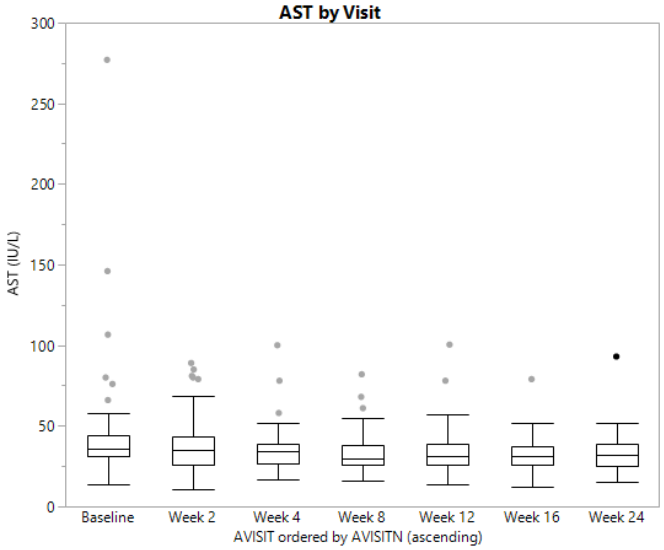
Creatinine

Serum creatinine remained stable through Week 24. There were no post-baseline outliers with elevated creatinine. Median creatinine was 0.32 mg/dL at baseline and 0.31 mg/dL at Week 24.

Liver Function Tests

Aspartate aminotransferase (AST) levels remained stable overall through Week 24. There were outliers at each time point, but the number of outliers was highest at baseline (6) and decreased over time through Week 24 (see Figure 2). Post baseline, outliers had only mild AST elevation up to approximately 100 IU/L.

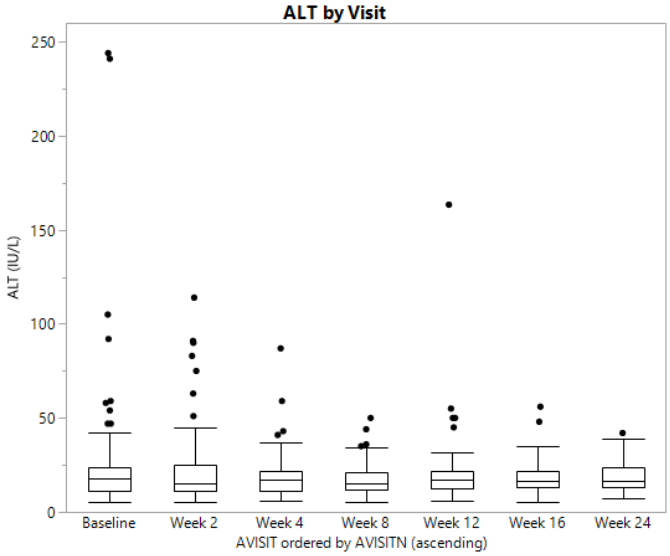
Figure 2: Aspartate Aminotransferase (AST) Values Over Time (P1093)



Source: Reviewer-generated using ADLB dataset

Alanine aminotransferase (ALT) levels followed a similar pattern with overall stable values and decreasing numbers of outliers over time (see Figure 3). There were 9 outliers at baseline which decreased to 1 by Week 24. The highest post-baseline ALT value was an isolated Grade 2 elevation to 163 IU/L at Week 12 in Subject (b) (6), a 3-month-old female in the 3-<6 kg weight band; however, this was her only elevated value.

Figure 3: Alanine Aminotransferase (ALT) Values Over Time (P1093)

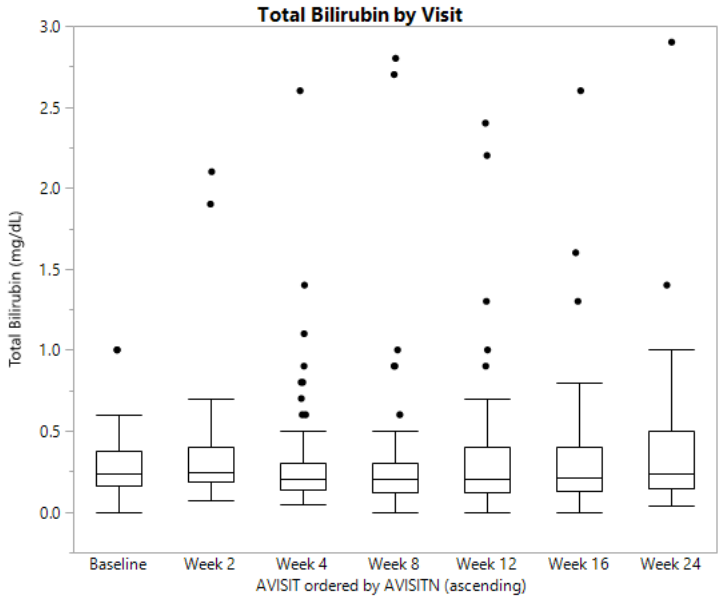


Source: Reviewer-generated using ADLB dataset

Reviewer comment: Most of the outliers shown above had mild elevations in AST and ALT that were not clinically significant. It is unlikely that these elevations were due to study drug as they did not persist or worsen over the course of the study.

Review of total bilirubin values did not show any clinically significant changes from baseline through Week 24 (see Figure 4). Median total bilirubin was 0.27 mg/dL at baseline and 0.26 mg/dL at Week 24. There were 11 subjects, ages 10-17 years and all in the >35 kg weight band, with outlier values (highest value 2.9 mg/dL). It is unclear why this finding was limited to older subjects; however, at these low levels these findings are unlikely to be clinically significant. Atazanavir use was minimal in this trial and there were no reports of hemolysis or jaundice.

Figure 4: Serum Total Bilirubin Values Over Time (P1093)

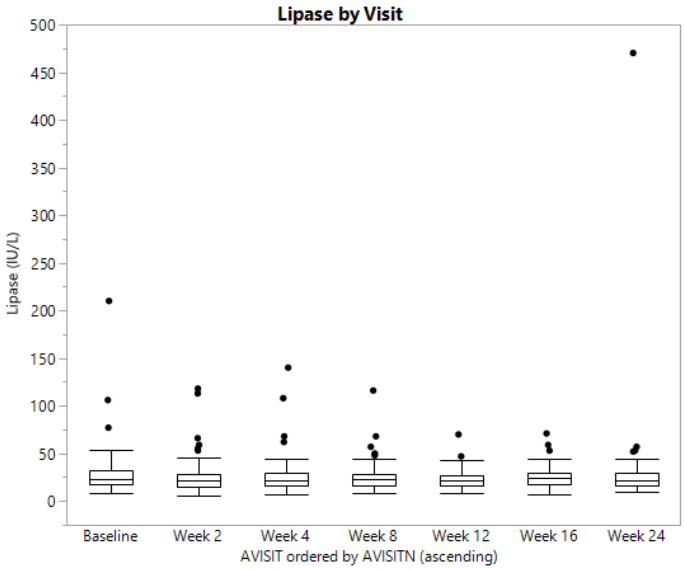


Source: Reviewer-generated using ADLB dataset

Serum albumin levels remained stable through Week 24 (data not shown). The median albumin level was 4.1 g/dL at baseline and 4.3 g/dL at Week 24. There were several subjects with low outlier values, but these were not sustained.

Lipase values remained stable through Week 24. There were several outliers with mild elevations, but there was one significant outlier at Week 24 (see Figure 5). Subject (b) (6) was a 1-year-old female in the 6-<10 kg weight band who had a Grade 4 lipase elevation at 470 IU/L at Week 24. She also had elevated amylase at 331 IU/L, but no reported clinical events or sequelae associated with these elevations, and the values improved without intervention. Amylase was rarely collected in this trial, but other than this particular outlier at Week 24, there were no clinically meaningful elevations in amylase or lipase, or any reports of pancreatitis.

Figure 5: Serum Lipase Values Over Time (P1093)



Source: Reviewer-generated using ADLB dataset

ODYSSEY

Many of the laboratory values in the submitted laboratory dataset were not given a toxicity grade, making it difficult to conduct cross-trial comparisons. The dataset, however, did provide a maximum treatment-emergent toxicity grade at Week 24, and a toxicity table was constructed for ≥ Grade 2 laboratory abnormalities in these subjects (Table 29).

Table 29: Maximum Grade Laboratory Toxicities (≥ Grade 2) Through Week 24 (ODYSSEY)

Parameter	Toxicity Grade	Baseline Weight Band*						Total n=97 (N%)
		6-<10kg (N=10)	10-<14kg (N=5)	14-<20kg (N=31)	20-<25kg (N=28)	25-<30kg (N=16)	30-<40kg (N=6)	
Alkaline phosphatase (IU/L)	2	0	0	1	0	0	0	1 (1)
Alanine aminotransferase (IU/L)	2	0	0	1	0	0	0	1 (1)
	3	0	0	0	1	0	0	1 (1)
	4	0	0	1	0	0	0	1 (1)
Aspartate aminotransferase (IU/L)	2	0	0	2	0	0	0	2 (2)
	3	0	0	0	1	0	0	1 (1)
	4	0	0	1	0	0	0	1 (1)
eGFR (ml/min/1.73m^2)	2	2	1	14	8	4	1	30 (31)
	3	3	1	5	6	3	3	21 (22)
	4	1	0	2	3	1	1	8 (8)

Hemoglobin (g/dL	2	1	0	3	1	0	1	6 (6)
	3	1	1	0	0	0	0	2 (2)
Low-density lipoprotein (mmol/L)	2	0	0	0	0	0	1	1 (1)
Neutrophils (10^9/L)	2	0	0	0	1	1	1	3 (3)
	3	0	0	1	2	0	0	3 (3)
	4	0	1	0	0	0	0	1 (1)
Platelets (10^9/L)	3	0	0	0	1	0	0	1 (1)

Source: Reviewer-generated using ADAE dataset
*There were no ≥ Grade 2 laboratory toxicities in the 3 to <6 kg weight band (n=1)

Overall, there were no new laboratory toxicities in the ODYSSEY trial not seen in Study P1093, except for the large number of subjects with decreased eGFR. In these subjects, eGFR decreases were reportedly not associated with any clinical events. The range was wide (33.5-216.6 mL/min/1.73m^2) but all values were ≥ 50 mL/min/1.73m^2, except for 1 subject (Subject (b) (6)) who had an isolated value of 33.5 mL/min/1.73m^2 that may have been a laboratory error. Per the Applicant, the variability in eGFR was likely due to factors such as growth of pediatric subjects, local assay variability, malnutrition or inhibition of transporters (e.g., OCT2).

It is also worth noting that while there was a high number of subjects in Study P1093 with decreased serum bicarbonate, the ODYSSEY trial did not report such findings. This further supports the hypothesis that the decreased bicarbonate reported in Study P1093 may have been spurious. Conversely, there were no reports of decreased eGFR in Study P1093.

8.4.7. Vital Signs

Study P1093

There were no reported clinically significant changes in vital signs.

ODYSSEY

Vital signs were not part of the clinical assessments described in the study protocol (see Section 8.3.3).

8.4.8. Electrocardiograms (ECGs)

Electrogram assessments were not part of the regular schedule of assessments in either trial. There were no cardiac adverse events reported through Week 24 in either trial.

8.4.9. QT

A thorough QT study was done for the original dolutegravir NDA and did not reveal a significant QT prolongation effect for DTG.

8.4.10. Immunogenicity

No immunogenicity studies were done.

8.5. Analysis of Submission-Specific Safety Issues

Based on previous experience with DTG and INSTIs, the following AESIs were identified for both trials: IRIS, hypersensitivity and rash, hepatobiliary disorders, psychiatric disorders including suicidality, gastrointestinal disorders, musculoskeletal disorders, and renal disorders. In addition, outcomes in subjects who became pregnant during study are described due to reports of neural-tube defects in infants born to women taking dolutegravir (see Section 3.1).

8.5.1. Immune Reconstitution Inflammatory Syndrome (IRIS)

Study P1093

The IRIS events reported through Week 24 are summarized in the table below. All subjects had recently experienced significant decreases in HIV-1 RNA viral load.

Table 30: IRIS Events through Week 24 (P1093)

Subject ID	Baseline Weight Band	Study Day	Associated Symptoms/ Diagnoses	SAE (Y/N)	Toxicity Grade	Relationship to Study Drug
(b) (6)	3-<6kg	14	Fever, lymphadenopathy, vomiting, diarrhea, cough, BCG scar inflammation	Y	3	Related
	3-<6kg	34	Abscess	N	2	Not related
	6-<10kg	34	Mycobacterium avium complex, nasopharyngitis	Y	2	Related
	6-<10kg	36	Herpes zoster and otitis media	Y	2	Related

Reviewer-generated
Abbreviations: Bacillus Calmette-Guerin

These cases were all likely related to ART in general, which includes study drug. Study drug was continued in all cases and the subjects recovered from IRIS.

ODYSSEY

No cases of IRIS were reported.

8.5.2. Hypersensitivity and Rash

Study P1093

There were no cases of hypersensitivity reactions or serious skin reactions such as Stevens Johnson syndrome. Three subjects had the following Grade 3 events: urticaria, angioedema and alopecia, none of which were considered related to study drug. In addition, a 12-year-old female (Subject (b) (6)) developed a Grade 2 rash two weeks after starting study drug, which was considered possibly related to study drug. The rash was not described further. She was also started on atazanavir (ATV), RTV and tenofovir disoproxil fumarate (TDF) on the same day and had been on emtricitabine (FTC) previously. Her rash had multiple recurrences and the subject was diagnosed with acrodermatitis and atopic dermatitis.

Reviewer comment: The rash event in Subject (b) (6) is confounded by multiple concomitant drugs initiated at the same time. The diagnosis of atopic dermatitis provides another plausible etiology.

ODYSSEY

There were no hypersensitivity or serious skin reactions. One 9-year-old female (Subject (b) (6)) developed a Grade 2 generalized macular rash on Day 25. Other concomitant medications included abacavir (ABC), 3TC, and trimethoprim-sulfamethoxazole. She improved with a 6-day course of prednisolone and no changes were made to study drug. This was considered possibly related to study drug by the investigator.

Reviewer comment: Although DTG as a cause of rash cannot be excluded given the temporal relationship, the above case is confounded by multiple concomitant medications that may also cause rash.

8.5.3. Hepatobiliary Disorders

Study P1093

There were 6 subjects with hepatomegaly and 1 subject with ocular icterus. None of these AEs were thought to be related to study drug.

ODYSSEY

There were no hepatobiliary AEs aside from two subjects with acute hepatitis A who are discussed in Section 8.4.3.

8.5.4. Psychiatric Disorders Including Suicidality

Study P1093

Overall, 15 participants (9%) reported psychiatric AEs through Week 24 in the AT Population (N=159); only 8 were in the PD population.

Three subjects had Grade 3 or 4 psychiatric SAEs; none of the events were considered related to study drug and none of these 3 subjects were in the PD population.

- Subject (b) (6) was a 9-year-old male with an SAE of abnormal behavior. Abnormal behaviors were reported at each visit from Week 108 to Week 180 and included aggression, violence, destructive behavior and running away. This subject also had post-traumatic stress disorder (PTSD), depression, attention-deficit/hyperactivity disorder (ADHD), and a history of similar behaviors since age 3.
- Subject (b) (6) was a 6-year-old male with the SAE of suicidal ideations. At Week 168, he reported suicidal ideations, insomnia and PTSD. Reportedly, this child had a history of trauma including loss, grief, and international adoption.
- Subject (b) (6) was a 17-year-old female with the SAE of suicide attempt. At Week 120, pregnancy, intentional overdose, suicide attempt and depression were reported. She had a long history of depression.

There were also 12 Grade 1-2 events in the AT Population, most commonly anxiety, ADHD, depression, irritability, major depression and PTSD. None of these events were thought to be related to study drug except in 1 subject who had insomnia at Week 40 and Week 168.

Reviewer comment: Many of these psychiatric events occurred in subjects with history of psychiatric disorders. In addition to the stress of dealing with a chronic disease, many subjects were also struggling with other issues such as personal loss and pregnancy. There are no distinct patterns in these AEs that would suggest study drug as a causative factor.

ODYSSEY

There were no psychiatric AEs reported in the ODYSSEY trial.

8.5.5. Gastrointestinal Disorders

Study P1093

Over half (52%) of the AT population reported a gastrointestinal (GI) event. Most events were Grade 1 or 2, and none led to discontinuation of study drug. The most common GI events were abdominal pain, diarrhea, nausea, decreased appetite, gastroenteritis, and vomiting. There was one SAE of diarrhea (Subject (b) (6)), which was discussed in Section 8.4.2. Other ≥ Grade 3 AEs are displayed in Table 31; none of these were considered related to study drug by the investigators.

Table 31: ≥ Grade 3 GI Adverse Events in the All Treated Population (P1093)

Subject ID	Baseline Weight Band	Age/Sex/Cohort/ Formulation	Preferred Term(s)	Grade	Comments
(b) (6)	6-<10kg	5y/M/III-DT	Diarrhea	3	SAE; see Section 8.4.2
	3-<6kg	10m/F/IV-DT	Gastroenteritis	3	SAE; see Section 8.4.2
	3-<6kg	6m/F/IV-DT	Gastroenteritis; Diarrhea	5; 4	Death; see Section 8.4.1
	3-<6kg	10w/M/V-DT	Gastroenteritis	3	Not considered related
	6-<10kg	12m/F/IV (granule)	Gastroenteritis; Diarrhea	3; 3	Not considered related
	≥35kg	15y/F/I (FCT)	Gastritis; Abdominal pain	3; 3	Not considered related
	20-<25kg	11y/M/IIA (FCT)	Stomatitis necrotizing	3	Not considered related
	25-<35kg	15y/F/I (FCT)	Abdominal pain	3	Not considered related

Source: Adapted from clinical study report, Module 5.3.5.2
Abbreviations: DT = dispersible tablet; FCT = film-coated tablet; SAE = serious adverse event

Reviewer comment: Diarrhea is a known AE associated with DTG, but a causal relationship could not be established in the majority of cases due to multiple comorbidities and concomitant medications.

Gastrointestinal AEs in the PD population through Week 24 were analyzed by formulation as well, as displayed in Table 32.

Table 32: Selected Gastrointestinal AEs by Formulation in PD Population through Week 24 (P1093)

Adverse Event	Number (%) of Subjects	
	Dispersible Tablets (n=49)	Film-Coated Tablets (n=24)
Vomiting	13 (17)	1 (1)
Diarrhea	9 (12)	2 (3)
Gastroenteritis	5 (7)	1 (1)
Abdominal pain	0	4 (5)
Decreased appetite	6 (8)	3 (4)

Source: Reviewer-generated using ADAE dataset

The cases of vomiting did not include information regarding timing of onset in relation to study drug administration, which limits determination of causality; however, none of the events in the DT groups were considered related to study drug by the investigators. Indeed, only 3 GI events (abdominal pain, diarrhea and nausea) were considered related to study drug, and all occurred in adolescent subjects receiving the FCT formulation.

The higher rates of vomiting and diarrhea/gastroenteritis in the DT population may be related to extrinsic factors related to younger age. All of these participants were younger children, and most were from low to middle-income countries, as previously noted. The majority of AEs in both Study P1093 and ODYSSEY were those expected in this population, and frequently included respiratory infections and diarrheal illnesses for children < 5 years. While sucralose is included in the DT formulation, the negligible amount ((b) (4)% per tablet) is unlikely to cause clinically significant GI symptoms. It is also worth noting that U.S. subjects dosed with the DT formulation did not have reports related to GI events through Week 24, although the sample size was small (n=2). No other pattern in the proportion of GI events was noted across enrollment weight bands.

No additional safety concerns were identified through review of safety data by formulation.

ODYSSSEY

There was one event of Grade 3 diarrhea (with dehydration) in a 1-year-old male (Subject (b) (6)) at Day 14. The diarrhea resolved after 3 days without change to study drug and was not considered to be related.

8.5.6. Musculoskeletal Disorders

Study P1093

There were 26 subjects (16%) in the AT Population who experienced musculoskeletal AEs. There were no SAEs and only one Grade 3 event, described only as "pain in extremity," that was not considered related to study drug. The most common Grade 1 and 2 events were arthralgia, back pain, musculoskeletal chest pain, musculoskeletal pain and pain in extremity. There was only one subject who had a musculoskeletal AE (Grade 1 muscle spasm) thought to be related to study drug, but no further information was provided. Musculoskeletal AEs were more common in the higher weight band groups (>14kg). There was 1 report of elevated serum creatine kinase, but this was not associated with any musculoskeletal events.

Reviewer comment: Musculoskeletal complaints are not uncommon in older children and adolescents and are unlikely to be related to study drug given the lack of patterns observed.

ODYSSEY

There were no musculoskeletal AEs reported.

8.5.7. Renal Disorders

Study P1093

There were no renal SAEs or ≥Grade 3 AEs. Laboratory data are discussed in Section 8.4.6.

ODYSSEY

There was one 12-year-old male (Subject (b) (6)) who developed a Grade 4 AE of nephropathy 406 days after starting dolutegravir. He was hospitalized for cryptococcal meningitis and was being treated with amphotericin B and fluconazole. He developed hypernatremia (188.3 mmol/L) and hyperkalemia (K = 8.62 mmol/L). Amphotericin B was discontinued but ARV was continued, and he was treated with kayexalate and calcium gluconate. The nephrotoxicity was considered resolved after 3 days.

Reviewer comment: This subject's electrolyte abnormalities were likely secondary to amphotericin B treatment as they resolved upon discontinuation of that drug.

Decreases in eGFR observed in this trial are discussed in Section 8.4.6.

8.5.8. Pregnancy

Study P1093

There were 3 pregnancies reported as of the cut-off date of April 30, 2019. All participants were in the ≥35 kg weight band of the PD population. Subject (b) (6) was a 12-year-old female who had been taking dolutegravir for almost 4 years; she discontinued dolutegravir and her pregnancy was terminated. Subject (b) (6) was a 17-year-old female who had been taking DTG for over 2 years and discontinued dolutegravir when she was found to be pregnant. She gave birth to a healthy infant. Subject (b) (6) was a 13-year-old female who was found to be pregnant at the Week 144 visit. Although she had reported noncompliance with ARV, she continued dolutegravir "by private prescription" throughout the pregnancy and gave birth to a healthy infant.

ODYSSEY

There was 1 pregnancy reported in the ODYSSEY trial. Subject (b) (6) was a 17-year-old female who became pregnant 606 days after starting DTG. She discontinued DTG. A live birth was reported after the cut-off date of February 28, 2019, but no other details were provided.

Reviewer comment: No congenital anomalies were reported among the 3 live births in subjects taking DTG at any point in their pregnancy. This is a small sample size, however, with limited information provided regarding the pregnancies or births, therefore no conclusions can be drawn from these trials with respect to DTG effects on pregnancy outcomes.

8.6. Safety Analyses by Demographic Subgroups

As previously noted, although the numbers are small, there was a trend towards more AEs in the lower weight bands, which also encompasses the younger subjects and subjects taking the DT formulation by default.

The Applicant's analysis of the AT population showed higher frequencies of SAEs and ≥ Grade 3 AEs (neutropenia, anemia, decreased bicarbonate, decreased sodium) in the younger subjects (weighing <14 kg) compared to older participants, which was also noted in the FDA analysis of the PD population. They saw a similar pattern when analyzing by formulation or weight band at the time of AE. They did not find that higher doses within an age cohort were associated with higher incidence of AEs.

The SAEs were mostly in the Infections and Infestations System Organ Class, which is consistent with common pediatric infections, such as upper respiratory tract infections and gastroenteritis, that occur more frequently in younger children. They also note that diarrhea is a known adverse drug reaction of dolutegravir.

The Applicant attributed the higher rate of cytopenias in the lower weight bands to subject factors such as baseline anemia, concomitant medications (e.g., ZDV, trimethoprim-sulfamethoxazole, LPV/RTV), Black/African-American race, and higher risk of poor nutrition and infectious diseases based on geographical location. The decreased bicarbonate was thought to be laboratory error.

Younger subjects also had slightly higher overall drug exposures. Exposure-response analyses by the FDA Clinical Pharmacology review team, however, did not show a relationship between higher drug exposures and increased risk of adverse events (see the Clinical Pharmacology review for further details). In addition, at the Agency's request, the Applicant conducted analyses in subjects < 12 years of age comparing those in the lowest quartile of AUC and C_{max} exposures to those in the highest quartiles and did not find any differences with respect to type or frequency of AEs.

By way of providing context for the disparity observed in the lower weight bands with respect to SAEs and ≥ Grade 3 AEs, the Applicant compared these findings to another trial in a similar pediatric HIV population. The IMPAACT P1066 trial was conducted in HIV infected pediatric participants from 4 weeks of age treated with a raltegravir-based regimen had a similarly higher proportion of SAEs and ≥ Grade 3 AEs in younger (i.e., lower weight band) cohorts compared to older participants (i.e., higher weight bands). Therefore, the proportions of these events in P1066 and P1093 are similarly raised in participants under 2 years of age. This pattern of more severe/serious events in the lowest weight categories may be due to relevant background factors such as higher use of concomitant medications but is most likely because children under 2 years have the highest background risk of morbidity and mortality due to diarrhea or pneumonia in the countries where these trials were conducted.

There were no subjects in the 20-<35 kg weight bands in the PD population of Study 1093. To supplement the above analyses, safety data through Week 24 were reviewed for subjects in these weight bands (n=26) in the AT population. Eleven of these subjects received the oral granule formulation ([redacted](b) (4)) and most were treated with doses lower than the currently proposed dose of 50 mg daily for this weight band (FCT dose range: 25-70 mg daily; oral granule dose range: 16-44.8 mg daily). The one subject in this group who received 70 mg once daily had AEs relating to pre-existing asthma. Overall, there were no differences in safety for this weight band compared to the others.

Reviewer comment: In the AT population (n=159), the only AEs occurring at rates ≥ 5% were blood bicarbonate decreased (6%), blood glucose decreased (6%), blood sodium decreased (5%) and cough (8%). The safety profile was overall similar to that described for the PD Population, thus it is reasonable to extrapolate safety for the 20-<35 kg weight band to the PD Population.

8.7. Specific Safety Studies/Clinical Trials

No specific safety studies were done.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There is no known human carcinogenicity of dolutegravir. Nonclinical carcinogenicity studies in mice and rats did not show increases in the incidence of neoplasms at dolutegravir exposures 10-15 times the exposure of the maximum recommended dose in humans.

8.8.2. Human Reproduction and Pregnancy

See Section 8.5.8 for discussion of pregnancies observed during the submitted trials.

8.8.3. Pediatrics and Assessment of Effects on Growth

Analyses by the Applicant through Week 48 did not reveal any concerning trends with regards to weight, height or BMI changes in pediatric subjects > 4 weeks to 18 years of age in Study P1093. Likewise, there were no concerning trends in weight change from baseline in the ODYSSEY trial. In both trials, the mean weights increased from baseline over time, as expected in growing children.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Dolutegravir is not expected to have potential for drug abuse, withdrawal or rebound. There were no examples of acute or chronic overdosing in either submitted trial.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Postmarket safety concerns associated with dolutegravir use have included neural-tube defects in babies born to women taking dolutegravir during pregnancy, depression and suicidal behaviors, myalgia, arthralgia, anxiety, acute hepatic failure and increased weight. The Applicant's review of the literature on DTG use in pediatric patients revealed neutropenia, neuropsychiatric disorders (depression, suicidality, anxiety, sleep disturbance), and abdominal pain as potential safety concerns. The most common (reported in 3 or more individuals) preferred terms reported in postmarketing were off-label use, product use issue, headache, diarrhea, fatigue, exposure during pregnancy and vomiting. Overall, these findings were expected based on the known safety profile of the drug.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety profile of dolutegravir in pediatrics is expected to be consistent with the findings of this safety review and the postmarket experience described above.

8.9.3. Additional Safety Issues From Other Disciplines

As previously discussed, the difference in bioavailability between the DT and FCT dose forms could potentially lead to medication errors and overdosing if the DT formulation is substituted for the FCT formulation. The effects of such overdosing errors are not known. Labeling will include a warning that the two formulations are not substitutable and that doses should be adjusted for patients switching from one form to the other.

8.10. Integrated Assessment of Safety

Safety results from the P1093 and ODYSSEY trials were not pooled due to differences in study design and data collection; however, comparison of the major safety outcomes did not reveal any new safety signals in either trial. Laboratory concerns such as decreased neutrophils were unlikely to be related to study drug but can be monitored in clinical practice with routine bloodwork. There were some instances in which the study findings did not align between the two trials; decreased bicarbonate was a common finding in Study P1093 (although it was thought to be a laboratory error) and was not noted in ODYSSEY. Conversely, there were 59 subjects in ODYSSEY who had a decreased eGFR, but there were no clinical renal events, and decreased eGFR was not a concern in P1093.

There were more AEs in the lower weight bands, which is discussed in Section 8.6, and may have been related to more common pediatric infections and other extrinsic subject factors.

There were no adverse pregnancy outcomes noted in these trials, however, the sample size of live births was very limited (n=3).

Although the effects of overdose are not known, there is a potential for overdose if the incorrect dosage form is prescribed (e.g., 25 mg DT instead of 25 mg FCT). Providers should be vigilant when prescribing dolutegravir to ensure that the correct dose and dosage form are communicated to the pharmacist and patient/caregiver. The Applicant intends to address this concern with labeling, healthcare provider education, and a modified name for the DT formulation (TIVICAY PD).

Overall, dolutegravir had a favorable safety profile that was comparable to adults. Approval of dolutegravir would add another safe option to the treatment armamentarium for pediatric patients with HIV-1 infection.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was conducted. There were no external consultations.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Below is a summary of major changes to the Prescribing Information negotiated with the Applicant; refer to final approved labeling for full details.

- Section 2: Dosage and Administration
  - Section 2.3: Pediatric Patients
    - New dosing recommendations were added for the new dispersible tablet for oral suspension and dosing recommendations for the FCT in children weighing ≥ 14 kg were updated, with separate tables provided for each dosage form.
    - A recommendation was added that patients weighing <20 kg should use the DTs whenever possible and that tablets (if swallowed instead of dissolved) should be taken one at a time to reduce the risk of choking.
    - The dosing recommendation for the DT was simplified to 15 mg QD for all patients weighing 6 to <10 kg, (b) (4).
- Section 5: Warnings and Precautions
  - Added a new warning to emphasize that the two oral dosage formulations are not bioequivalent and that underdosing or overdosing could lead to loss of therapeutic effect or potential adverse reactions, respectively, if the dosage formulations are substituted for one another.
- Section 6: Adverse Reactions
  - Safety data from Study P1093 were added. The ODYSSEY trial was not included as it did not add any new safety information beyond that reported for P1093.
- Section 8: Use in Specific Populations
  - Section 8.4: Pediatric Use
    - Added the basis for pediatric approval, namely safety and PK data from Study P1093 and PK data from 2 PK sub-studies of the ODYSSEY trial.
- Section 12: Clinical Pharmacology
  - Added PK data from the two pediatric trials.
- Section 14: Clinical Studies
  - Section 14.3: Pediatric Subjects

        - Added description of Study P1093 and its results, including virologic and immunologic outcomes at Weeks 24 and 48 for the PD Efficacy Population (n=58).
- Section 17: Patient Counseling
    - Added information to advise patients/caregivers that the two oral dosage forms are not bioequivalent and about the need to adjust doses when switching between the two formulations.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS for dolutegravir was not deemed necessary based on this review.

12. Postmarketing Requirements and Commitments

No additional postmarketing requirements (PMRs) or postmarketing commitments (PMCs) were recommended. The results of these submissions are adequate to fulfill PREA PMRs 3091-1 and 3091-2 (see Section 3.1), as agreed to by the Pediatric Review Committee (PeRC) at a meeting held on April 28, 2020. Outstanding pediatric PMRs (3091-4 and 3091-5) pertain to trials evaluating safety, PK and antiviral activity of dolutegravir in HIV-1 infected pediatric subjects weighing at least 20 kg who are INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.

These submissions also fulfill Study 1 (b) (4)
(See Section 3.1), but Study 2 (a multiple-dose PK and safety evaluation of dolutegravir in pediatric patients from birth to less than 4 weeks of age who are HIV-exposed and at-risk of infection) is outstanding.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): P1093

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 291		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 18		
Is an attachment provided with the reason:	Yes ☒ "Clinical investigator not located"	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): ODYSSEY

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 11		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

PETER S MIELE
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