Clinical Review and Cross Discipline Team Leader Summary Review

Date	June 14, 2023
From	Virginia Long, DO, MS, FAAP Medical Officer Division of Antivirals Primary Reviewer Timothy Jancel, PharmD, MHS Clinical Reviewer Division of Antivirals
Through	Natalie Pica, MD, PhD Acting Team Lead Division of Antivirals
Subject	Clinical Review

Supplemental NDA #	NDA 205551/S-031 (TRIUMEQ) NDA 215413/S-002 (TRIUMEQ PD)
Applicant	ViiV Healthcare
Date of Submission	December 15, 2022
PDUFA Goal Date	June 15, 2023
Proprietary Name/ Established (USAN) names	TRIUMEQ, TRIUMEQ PD
Approved dosage forms / Strength	TRIUMEQ (tablets for oral use): ▪ 600 mg ABC, 50 mg DTG, and 300 mg 3TC TRIUMEQ PD (tablets for oral suspension): ▪ 60 mg ABC, 5 mg DTG, and 30 mg 3TC
Applicant Proposed Indication(s)/Populations(s)	TRIUMEQ and TRIUMEQ PD are indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients aged at least 3 months and weighing at least 6 kg.
Applicant Proposed Dosing Regimen(s)	Weight based dosing (see Section 12 Labeling)
Recommendation on Regulatory Action	Approval

Table of Tables 3
Table of Figures 3
1. Benefit-Risk Integrated Assessment 4
2. Background 7
2.1 Introduction 7
2.2 Analysis of Condition 7
2.3 Available Pediatric Treatment Options 8
2.4 Important Safety Issues With Consideration to Related Drugs 9
2.5 Product Information 9
2.6 Summary of Pre-submission Regulatory Activity Related to Submission 11
2.7 Review Approach for Current Submission 12
3. Nonclinical Pharmacology/Toxicology 13
4. Clinical Pharmacology 13
5. Clinical Virology 14
6. Clinical/Statistical- Efficacy 14
6.1. Study design and protocol summary 14
6.2 Results 15
6.2.1 Antiviral (virologic) response 16
6.2.2 Confirmed Virologic Failure 16
7. Safety 15
7.1 Approach to Safety Review 16
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 16
7.1.2 Categorization of Adverse Events 16
7.1.3 Pooling of Data Across Studies to Estimate and Compare Incidence 16
7.2 Safety Findings 16
7.2.1 Treatment Emergent Adverse Events and Adverse Drug Reactions 16
7.2.2 Deaths 21
7.2.3 Serious Adverse Events 21
7.2.4 Dropouts and/or Discontinuations Due to Adverse Events (AEs) 23
7.2.5 Adverse Events of Special Interest 23
7.3 Growth 24
7.4 Graded Laboratory abnormalities 24
7.4.1 Hepatic Laboratory Abnormalities 24
7.4.2 Renal Laboratory Parameters 24
8 Therapeutic Individualization 26
8.1 Drug Interactions 26
8.2 Pediatric Populations 26
8.3 Pregnancy and Lactation 26
9 Advisory Committee Meeting 26
10 Other Relevant Regulatory Issues 27

10.1 Submission Quality and Integrity 27
10.2 Compliance with Good Clinical Practices 27
11 Financial Disclosures 27
12 Labeling 27
13 Postmarketing Recommendations 28
14 Recommended Comments to the Applicant 28
15 Patient Experience Data 28
Appendix A. Supplemental Tables and Figures 30
Appendix B. Financial Disclosure 35

Table of Tables

Table 1. Weight Band Dosing of Study Drug, IMPAACT 2019 (Study 205860) 14
Table 2. Summary of Proportion of Participants with Plasma HIV-1 RNA <200 c/mL and <50 c/mL by Enrollment Weight Band and ART Experience at Week 24 and Week 48 – Standard Snapshot Analysis (All Treated Population), IMPAACT 2019 (Study 205860) 16
Table 3. HIV-1 RNA Results of ART-Naïve Participants, IMPAACT 2019 (Study 205860) 16
Table 4. Most Common Adverse Events Through Week 48 for Weight Band ≥6 kg to <10kg by Maximum Severity, IMPAACT 2019 (Study 205860) 19
Table 5. Most Common Adverse Events Occurring in at Least 5% of Participants Through Week 48 for All Weight Bands by Maximum Severity, IMPAACT 2019 (Study 205860) 21
Table 6. Adverse Drug Reactions through Week 48 for All Weight Bands (All Treated Population), IMPAACT 2019 (Study 205860) 22
Table 7. Summary of Laboratory Results for the DILI Case, IMPAACT 2019 (Study 205860) 24
Table 8. Patient Experience Data Relevant to this Application 30
Table 9. Most Common Adverse Events Through Week 48 for All Weight Bands by Maximum Severity, IMPAACT 2019 (Study 205860) 32
Table 10. Serum Creatinine Change from Baseline by Visit and Weight Band (All Treated Population) 35
Table 11. Estimated Glomerular Filtration Rate Change from Baseline by Visit and Weight Band (All Treated Population) 36

Table of Figures

Figure 1. CVF Participant Trend of HIV-1 RNA and CD4%, IMPAACT 2019 (Study 205860) 17
Figure 2. Weight Band Versus Toxicity Grade Categorized by Related and Non-related Treatment Emergent Adverse Events, IMPAACT 2019 (Study 205860) 22
Figure 3. Median Serum Creatinine and Change in Serum Creatinine from Baseline by Visit and Weight Band (All Treated Population), IMPAACT 2019 (Study 205860) 27
Figure 4. Median Estimated Glomerular Filtration Rate and Change in Estimated Glomerular Filtration Rate by Visit and Weight Band (All Treated Population), IMPAACT 2019 (Study 205860) 27

1. Benefit-Risk Integrated Assessment

TRIUMEQ is a fixed-dose combination (FDC) tablet containing three antiretroviral (ARV) drugs: abacavir (ABC) 600 mg, dolutegravir (DTG) 50 mg, and lamivudine (3TC) 300 mg. TRIUMEQ PD is a FDC dispersible tablet (ABC 60 mg/DTG 5 mg/3TC 30 mg). TRIUMEQ and TRIUMEQ PD are currently indicated for the treatment of HIV-1 infection in adults and in pediatric patients weighing ≥10 kg. With the current submissions, the Applicant seeks to extend the indication to pediatric patients aged ≥3 months and weighing ≥6 kg. As proposed, pediatric patients weighing ≥6 kg would receive TRIUMEQ PD as a single-tablet regimen for the treatment of HIV-1. No new formulations of TRIUMEQ or TRIUMEQ PD were developed for these submissions.

Safety and Efficacy
The safety and efficacy of TRIUMEQ PD for patients ≥3 months and weighing ≥6 kg are primarily supported by the IMPAACT 2019 study, a multicenter, open-label, non-comparative study of pediatric subjects with HIV-1 infection <12 years of age. In addition to IMPAACT 2019, data supporting use of TRIUMEQ and TRIUMEQ PD in pediatric patients with HIV-1 infection aged ≥3 months and weighing ≥6 kg were derived from pediatric studies using the individual components of TRIUMEQ and TRIUMEQ PD, which have been reviewed previously.

In IMPAACT 2019, 57 subjects weighing ≥6 kg at enrollment received the recommended dose (determined by weight) and formulation and were followed for 48 weeks. Overall, the exposures observed in subjects ≥3 months and weighing ≥6 kg were comparable to the exposures observed in adults, supporting the extrapolation of efficacy from the adult data to pediatric subjects in this weight and/or age group. The supportive efficacy analysis conducted at Week 48 showed that 79% of subjects achieved HIV-1 RNA <50 c/mL and 95% achieved HIV-1 RNA <200 c/mL. Two subjects reported Grade 3 or 4 adverse drug reactions. One subject, an 8-year-old female who weighed 22 kg at baseline, experienced Grade 3 increased blood creatinine and Grade 3 decreased glomerular filtration rate. By Week 48, the glomerular filtration rate was improving, and the events did not lead to discontinuation of TRIUMEQ. The second subject, a 7-year-old male who weighed 20 kg at baseline, experienced drug-induced liver injury with Grade 4 increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) following 36 weeks of treatment with TRIUMEQ PD. Clinical signs or symptoms of hepatitis were not reported, and ALT and AST values normalized after TRIUMEQ PD was discontinued.

Overall, the safety and efficacy profile of TRIUMEQ and TRIUMEQ PD in pediatric patients is comparable to what has been observed in adults.

Throughout the review of the supplemental New Drug Applications (sNDAs), no deficiencies that would preclude approval for pediatric patients aged ≥3 months and weighing ≥6 kg were identified. The review team concluded that the overall benefit relative to overall risk supports extension of the indication.

Conclusion: Benefit and Risk Assessment
In conclusion, based on the review of data from the IMPAACT 2019 study and data from pediatric studies using the individual components of TRIUMEQ and TRIUMEQ PD, the Division of Antivirals has determined that the benefits of TRIUMEQ and TRIUMEQ PD outweigh the risks and recommends approval for the treatment of HIV-1 infection in children aged ≥3 months and weighing ≥6 kg.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	HIV-1 infection, if untreated, is a life-threatening and serious disease of major public health significance. Approximately 38.4 million people are infected worldwide, including an estimated 1.7 million children (range 1.2 to 2.2 million) <15 years of age. Globally, approximately 160,000 children <15 years of age acquired HIV in 2021. There is no vaccine available to prevent HIV acquisition.	HIV-1 remains a major cause of morbidity and mortality worldwide. If untreated, HIV-1 is a life-threatening condition, one that affects a large population. HIV-1 infection is a significant public health concern.
Current Treatment Options	Integrase Strand Transfer Inhibitors (INSTIs) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) have become preferred regimens for HIV treatment as recommended by the Department of Health and Human Services HIV treatment guidelines for children, adolescents, and adults. Several single tablet regimens (STRs) are currently approved for once daily administration for the treatment of HIV-1 infection in pediatric patients including: Abacavir/dolutegravir/lamivudine (TRIUMEQ/TRIUMEQ PD) Bictegravir/emtricitabine/tenofovir alafenamide [TAF] (BIKTARVY) Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (SYMTUZA) Efavirenz/emtricitabine/tenofovir disoproxil fumarate [TDF] (ATRIPLA) Efavirenz/lamivudine/TDF (SYMFI/SYMFI LO) Elvitegravir/cobicistat/emtricitabine/TDF (STRIBILD) Elvitegravir/cobicistat/emtricitabine/TAF (GENVOYA) Emtricitabine/rilpivirine/TDF (COMPLERA) Emtricitabine/rilpivirine/TAF (ODEFSEY) Fixed-dose combination (FDC) STR treatments are a convenient option for treatment; however, in those weighing <25 kg there are fewer FDC or STR options. There are currently no INSTI-containing STRs approved for children weighing <10 kg.	A once daily single-tablet regimen has been shown to significantly improve adherence, treatment satisfaction, and virologic outcome for people living with HIV-1. Pediatric patients also benefit from the availability of a simplified, once daily, STR that combines potent efficacy, tolerability, a favorable toxicity profile, a low potential for drug-drug interactions, and practical, convenient dosing. While many STR options are available for older children and adolescents, options remain limited for younger children.
Benefit	A bioavailability/bioequivalence study (205894) confirmed that dosing with TRIUMEQ PD yields pharmacokinetic (PK) exposures that are associated with efficacy for all three individual drug components in TRIUMEQ or TRIUMEQ PD. TRIUMEQ and TRIUMEQ PD were found to not be interchangeable due to differences in the PK profile of DTG. To support an efficacy claim for the use TRIUMEQ/TRIUMEQ PD for the treatment of HIV-1 infection in children aged ≥3 months and weighing ≥6 kg, the Applicant submitted the completed IMPAACT 2019 study, a multicenter, open-label, non-comparative study of pediatric subjects with HIV-1 infection <12 years of age. The primary evidence for the effectiveness of TRIUMEQ/TRIUMEQ PD is derived from PK to support extrapolation of efficacy from adults to pediatric subjects. In this study, 57 subjects, with a median age of 6.4 years (range: 1 to 11.3) and median weight of 17 kg (range: 8.2 to 39.3) received the recommended dose and formulation of TRIUMEQ	Dosing with TRIUMEQ PD yields PK exposures consistent with those achieved by dosing with the individual components; this information was previously established for TRIUMEQ tablets. It is well known that long-term viral suppression in children will prevent or lead to fewer complications later in their life. Overall, the totality of the data supports the conclusion that treatment with TRIUMEQ and TRIUMEQ PD will provide effective treatment for children living with HIV-1 infection who are aged ≥3 months and weigh ≥6 kg.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and TRIUMEQ PD and contributed to the efficacy analysis at Week 48. At this timepoint, 79% of subjects achieved HIV1 RNA <50 c/mL and 95% achieved HIV-1 RNA <200 c/mL Participants in this study had virologic and immunologic outcomes similar to adults. Although the dose of the individual components in TRIUMEQ and TRIUMEQ PD differs from the approved dose in some weight bands, the proposed doses achieved exposures comparable to those correlated with efficacy in adult studies.	
Risk and Risk Management	The safety of TRIUMEQ and TRIUMEQ PD for pediatric patients is primarily informed by the IMPAACT 2019 clinical study. Two subjects reported Grade 3 or 4 adverse drug reactions: An 8-year-old female who weighed 22 kg at baseline experienced Grade 3 increased blood creatinine and Grade 3 decreased glomerular filtration rate (GFR). By Week 48, the GFR was improving, and the events did not lead to discontinuation of TRIUMEQ. A 7-year-old male who weighed 20 kg at baseline experienced drug-induced liver injury with Grade 4 increased ALT and AST following 36 weeks of treatment with TRIUMEQ PD. Clinical signs or symptoms of hepatitis were not reported, and ALT and AST values normalized after TRIUMEQ PD was discontinued. As stated above, IMPAACT 2019 enrolled 57 subjects, with a median age of 6.4 years (range: 1 to 11) and median weight of 17 kg (range: 8.2 to 39.3); this approval will however extend use of TRIUMEQ and TRIUMEQ PD to pediatric patients aged ≥3 months and weighing ≥6 kg.	The safety profile of TRIUMEQ and TRIUMEQ PD is primarily supported by the IMPAACT 2019 study; no new safety concerns were identified in this study. Safety concerns are adequately described in the label. Based on available data, no unique safety issues are anticipated for children aged ≥3 months and weighing ≥6 kg. Continued routine post-marketing pharmacovigilance is recommended with the approval of TRIUMEQ and TRIUMEQ PD for pediatric patients aged ≥3 months and weighing ≥6 kg.

2. Background

2.1 Introduction

The Applicant, ViiV Healthcare, seeks approval to extend the use of TRIUMEQ and TRIUMEQ PD to treat HIV-1 infection in pediatric patients aged ≥3 months and weighing ≥6 kg. The supplemental new drug applications submitted to the TRIUMEQ NDA 205551 (sNDA S-031) and TRIUMEQ PD NDA 215413 (sNDA S-002) contain final safety and efficacy data from the completed IMPAACT 2019 study.

IMPAACT 2019 was a phase 1/2, multi-site, open-label, multiple-dose, non-comparative study that assessed the pharmacokinetics (PK), safety, and tolerability of fixed-dose combination (FDC) abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) in children living with HIV-1 <12 years of age. The study evaluated both the existing FDC immediate-release tablet (TRIUMEQ) and the novel dispersible tablet (DT; TRIUMEQ PD). IMPAACT 2019 previously provided preliminary safety and efficacy data for the supplemental new drug application (sNDA S-028) submitted to the TRIUMEQ NDA 205551, and the original TRIUMEQ PD NDA application (NDA 215413), which allowed for the use of these products in children weighing ≥10 kg. Additional data from this completed study has been submitted in support of the expanded indication.

2.2 Analysis of Condition

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 38.4 million people infected worldwide, including an estimated 1.7 million children (range 1.2 to 2.2 million) under 15 years of age.[1] Globally, approximately 160,000 children under 15 years of age acquired HIV in 2021. Of the estimated 4,000 HIV infections that occur each day globally in adults and adolescents aged 15 years and older, about 31% are in young people 15 to 24 years of age.[2] Standard of care for the treatment of HIV-1 infection uses combination antiretroviral (ARV) therapy (ART) to suppress viral replication to below detectable limits, allow $CD4^+$ T cell counts to increase, and stop disease progression.

For ART-naive patients with HIV-1 infection, current treatment guidelines recommend that initial therapy consist of two nucleo(s/t)ide reverse transcriptase inhibitors (N[t]RTIs) in combination with a third agent (a nonnucleoside reverse transcriptase inhibitor [NNRTI], a boosted protease inhibitor [PI], or an integrase strand-transfer inhibitor [INSTI]). For the treatment of pediatric patients with HIV infection, the choice of ARVs should consider age and sexual maturity rating.[3] Virologically suppressed patients with HIV infection may switch from their current regimen because of safety or tolerability concerns or for regimen simplification. A single-tablet regimen (STR) with once-daily dosing has been shown to significantly improve adherence,

[1] Joint United Nations Programme on HIV/AIDS (UNAIDS). UNAIDS Data. Geneva, Switzerland. 2021.
[2] UNAIDS. Core Epidemiology slides. July 2021.
[3] Department of Health and Human Services (DHHS), Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Available at https://aidsinfo.nih.gov/guidelines. Last Updated: Jan 31. 2023

treatment satisfaction, and virologic outcome for patients with HIV-1 infection.[4,5,6,7,8] Many pediatric patients would also benefit from the availability of a simplified, once-daily STR that combines potent efficacy, tolerability, a favorable toxicity profile, a low potential for drug-drug interactions, and practical, convenient dosing.

TRIUMEQ, a FDC tablet containing an INSTI with a dual NRTI backbone, is an example of an STR that confers these desirable properties. TRIUMEQ was initially approved for use in adult patients in the U.S. on August 22, 2014, and in pediatric patients aged 12 to 18 years and weighing ≥40 kg on November 21, 2017. TRIUMEQ was subsequently approved for use in children weighing ≥25 kg to <40 kg on March 30, 2022. In addition, a novel formulation of TRIUMEQ, TRIUMEQ PD (tablets for oral suspension), was approved for use in children weighing ≥10 kg to <25 kg on March 30, 2022. TRIUMEQ PD has been shown to provide a potent, convenient, well-tolerated, and practical regimen for the long-term treatment of HIV-1 infection. Several other STRs are currently approved for once-daily administration for the treatment of HIV-1 infection in adolescents and younger children, but options remain limited for patients weighing <25 kg.

2.3 Available Pediatric Treatment Options

INSTI-based FDC regimens

- bictegravir (BIC)/emtricitabine (FTC)/tenofovir alafenamide (TAF) (BIKTARVY): approved for patients weighing ≥14 kg
- elvitegravir (EVG)/cobicistat (COBI)/FTC/ tenofovir disoproxil fumarate (TDF) (STRIBILD): approved for patients weighing ≥35 kg
- EVG/COBI/FTC/TAF (GENVOYA): approved for patients weighing ≥25 kg

NNRTI-based FDC regimens

- abacavir (ABC)/dolutegravir (DTG)/lamivudine (3TC) (TRIUMEQ/TRIUMEQ PD): approved for patients weighing ≥10 kg
- efavirenz (EFV)/FTC/TDF (ATRIPLA): approved for patients weighing ≥40 kg
- EFV/3TC/TDF (SYMFI/SYMFI LO): approved for patients ≥35 kg
- FTC/rilpivirine (RPV)/TDF (COMPLERA): approved for patients weighing ≥35 kg
- FTC/RPV/TAF (ODEFSEY): approved for patients weighing ≥35 kg

PI-based FDC regimens

- darunavir (DRV)/COBI/FTC/TAF (SYMTUZA): approved for patients weighing ≥40 kg

With the current submissions, the Applicant seeks to expand treatment options for children weighing <10 kg by extending the indication for TRIUMEQ PD to include pediatric patients aged ≥3 months and weighing ≥6 kg.

[4] Airoldi M, Zaccarelli M, Bisi L, Bini T, Antinori A, Mussini C, et al. One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects. Patient preference and adherence 2010;4:115-25.
[5] Bangsberg DR, Ragland K, Monk A, Deeks SG. A single tablet regimen is associated with higher adherence and viral suppression than multiple tablet regimens in HIV+ homeless and marginally housed people. AIDS 2010;24 (18):2835-40.
[6] Dejesus E YB, Morales-Ramirez JO, Sloan L, Ward DJ, Flaherty JF, et al. . Simplification of Antiretroviral Therapy to a Single-Tablet Regimen Consisting of Efavirenz, Emtricitabine, and Tenofovir Disoproxil Fumarate Versus Unmodified Antiretroviral Therapy in Virologically Suppressed HIV-1-Infected Patients. Acquir Immune Defic Syndr 2009;51 (2):163-74.
[7] Hodder SL, Mounzer K, Dejesus E, Ebrahimi R, Grimm K, Esker S, et al. Patient-Reported Outcomes in Virologically Suppressed, HIV-1-Infected Subjects After Switching to a Simplified, Single-Tablet Regimen of Efavirenz, Emtricitabine, and Tenofovir DF. AIDS Patient Care STDS 2010;24 (2):87-96.
[8] Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double blind, phase 3, non-inferiority trials. Lancet 2015;385:2606-15.

2.4 Important Safety Issues With Consideration to Related Drugs

The individual components of TRIUMEQ and TRIUMEQ PD (ABC, DTG, and 3TC) have established safety profiles. ABC has a boxed warning cautioning about the risk of lactic acidosis, severe hepatomegaly with steatosis, and severe hypersensitivity reactions. DTG has warnings language about the risk of hypersensitivity reactions, hepatotoxicity, and immune reconstitution syndrome. 3TC has a boxed warning cautioning about the risk of lactic acidosis and severe acute exacerbations of hepatitis B virus (HBV) infection, and warning language about the risk of severe hepatomegaly with steatosis. The combination drug EPZICOM (ABC and 3TC) has a boxed warning cautioning about severe hypersensitivity reactions, lactic acidosis and severe hepatomegaly with steatosis, and severe acute exacerbations of HBV infection. Similar to its component parts, the product labeling for TRIUMEQ and TRIUMEQ PD also includes boxed warning language for hypersensitivity reactions, lactic acidosis and severe hepatomegaly and exacerbation of hepatitis B, as well as warnings cautioning the risks of hepatic decompensation in HIV-1/hepatitis C virus (HCV) co-infected patients and immune reconstitution syndrome.

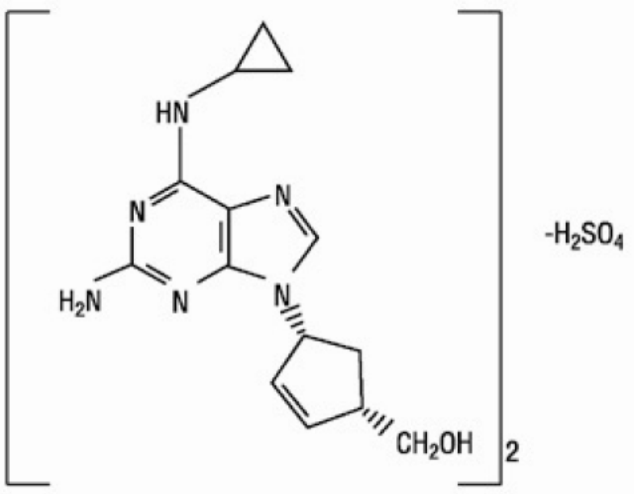
2.5 Product Information

TRIUMEQ and TRIUMEQ PD are FDC products containing ABC (NRTI), DTG (INSTI), and 3TC (NRTI).

Each film-coated tablet of TRIUMEQ, for oral use, contains 600 mg of ABC (present as 702 mg of abacavir sulfate), 50 mg of DTG (present as 52.6 mg of dolutegravir sodium), and 300 mg of 3TC. The inactive ingredients of TRIUMEQ tablets include D-mannitol, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The tablet film coating contains the inactive ingredients iron oxide black, iron oxide red, macrogol/PEG, polyvinyl alcohol–part hydrolyzed, talc, and titanium oxide. These film-coated tablets are purple, biconvex, oval, and debossed with “572 Tri” on one side.

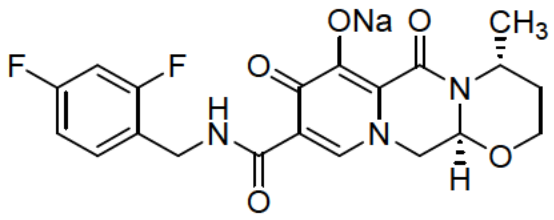
Each film-coated tablet of TRIUMEQ PD for oral suspension contains 60 mg of ABC (present as 70.2 mg of abacavir sulfate), 5 mg of DTG (present as 5.26 mg of dolutegravir sodium), and 30 mg of 3TC. The inactive ingredients of TRIUMEQ PD tablets include acesulfame potassium, crospovidone, mannitol, microcrystalline cellulose, povidone K29/32, silicified microcrystalline cellulose, sodium starch glycolate, sodium stearyl fumarate, strawberry cream flavor and sucralose. The tablet film-coating contains the inactive ingredients: ferric oxide yellow, macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc and titanium dioxide. These film-coated tablets are yellow, capsule-shaped, strawberry cream flavored, biconvex, and debossed with “SV WTU” on each side. TRIUMEQ PD tablets are not meant to be chewed, cut, or crushed, but dispersed fully for oral suspension in 20 mL of drinking water in the supplied cup.

The chemical name of abacavir sulfate is *(1S,cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 g/mol. It has the following structural formula:



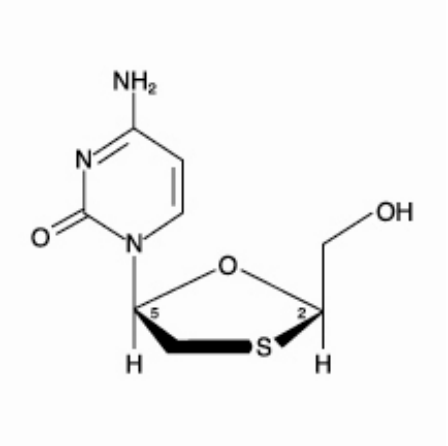
Abacavir sulfate is a white to off-white solid and is soluble in water.

The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is $C_{20}H_{18}F_2N_3NaO_5$ and the molecular weight is 441.36 g/mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

The chemical name of 3TC is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. 3TC is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2′,3′-dideoxy, 3′-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3 g/mol. It has the following structural formula:



Lamivudine is a white to off white crystalline solid and is soluble in water.

2.6 Summary of Pre-submission Regulatory Activity Related to Submission

TRIUMEQ was approved as an STR for the treatment of HIV-1 infection in adults on August 22, 2014 and for pediatric patients aged 12 to 18 years weighing ≥40 kg on November 21, 2017. TRIUMEQ was subsequently approved for use in pediatric patients weighing ≥25 kg to <40 kg on March 30, 2022. A novel formulation of TRIUMEQ, TRIUMEQ PD, was approved for use in pediatric patients weighing ≥ 10 kg to < 25 kg on March 30, 2022.

History of Post-Marketing Requirements and Written Requests

The following PMRs were issued following the approval of NDA 205551 on August 22, 2014:

2768-1*: Conduct a pediatric trial to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in HIV infected pediatric participants 2 years to less than 6 years of age. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/ lamivudine FDC tablets in pediatric participants should be evaluated for a minimum of 24 weeks.*

2768-2 [Fulfilled*]: Conduct a pediatric trial to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in HIV infected pediatric participants 6 years to less than 12 years of age and in children older than 12 years of age who weigh less than 40 kg. The safety and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets in pediatric participants should be evaluated for a minimum of 24 weeks.*

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

The following PMR was issued following the approval of NDA 215413 on March 30, 2022:

4247-1*: Conduct a pediatric trial to evaluate the pharmacokinetics (PK), safety, and antiviral activity (efficacy) of abacavir/dolutegravir/lamivudine FDC tablets for oral suspension in HIV-infected pediatric subjects 2 years to less than 6 years of age. The safety and antiviral activity (efficacy) of abacavir/ dolutegravir/lamivudine FDC tablets for oral suspension in pediatric subjects should be evaluated for a minimum of 24 weeks.*

An efficacy supplement was submitted to NDA 205551 (S-011; TRIUMEQ tablets) which proposed to expand the patient population to include patients aged 12 to <18 years and weighing ≥40 kg. Following the review of data from Trial 4184712, this indication was approved on November 21, 2017, and PMR 2768-3 was considered fulfilled. An additional efficacy supplement was submitted to sNDA 205551(S-028; TRIUMEQ

tablets), along with NDA 215413 (TRIUMEQ PD), which proposed to allow for the use of TRIUMEQ and TRIUMEQ PD in pediatric patients weighing 14 to <40 kg. During the review of NDA 215413, the FDA proposed to expand the indication for TRIUMEQ PD to include patients ≥10 kg. On March 30, 2022, the FDA approved TRIUMEQ and TRIUMEQ PD for use in pediatric patients weighing ≥10 kg and PMR 2768-2 was considered fulfilled.

The Applicant previously requested a Type B pre-sNDA meeting to reach agreement with the Division on their proposed sNDAs to expand the use of TRIUMEQ PD to treat patients weighing ≥6 kg to <10 kg. These supplemental NDA applications (sNDAs) sought to extend the indication of TRIUMEQ and TRIUMEQ PD to treat patients weighing ≥6 kg to <10 kg, and to fulfill post-marketing requirements (PMRs) 2768-1 and 4247-1 as well as the TRIUMEQ Written Request-Amendment 2 (issued to NDA 205551 and NDA 215413).

The proposed use of TRIUMEQ PD for the treatment of pediatric patients weighing ≥6 kg is based upon PK, efficacy, tolerability, and safety data from IMPAACT 2019 and is supported by extrapolation of data generated in adults, and data in pediatric patients with the single entities. The IMPAACT 2019 study provided intensive and sparse PK samples through Week 24 and Week 48 visits. The Applicant concluded that the PK profiles of DTG/ABC/3TC tablets and DTs, at the proposed dose(s) in pediatric patients are comparable to the PK data observed in adults from each of the approved single entities. In addition, the Applicant provided an authorization letter for IND 141131 (DTG/ABC/3TC) in support of the current sNDAs and previously submitted IMPAACT P1093 (TIVICAY) virology data (N240790.S-025.758) in support of the proposed TRIUMEQ and TRIUMEQ PD labeling.

Protocol Amendments and Clarification Memoranda:
There was a single amendment to the original protocol and three clarification memoranda to the protocol as listed below.
Amendment 1 (September 04, 2019): This amendment adjusted enrollment age from 2 years to <12 years of age, to <12 years of age without a lower age limit. The lower age cohort was adjusted from ≥2 years to <6 years of age, to subjects <6 years of age without a lower age limit. The HIV treatment-naïve population was adjusted to include INSTI-experienced subjects after having previously been excluded from the study.

Clarification Memorandum 1 (June 11, 2020): Clarified the types of tests that could be used for confirmation of HIV-1 infection in participants who were <2 years of age or had been exposed to breast milk in the past 28 days.

Clarification Memorandum 2 (August 14, 2020): Issued to protect the health and well-being of IMPAACT 2019 study participants in the setting of SARS-CoV-2 circulation and associated COVID-19 disease. The purpose was to provide operational flexibility for conducting study visits and procedures when needed to ensure ongoing access to study drug and to prioritize the conduct of clinically and scientifically important evaluations.

Clarification Memorandum 3 (April 09, 2021): Updated protocol specifications to reflect current policies of the Division of AIDS (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID), and National Institutes of Health (NIH). It also updated wording related to the IMPAACT Network Certificate of confidentiality and updates the protocol team and site representative rosters. The updates did not impact the study design or study-specific procedures.

2.7 Review Approach for Current Submission

The efficacy supplements were reviewed by a multidisciplinary team, including clinical, clinical pharmacology, and clinical virology. As there were no new product quality information to review, no additional CMC-related reviews were conducted. The safety and efficacy of TRIUMEQ PD for patients aged ≥3 months and weighing ≥6 kg is primarily supported by the IMPAACT 2019 study, a phase 1/2, multicenter, open-label, non-comparative study of pediatric subjects with HIV-1 infection <12 years of age. Data from this study was included with this application. IMPAACT 2019 was sponsored by NIAID, DAIDS, and conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network under IND 141131. In

addition to IMPAACT 2019, data supporting use of TRIUMEQ and TRIUMEQ PD in pediatric patients with HIV-1 infection aged ≥3 months and weighing ≥6 kg are derived from previously conducted pediatric studies of the individual components of TRIUMEQ and TRIUMEQ PD, which have been reviewed previously.

For additional details, please refer to the detailed reviews by Drs. Zhang, Liu, and Colberg Poley for clinical pharmacology, pharmacometrics and virology considerations, respectively. This clinical review considered all the conclusions from the relevant disciplines to determine benefit and risks of TRIUMEQ and TRIUMEQ PD for the treatment of HIV-1 in pediatric patients.

The key review issue for this submission relates to the limited safety and efficacy data in children <10kg. IMPAACT 2019 included 57 subjects, with a median age of 6.4 years (range: 1 to 11.3) and median weight of 17 kg (range: 8.2 to 39.3). Extrapolation of PK data, as well as data from previously conducted pediatric studies using the individual components of TRIUMEQ and TRIUMEQ PD, support the approval for use of TRIUMEQ and TRIUMEQ PD in pediatric patients with HIV-1 infection aged ≥3 months and weighing ≥6 kg to <10 kg.

3. Nonclinical Pharmacology/Toxicology

All of the components of TRIUMEQ and TRIUMEQ PD (ABC/DTG/3TC) are FDA-approved drugs. No additional nonclinical data were submitted.

4. Clinical Pharmacology

A brief description of the Clinical Pharmacology review is included here. Please refer to Dr. Zhang's Clinical Pharmacology Review for full details. In addition, please refer to Dr. Jiajun Liu's Pharmacometrics Review for full details.

The Clinical Pharmacology review of these sNDAs focused on the following aspects:
To evaluate the appropriateness of the proposed dosing regimen of TRIUMEQ PD in pediatric patients weighing ≥6 kg to <10 kg.
To assess pediatric PK data for DTG, ABC, and 3TC with the recommended dosing of TRIUMEQ PD and TRIUMEQ from Study IMPAACT 2019.

The proposed dosing regimen of TRIUMEQ PD for pediatric patients ≥6 to <10 kg achieved comparable exposures to those observed at the recommended doses in adults (with individual products) and in older pediatric patients (with TRIUMEQ/TRIUMEQ PD or individual products). The values for the various PK parameters (i.e., $AUC_{0\text{-}24h}$, C_{max}, and C_{24h}) for DTG, ABC, and 3TC with TRIUMEQ PD in pediatric patients were similar across all weight bands (within study IMPAACT 2019) and are considered comparable to those observed in older pediatric patients, and in adults and pediatric patients at the recommended doses of the individual products.

The proposed dose of DTG in the ≥6 to <10 kg weight band (15 mg) is the same as the approved pediatric dose with TIVICAY PD for patients of the same weight band. The DTG exposures following the administration of TRIUMEQ PD in this weight band were slightly higher than the historical data, but comparable to those observed in IMPAACT 1093 in the same weight band.

The proposed dosing of ABC in pediatric patient weighing ≥6 to <10 kg is slightly higher than the recommended ZIAGEN (ABC) dose for both 6-kg subjects and subjects weighing <10 kg. Subsequently, the observed ABC exposures are slightly higher than those observed in pediatric patients <14 kg receiving oral ZIAGEN but are still within the observed exposure ranges at the recommended dose of ABC in pediatrics when comparing weight bands. The proposed 3TC dose (90 mg) is within the range of the approved doses with EPIVIR (3TC) oral solution (60 to 100 mg) for the weight band. The observed 3TC exposures following TRIUMEQ PD administration in this weight band were slightly higher than those observed in pediatric patients <14 kg receiving the oral solution of EPIVIR but were still within the observed exposure ranges at the recommended dose of lamivudine in pediatrics when comparing exposures by weight band.

The Office of Clinical Pharmacology has reviewed the application and determined that the application is approvable from a clinical pharmacology perspective to extend the indication to pediatric patients aged ≥3 months and weighing ≥6 kg.

5. Clinical Virology

A brief description of the Clinical Virology review is included here. Please refer to Dr. Colberg Poley's Clinical Virology Review for full details.

The IMPAACT 2019 pediatric study provided data supporting the activity (efficacy) TRIUMEQ and TRIUMEQ PD, measured by the proportion of pediatric subjects with HIV-1 RNA suppression (at <200 c/mL and <50 c/mL, using snapshot analyses) through treatment of ART-experienced, virologically suppressed and ART-naïve children (≥6 kg to ≥25 kg) over 48 weeks.

While one ART-naïve subject of the total 57 enrolled pediatric subjects in IMPAACT 2019 met confirmed virologic failure (CVF) criteria at Week 24, it is notable that this subject had a higher baseline HIV-1 RNA and a lower rate of HIV-1 RNA decline. The significant baseline HIV-1 RNA and lower rate of decline were possibly due to the IN L74I substitution known to impact efficacy of cabotegravir, another HIV-1 INSTI. The CVF subject's HIV-1 RNA values and those of the other pediatric ART-naïve subjects treated with TRIUMEQ PD continued to decrease through the end of the study with final measured HIV-1 RNA values below the suppression threshold (<200 c/mL.) Notably, there was no virologic evidence of HIV-1 RNA rebound during TRIUMEQ treatment. Treatment-emergent INSTI or RT RASs during the 48 weeks of treatment in the clinical study seem unlikely as the HIV-1 replication did not detectably rebound in the CVF Subject.

Although the Applicant stated that no participants had known treatment emergent NRTI or INSTI associated resistance through Week 48 (CSR 205860, 9. Virologic Outcomes), genotypic or phenotypic analysis of the one CVF subject's sample at the time of failure (Week 24) did not provide any data to verify the Applicant's statement. Further, no supportive virology resistance data were provided from any TRIUMEQ-treated pediatric subjects (≥6 kg to ≥25 kg).

6. Clinical/Statistical- Efficacy

6.1. Study design and protocol summary

IMPAACT 2019 was a phase 1/2, multi-site, open-label, multiple dose, non-comparative PK and safety study of DTG/ABC/3TC DTs and tablets in ART-naïve and ART-experienced children living with HIV who were <12 years of age and weighed ≥6 to <40kg. Enrolled children who completed the study received the study drug for at least 48 weeks (through the Week 48 visit) and for up to 144 weeks if they were unable to access the drug locally or transfer to a non-study source upon completion of the Week 48 visit. A total of 57 children were enrolled in the study, with 28 children <6 years of age and 29 children ≥ 6 to <12 years of age. The median age of participants was 6.4 years (range: 1 to 11.3) and median weight was 17 kg (range: 8.2 to 39.3). Three of the children enrolled were ART-naïve (all in the ≥6 kg to >10 kg weight band) and all remaining children enrolled were ART-experienced. Children were enrolled into cohorts (weight band groups) according to their baseline weight and received study drug as shown in Table 1.

Table 1. Weight Band Dosing of Study Drug, IMPAACT 2019 (Study 205860)

Group	Weight Band	Number of Tablets Formulation	DTG/ABC/3TC Daily Dose
1	≥6 to <10 kg	3 DTs	15/180/90 mg
2	≥10 to <14 kg	4 DTs	20/240/120 mg
3	≥14 to <20 kg	5 DTs	25/300/150 mg
4	≥20 to <25 kg	6 DTs	30/360/180 mg
5	≥25 to <40kg	1 Tablet	50/600/300 mg

Source: Applicant's Clinical Study Report for IMPAACT 2019 (Table 1, page 23).

Abbreviations: ABC, abacavir; DT, dispersible tablet; DTG, dolutegravir; 3TC, lamivudine.

Primary Endpoint
The primary safety endpoint for all cohorts:
Evaluate the safety profile of 24 weeks of treatment with DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age.

The primary PK endpoint (to support efficacy) for all cohorts:
Determine the steady-state AUC_{0-24h}, C_{max}, and C_{24h} of DTG, ABC, and 3TC and confirm the dosing of DTG/ABC/3TC DTs and Tablets that achieves protocol defined PK targets for DTG, ABC, and 3TC in children <12 years of age.

Secondary Endpoints
The secondary safety endpoints:
Evaluate the safety profile of 48 weeks, and additionally up to 144 weeks, of treatment with DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age.
Evaluate changes in lipid profiles at 24 and 48 weeks of treatment with DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age

The secondary efficacy endpoints:
Evaluate antiviral (virologic) and immunologic responses at 4, 24, and 48 weeks, and additionally up to 144 weeks, of treatment with DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age
Evaluate changes in lipid profiles at 24 and 48 weeks of treatment with DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age

Enrollment eligibility:
Inclusion Criteria
Age: <12 years
Weight: 6 to <40kg
Either ART-naïve or on a stable ART regimen
ART-experienced children (on a stable ART regimen) were required to have HIV-1 RNA <200 c/mL for at least 6 consecutive months prior to entry

Exclusion Criteria
Documented resistance to ABC, DTG or 3TC (except M184V)
History of malignancy
Known hypersensitivity reaction to ABC
Receipt of prohibited medications within 30 days prior to entry
Current evidence of pancreatitis, active tuberculosis, AIDS-defining opportunistic infection, or any other medical condition that may interfere with participation or interpretation of study outcomes
≥Grade 3 laboratory test results for hemoglobin at screening
Child not expected to be available for 48 weeks of follow-up
No HLA-B*5701-negative based on documented testing at any time prior to entry
For ART-experienced children (on a stable ART regimen), have documented HIV-1 RNA result ≥200 c/mL based on a specimen collected within 6 months prior to entry

6.2 Results

6.2.1 Antiviral (virologic) response

Efficacy was evaluated by measuring HIV-1 RNA at Weeks 4, 24, and 48 (Table 2). Additionally, $CD4^+$ cell count and percentage at Weeks 4, 24, and 48 was measured. Of note, baseline HIV-1 genotype was not tested in cases without CVF, and HIV-1 resistance testing (genotype and/or phenotype) was not required for study inclusion.

A virologic response was seen in almost all participants (Table 2). One participant met the protocol-specified definition of CVF among the ART-naïve participants in the ≥6 to <10 kg weight band (Table 3), which is discussed in detail in section 6.2.2. It is noted, however, that this subject's HIV-1 RNA continued to decrease through Week 48 (the end of the study) with a final HIV-1 RNA value below the suppression threshold (<200 c/mL). Importantly, neither the CVF participant nor the remaining ART-naïve participants had evidence of HIV-1 rebound or increased replication during the TRIUMEQ PD treatment course. Overall, during the 48-weeks of treatment, TRIUMEQ PD was effective in suppressing viral replication in all weight bands, including the ≥6 kg to <10 kg weight band, and regardless of prior treatment history (i.e., treatment- naïve or experienced).

Table 2. Summary of Proportion of Participants with Plasma HIV-1 RNA <200 c/mL and <50 c/mL by Enrollment Weight Band and ART Experience at Week 24 and Week 48 – Standard Snapshot Analysis (All Treated Population), IMPAACT 2019 (Study 205860)

Weight Band	ART Status	Week 24		Week 48	
		<200 c/mL n (%)	<50 c/mL n (%)	<200 c/mL n (%)	<50 c/mL n (%)
All Weight Bands	**Naïve and Experienced (N=57)**	**54 (94.7)**	**53 (91.2)**	**54 (94.7)**	**45 (78.9)**
	Experienced only (N=54)	**52 (96.3)**	**50 (92.6)**	**51 (94.4)**	**43 (79.6)**
≥6 to <10 kg	Naïve and Experienced (N=9)	7 (77.8)	7 (77.8)	8 (88.9)	7 (77.8)
	Naïve (N=3)	2 (66.7)	2 (66.7)	3 (100)	2 (66.7)
	Experienced (N=6)	5 (83.3)	5 (83.3)	5 (83.3)	5 (83.3)
≥10 to <14 kg	All experienced (N=12)	11 (91.7)	10 (83.3)	11 (91.7)	8 (66.7)
≥14 to <20 kg	All experienced (N=15)	15 (100.0)	14 (93.3)	15 (100.0)	13 (86.7)
≥20 to <25 kg	All experienced (N=10)	10 (100.0)	10 (100.0)	9 (90.0)	7 (70.0)
≥25kg	All experienced (N=11)	11 (100.0)	11 (100.0)	11 (100.0)	20 (90.9)

Source: Applicant's Clinical Study Report for IMPAACT 2019 (Table 46, page 123) and Clinical Reviewer's analysis (JMP v.16.2.0) of the adeff.xpt dataset.
Note: n (%) = Number (percent) of participants in each subcategory in each group (weight band or ART experience).
Note: Virologic success includes HIV-1 RNA under the threshold for virologic suppression (<200 c/mL or <50 c/mL).
Abbreviations: ART, antiretroviral therapy.

Table 3. HIV-1 RNA Results of ART-Naïve Participants, IMPAACT 2019 (Study 205860)

Timepoint	HIV-1 RNA (c/mL)		
	PID (b) (6)	PID (b) (6)	PID (b) (6)
Baseline	186,419	3,519,602	500,885
Week 4	625	14,155	108
Week 24	46	419*	<40
Week 48	<40	76	<40

Source: Applicant's Clinical Study Report for IMPAACT 2019 (Table 47, page 123) and Clinical Reviewer's analysis (JMP v.16.2.0) of the adlb.xpt dataset.
* Confirmed virologic failure at 358 c/mL; discussed in section 6.2.2.
Abbreviations: PID, participant identifier.

6.2.2 Confirmed Virologic Failure

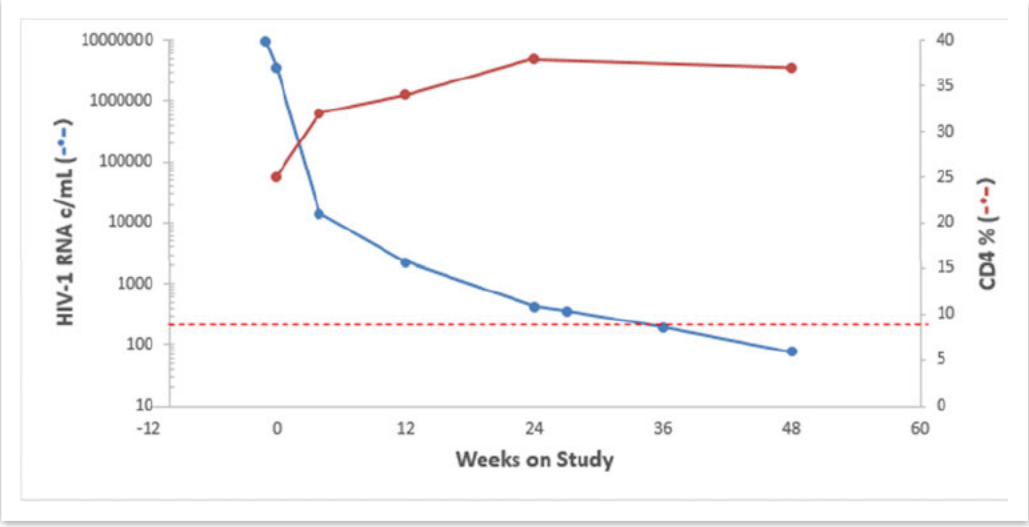
In the IMPAACT 2019 study, CVF in an ART-naïve participant was defined as two consecutive plasma HIV-1 RNA test results ≥200c/mL collected at or after Week 24; for ART-experienced participants, two consecutive results were from specimens collected at any time after enrollment.

There was one CVF identified over the course of the IMPAACT 2019 study. Participant (b) (6) was an ART-naïve, 1-year-old male from Thailand enrolled in the ≥6 kg to >10 kg weight band. Baseline genotyping for this participant detected an HIV-1 subtype AE variant; this subtype is prevalent in Asia and was an expected result for this participant. At baseline, this participant had one resistance associated

substitution, L74I. The participant's baseline HIV-1 RNA was 3,519,602 c/mL At Week 24 of TRIUMEQ PD treatment, the participant had a significant decrease in HIV-1 RNA from baseline (-3.92 $\log_{10}$); however, with an absolute HIV-1 RNA value of 419 c/mL, this subject met the protocol-specified definition for CVF (see Table 3). Protocol-specified CVF was confirmed 3 weeks later with an HIV-1 RNA value of 358 c/mL. At the time of CVF, resistance testing was unsuccessful and no genotypic or phenotypic results were obtained. Despite meeting the definition of CVF at Week 24, the participant's HIV-1 RNA values were still decreasing (<200 c/mL) by Week 48 (76 c/mL). Per the Applicant, no additional HIV-1 RNA values from Participant 3041436 were available after Week 48 because the participant completed the study at Week 48.

The participant's baseline CD4% was 25%. At the time of CVF, the participant's CD4% was 38%. The CD4% remained stable through Week 48 and study completion. Figure 1 demonstrates the participant's trends in HIV-1 RNA c/mL and CD4% over the course of the study.

Figure 1. CVF Participant Trend of HIV-1 RNA and CD4%, IMPAACT 2019 (Study 205860)



Source: Applicant's Clinical Study Report for IMPAACT 2019 (Figure 12, Page 158)
Note: The dotted-red line represents 200 c/mL HIV-1 RNA

Clinical Reviewer's Comment: The participant's baseline HIV-1 RNA (over 3.5 million c/mL) was higher than that of other participants, including the other ART-naïve participants, and showed a dramatic reduction by Week 24 to 419 c/mL (-3.92 $\log_{10}$ change). Although this participant met protocol-specific CVF criteria at Week 24 (HIV-1 RNA ≥200 c/mL), this is likely attributable to the high initial HIV-1 RNA versus failure of therapy, and viral suppression (HIV-1 RNA <200 c/mL) was achieved by Week 48 (expected biphasic decline of HIV-1 RNA, with a slower second phase decline). The PK parameters (AUC, C_{max}, C_{min}) of DTG, ABC, and 3TC of this participant were reviewed with Clinical Pharmacology, and the observed PK parameters were consistent with historical data in adults and pediatric participants. Additionally, it is also reassuring that the participant's $CD4^+$ count improved after starting study drug and CD4% improved and remained stable for the duration of therapy (see Figure 1).

7. Safety

IMPAACT 2019 demonstrated that TRIUMEQ and TRIUMEQ PD are well-tolerated treatments for HIV-1 infection in children as young as 3 months of age weighing at least 6kg. The adverse events reported in this study are similar to those previously described in adult and adolescent studies of patients with HIV-1. No deaths were reported. One treatment-related serious adverse event leading to premature study discontinuation occurred and is discussed in section 7.2.3. The most common laboratory abnormalities were changes from baseline estimated glomerular

filtration rate (eGFR) and serum creatinine, without associated clinical events including renal failure (further discussed in 7.4.2). Overall, the safety review did not identify any new safety concerns.

7.1 Approach to Safety Review

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The results of IMPAACT 2019, a single phase 1/2, open-label study of DTG/ABC/3TC DTs and Tablets in ART-naïve and ART-experienced children living with HIV who were aged <12 years and weighed ≥6 to <40 kg. Enrolled children received study drug for at least 48 weeks (through the Week 48 visit) and for up to 144 weeks, if needed.

The All Treated Population was used to perform the analyses in this review and included 57 participants. The All Treated Population was defined as all participants who received at least one dose of study drug; it included participants whose study drug doses were modified due to other reasons (not due to weight gain) or who received doses other than the final confirmed dose for their weight band. No enrolled participants were excluded from the All Treated Population. In total, 55 participants (96.5%) completed the Week 24 and Week 48 visits.

The source of data for the safety review is from the IMPAACT 2019 study. Using the Applicant's STDM and ADAM datasets, the primary clinical reviewer conducted all safety analyses presented in this section using JMP v.16.2.0 and Analysis Studio v1.7.0, unless otherwise specified.

7.1.2 Categorization of Adverse Events

Investigator-reported verbatim terms were translated into preferred terms using the MedDRA dictionary Version 25.0 used by the Applicant. Coding of adverse events appeared to be an accurate reflection of those noted in the case report forms.

7.1.3 Pooling of Data Across Studies to Estimate and Compare Incidence

Not applicable.

7.2 Safety Findings

7.2.1 Treatment Emergent Adverse Events and Adverse Drug Reactions

The primary goal of the safety review was to identify any differences in frequency, severity, or type of treatment emergent adverse events (TEAEs) and adverse drug reactions (ADRs) reported between subjects in the lowest weight-band (≥6 kg to <10 kg) and subjects in higher weight bands (e.g., previously approved weight bands:10 kg to ≥25 kg).

Following review of IMPAACT 2019 data, no new safety concerns were identified in the ≥6 kg to <10 kg age group. The TEAEs and ADRs evaluated in this study have been previously noted with use of TRIUMEQ and TRIUMEQ PD or the individual components. There were no unexpected TEAEs or ADRs.

The most common TEAEs overall (in all weight bands) were the MedDRA preferred terms *Glomerular filtration rate decreased* and *Blood creatinine increased* as shown in Table 4 and Table 5 (and Table 9 in Appendix A). Review of changes in estimated glomerular filtration rate (eGFR) and serum creatinine showed these were mostly based on change from baseline rather than the measured values and were not considered associated with clinical events such as renal dysfunction/toxicity. In addition, there was only one TEAE that was reported under the renal and urinary disorders MedDRA SOC. This was a Grade 1

dysuria that was assessed as not serious and not related to study drug. Decreased eGFR and increased serum creatinine are discussed in Section 7.4.2.

Table 4. Most Common Adverse Events Through Week 48 for Weight Band ≥6 kg to <10kg by Maximum Severity, IMPAACT 2019 (Study 205860)

System Organ Class Preferred Term	Weight Band 1 6 to <10 kg (N=9)											
	Grade 1 to 5		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants with ≥1 adverse events	**8**	**(88.9)**	**1**	**(11.1)**	**4**	**(44.4)**	**3**	**(33.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Investigations	**7**	**(77.8)**	**1**	**(11.1)**	**6**	**(66.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Glomerular filtration rate decreased	6	(66.7)	0	(0.0)	6	(66.7)	0	(0.0)	0	(0.0)	0	(0.0)
Blood creatinine increased	4	(44.4)	1	(11.1)	3	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)
Alanine aminotransferase increased	2	(22.2)	2	(22.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hemoglobin decreased	2	(22.2)	2	(22.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood cholesterol increased	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Low density lipoprotein increased	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neutrophil count decreased	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**6**	**(66.7)**	**3**	**(33.3)**	**3**	**(33.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Cough	6	(66.7)	4	(44.4)	2	(22.2)	0	(0.0)	0	(0.0)	0	(0.0)
Rhinorrhoea	4	(44.4)	4	(44.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nasal congestion	2	(22.2)	2	(22.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngeal erythema	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Productive cough	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tonsillar exudate	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Tonsillar inflammation	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Metabolism and nutrition disorders	**5**	**(55.6)**	**2**	**(22.2)**	**2**	**(22.2)**	**1**	**(11.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Decreased appetite	4	(44.4)	3	(33.3)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Underweight	2	(22.2)	0	(0.0)	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)
Abnormal loss of weight	1	(11.1)	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)
Malnutrition	1	(11.1)	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)
Infections and infestations	**4**	**(44.4)**	**1**	**(11.1)**	**2**	**(22.2)**	**1**	**(11.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Upper respiratory tract infection	2	(22.2)	0	(0.0)	2	(22.2)	0	(0.0)	0	(0.0)	0	(0.0)
Covid-19	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Gastroenteritis	1	(11.1)	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)
Nasopharyngitis	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pneumonia	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Tinea faciei	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Tonsillitis	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Blood and lymphatic system disorders	**3**	**(33.3)**	**0**	**(0.0)**	**2**	**(22.2)**	**1**	**(11.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Anemia	2	(22.2)	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Lymphadenopathy	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	1	(11.1)	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)
Secondary thrombocytosis	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**3**	**(33.3)**	**1**	**(11.1)**	**2**	**(22.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Abdominal discomfort	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal pain	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Diarrhoea	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Flatulence	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stomatitis	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Vomiting	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**2**	**(22.2)**	**1**	**(11.1)**	**0**	**(0.0)**	**1**	**(11.1)**	**0**	**(0.0)**	**0**	**(0.0)**
Pyrexia	2	(22.2)	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)
Feeling hot	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**2**	**(22.2)**	**1**	**(11.1)**	**1**	**(11.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Hyperhidrosis	1	(11.1)	0	(0.0)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)

System Organ Class Preferred Term	Weight Band 1 6 to <10 kg (N=9)											
Skin plaque	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**1**	**(11.1)**	**1**	**(11.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Adverse event following immunization	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Contusion	1	(11.1)	1	(11.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Source: OCS Analysis Studio, Safety Explorer; adae.xpt dataset.
N = Number of all treated population participants in Weight Band 1 (6 to <10 kg).
n (%) = Number (percent) of participants in each subcategory
Participants may have reported more than one event within each PT or SOC.
For each PT or SOC, a participant was only counted for the worst reported grade.
Grade: 1= Mild, Grade 2= Moderate, Grade 3 = Severe, 4 = Potentially Life-Threatening, 5 = Death.

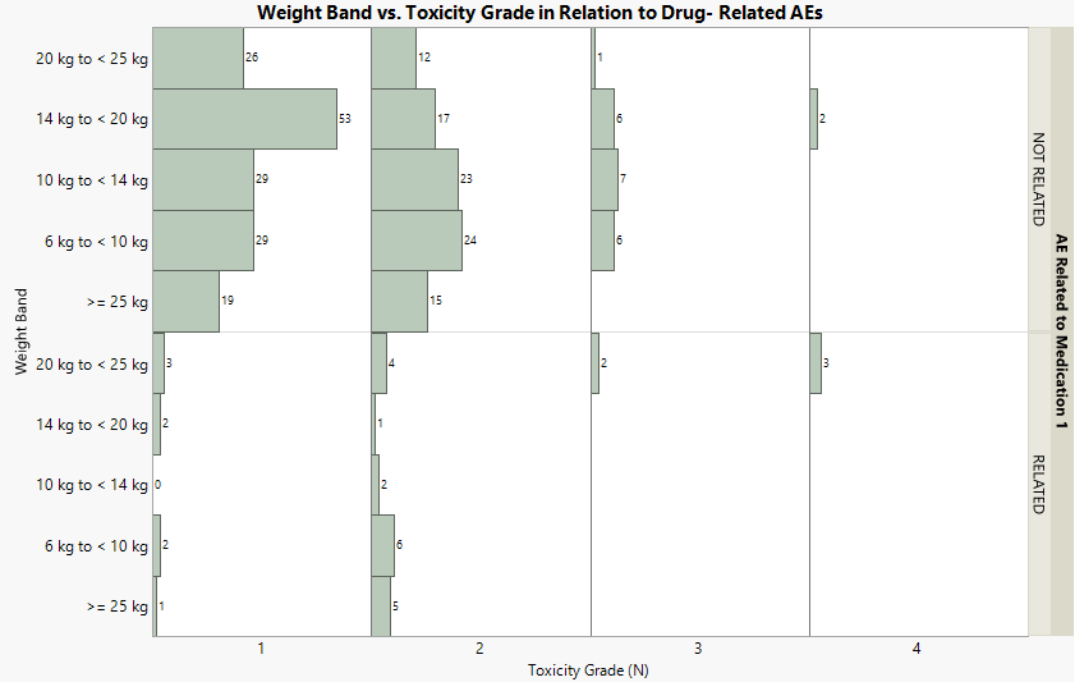
Table 5. Most Common Adverse Events Occurring in at Least 5% of Participants Through Week 48 for All Weight Bands by Maximum Severity, IMPAACT 2019 (Study 205860)

System Organ Class Preferred Term	All Weight Bands *(N=57)*					
	Grade 1 to 5 n (%)	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Investigations	**48 (84.2)**	**5 (8.8)**	**33 (57.9)**	**8 (14.0)**	**2 (3.5)**	**0 (0.0)**
Glomerular filtration rate decreased	36 (63.2)	0 (0.0)	29 (50.9)	6 (10.5)	1 (1.8)	0 (0.0)
Blood creatinine increased	26 (45.6)	4 (7.0)	16 (28.1)	5 (8.8)	1 (1.8)	0 (0.0)
Alanine aminotransferase increased	21 (36.8)	18 (31.6)	1 (1.8)	1 (1.8)	1 (1.8)	0 (0.0)
Aspartate aminotransferase increased	13 (22.8)	12 (21.1)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Blood cholesterol increased	9 (15.8)	6 (10.5)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Low density lipoprotein increased	5 (8.8)	2 (3.5)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin decreased	4 (7.0)	4 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil count decreased	4 (7.0)	1 (1.8)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	3 (5.3)	1 (1.8)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine renal clearance decreased	3 (5.3)	0 (0.0)	2 (3.5)	1 (1.8)	0 (0.0)	0 (0.0)
Infections and infestations	**23 (40.4)**	**12 (21.1)**	**9 (15.8)**	**2 (3.5)**	**0 (0.0)**	**0 (0.0)**
Upper respiratory tract infection	6 (10.5)	2 (3.5)	4 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	5 (8.8)	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Covid-19	4 (7.0)	1 (1.8)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Tonsillitis	3 (5.3)	1 (1.8)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	**23 (40.4)**	**15 (26.3)**	**8 (14.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Cough	20 (35.1)	15 (26.3)	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhea	13 (22.8)	11 (19.3)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal congestion	6 (10.5)	6 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Productive cough	5 (8.8)	4 (7.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	**11 (19.3)**	**6 (10.5)**	**3 (5.3)**	**2 (3.5)**	**0 (0.0)**	**0 (0.0)**
Neutropenia	7 (12.3)	4 (7.0)	1 (1.8)	2 (3.5)	0 (0.0)	0 (0.0)
Lymphadenopathy	3 (5.3)	2 (3.5)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**11 (19.3)**	**6 (10.5)**	**3 (5.3)**	**2 (3.5)**	**0 (0.0)**	**0 (0.0)**
Decreased appetite	7 (12.3)	6 (10.5)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Underweight	6 (10.5)	3 (5.3)	1 (1.8)	2 (3.5)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	**8 (14.0)**	**6 (10.5)**	**2 (3.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Vomiting	3 (5.3)	2 (3.5)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**8 (14.0)**	**5 (8.8)**	**2 (3.5)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**
Pyrexia	7 (12.3)	6 (10.5)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Nervous system disorders	**6 10.5)**	**6 (10.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Headache	3 (5.3)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer; adae.xpt dataset.
Filters: TRT01A = "ABC/DTG/3TC" and ENRLFL = "Y" (All Weight Bands); TRTEMFL = "Y" and ATOXGRN = ("Grade 1 to 5", "Grade 1", "Grade 2", "Grade 3", "Grade 4", or "Grade 5") (Adverse Events).
Percent Threshold: All Weight Bands - Grade 1 to 5 ≥ 5%.
N = Number of all treated population participants in all weight bands.
n (%) = Number (percent) of participants in each subcategory.
Participants may have reported more than one event within each PT or SOC.
For each PT or SOC, a participant was only counted for the worst reported grade.
Grade: 1= Mild, Grade 2= Moderate, Grade 3 = Severe, 4 = Potentially Life-Threatening, 5 = Death

The distribution of TEAEs and ADRs and their severities was similar across all weight bands with no significant outliers in the ≥6 kg to <10 kg weight band as shown in Figure 2.

Figure 2. Weight Band Versus Toxicity Grade Categorized by Related and Non-related Treatment Emergent Adverse Events, IMPAACT 2019 (Study 205860)



Source: Clinical Reviewer's Analysis (JMP 16 2 0, adae xpt dataset)
Abbreviations: AE, adverse event
Toxicity Grade: 1, mild, 2, moderate, 3, severe, 4, potentially life-threatening
Medication 1 refers to TRIUMEQ for weight band ≥25 kg and TRIUMEQ PD for all other weight bands

ADRs are shown in Table 6. Most of the ADRs were the MedDRA preferred terms of *Glomerular filtration rate decreased* (13 of 57 of participants [22.8%]) and *Blood creatinine increased* (10 of 57 participants [17.5%]). Out of 15 participants experiencing an ADR, only 1 participant experienced a drug-related SAE (Grade 4 DILI described in section 7.2.3). Through Week 48, two participants, both in the ≥20 kg to <25 kg enrollment weight band, experienced a total of five ADRs that had a severity of Grade 3 or Grade 4; all other ADRs had a severity of Grade 1 or Grade 2.

Table 6. Adverse Drug Reactions through Week 48 for All Weight Bands (All Treated Population), IMPAACT 2019 (Study 205860)

System Organ Class Preferred Term	All Weight Bands (N=57)					
	Grade 1 to 5 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Participants with ≥1 drug-related AE	**15 (26.3)**	**1 (1.8)**	**12 (21.1)**	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**
Investigations	**14 (24.6)**	**0 (0.0)**	**12 (21.1)**	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**
Glomerular filtration rate decreased	13 (22.8)	0 (0.0)	12 (21.1)	1 (1.8)	0 (0.0)	0 (0.0)
Blood creatinine increased	10 (17.5)	4 (7.0)	5 (8.8)	1 (1.8)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	3 (5.3)	2 (3.5)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Aspartate aminotransferase increased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Blood bilirubin increased	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Neutropenia	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (1.8)**	**0 (0.0)**

System Organ Class Preferred Term	All Weight Bands (N=57)					
	Grade 1 to 5 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Drug-induced liver injury	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Nervous system disorders	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Headache	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	**1 (1.8)**	**0 (0.0)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Nightmare	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer; adae.xpt dataset.
Filters: TRT01A = "ABC/DTG/3TC" and ENRLFL = "Y" (All Weight Bands); TRTEMFL = "Y" and AEREL01 = "RELATED" and ATOXGRN = ("Grade 1 to 5", "Grade 1", "Grade 2", "Grade 3", "Grade 4", or "Grade 5") (Adverse Events).
N = Number of all treated population participants in all weight bands.
n (%) = Number (percent) of participants in each subcategory.
Participants may have reported more than one event within each PT or SOC.
For each PT or SOC, a participant was only counted for the worst reported grade.
Grade: 1= Mild, Grade 2= Moderate, Grade 3 = Severe, 4 = Potentially Life-Threatening, 5 = Death

Clinical Reviewer's Comment: ADRs in IMPAACT 2019 were similar to those previously described in adult and pediatric studies of TRIMEQ and TRIUMEQ PD. All of the ADRs in IMPAACT 2019 are adequately described in the finalized labeling.

7.2.2 Deaths

No deaths occurred through the end of the study (Week 48) in IMPAACT 2019.

7.2.3 Serious Adverse Events

There were a total of three SAEs in three participants in the IMPAACT 2019 study, which included one treatment-related SAE. The three SAEs are summarized below.

Drug Induced Liver Injury (Grade 4):
One participant developed Grade 4 drug-induced liver injury (DILI), which led to permanent discontinuation of study drug. The event was considered drug-related by the clinical investigator and the Applicant. This DILI case was reviewed and assessed in the supplemental NDA (S-028) and NDA approving TRIUMEQ and TRIUMEQ PD, respectively, for patients weighing ≥10 kg.

The DILI case occurred in a 7-year-old male in Thailand with a past medical history of perinatally-acquired HIV and chronic otitis media. This patient's oral ART regimen prior to study enrollment was zidovudine (ZDV)/3TC and lopinavir (LPV)/ritonavir (RTV) twice daily, which he took for several months prior to study participation. After the participant was enrolled in the IMPAACT P2019 study, he transitioned to TRIUMEQ PD, dosed per protocol based on body weight. His clinical course was unremarkable until the Week 36 visit, during which he reported good health except an episode of coughing 1.5 months prior. His physical exam revealed rhinorrhea with pale conjunctivae, but no jaundice was noted. Laboratory results were notable for elevated hepatic enzymes and total bilirubin, as shown in Table 7. Study drug was held according to the protocol and permanently discontinued the following day because of the concern for DILI. Investigations carried out to exclude viral etiologies included tests for hepatitis A, B, C, E, cytomegalovirus, Epstein-Barr virus, SARS CoV-2, and stool adenovirus. Other measurements included ceruloplasmin, stool for ova and parasite, syphilis, blood ammonia, anti-nuclear antibodies, anti-smooth muscle antibodies, anti-liver kidney microsomal antibodies, alpha-1-antitrypsin and blood IgG. A liver ultrasound was also performed and was normal. The participant was seen by a pediatric gastrointestinal specialist at an unscheduled visit during Week 38 and the most likely diagnosis was felt to be DILI. The DILI event was considered drug-related by the clinical investigator and the Applicant. At the Week 43 visit, the participant was re-initiated on his previous ARV regimen prior to enrollment (ZDV/3TC + LPV/RTV) and the DILI event was reported as resolved on the last study visit.

Table 7. Summary of Laboratory Results for the DILI Case, IMPAACT 2019 (Study 205860)

Test name	Results					
	Week 24	Week 36	Week 38	Week 40	Week 42	Week 44
Total bilirubin (mg/dL)	0.61	0.62 (Grade 1)	0.62 (Grade 1)	0.49 (Grade 1)	0.87 (Grade 2)	0.67 (Grade 2)
Direct bilirubin (mg/dL)	0.14	0.31	0.52	0.30	0.33	0.32
Alanine aminotransferase (U/L)	33	272 (Grade 4)	953 (Grade 4)	352 (Grade 4)	110 (Grade 2)	32 (Grade 1)
Aspartate aminotransferase (U/L)	40	275 (Grade 3)	1045 (Grade 4)	262 (Grade 3)	115 (Grade 2)	43

Source: Clinical Reviewer's analysis (JMP v.16.2.0) of the adlb.xpt dataset.

Clinical Reviewer's Comment: The case of DILI is assessed as related to study drug. Although the long latency for the development of DILI in this participant is unusual (36 weeks), DILI may still occur at this late stage as seen in the OSE/DPV review of DTG-containing products (Debra Boxwell; DARRTS, May 11, 2017), which showed the onset of clinical hepatitis or liver failure can take several months (up to 30 weeks) after starting DTG-containing products. There is a known potential for hepatotoxicity from ABC and DTG. Clinical trials in adults of DTG/ABC/3TC demonstrated Grade 3 to 4 hepatic AEs in 1% of the population. Notably, no subjects had Grade 3 or 4 AEs in pediatric trials of DTG; however, one patient in the ARROW trial who received ABC/3TC developed Grade 3 or 4 hepatotoxicity of unknown causality. In this case, no alternate etiology was identified, and the patient's transaminases improved once TRIUMEQ was discontinued. Because the participant was receiving 3TC and was restarted on 3TC after the development of DILI, it is therefore likely the elevated LFTs were related to the ABC or DTG components specifically. In addition, the review team assessed the intensive and sparse PK results for this participant and noted the exposures of all three entities (DTG, ABC, and 3TC) were consistent with the geometric mean values of the weight band as whole and within the predicted exposure ranges. Although the TRIUMEQ label includes the potential for hepatoxicity in adults, labeling was adjusted to include additional details of this pediatric DILI case.

Gastroenteritis (Grade 3):
The gastroenteritis event occurred in a 22-month-old male participant from Botswana enrolled into weight band 1 (≥6 to <10 kg). The participant was started on DTG/ABC/3TC 15/180/90 mg orally once daily and switched to a dose of 20/240/120 mg approximately 3 months later after growing into the next weight band. The participant's overall course was complicated by intermittent infections: upper respiratory tract infection (URTI) at the Week 1 visit treated with amoxicillin, paracetamol, saline drops, and chlorpheniramine maleate; acute tonsillitis (Grade 2 severity AE) at the Week 4 visit treated with benzathine penicillin and paracetamol; and cough with pharyngeal erythema (2 weeks after a COVID-19 infection) at the Week 12 visit treated with a single dose of intramuscular ceftriaxone.

At Week 24, the participant's labs revealed a Grade 2 serum creatinine change from baseline and a Grade 2 eGFR change from baseline despite having creatinine and eGFR value within normal limits. Ten days later (Study Day 180) the participant developed Grade 3 acute gastroenteritis that necessitated hospitalization. The participant was admitted to the hospital with a 1-day history of diarrhea, vomiting, and abdominal pains. On examination, the participant's vital signs included a temperature of 36.5ºC, pulse 136 beats per minute, and respiratory rate of 40. He was alert and conscious, in mild respiratory distress with no signs of dehydration. Respiratory examination revealed good air entry bilaterally and no added sounds. Cardiovascular examination revealed normal heart sounds with no added sounds. On abdominal examination the participant was non-distended, soft, and non-tender with no organomegaly.

A diagnosis of acute gastroenteritis and reactive thrombocytosis was made. Given the event of hospitalization, this was considered an SAE. The participant was discharged on hospital day 4, and the site confirmed that there was no history of the participant's exposure to unsafe food and water. No cause of

gastroenteritis was provided, and the site investigator had assessed the event as not related to study drug. Study drug was continued with no change and the outcome of the acute gastroenteritis was recovered/resolved.

Clinical Reviewer's Comment: We agree with the Investigator that the event of gastroenteritis was not related to study drug, which was received throughout and after the event.

Pneumonia (Grade 3):
This case occurred in 4-year-old female participant from Botswana enrolled in the ≥10 kg to <14kg weight band. The participant received DTG/ABC/3TC 25/300/150 mg once daily through week 48. The participant's medical history was significant for pulmonary tuberculosis infection in 2018.

The participant's clinical course was complicated by a maculopapular rash at study entry that resolved by Week 12, a URTI at the Week 4 visit treated with chlorphenamine maleate, paracetamol, and amoxicillin, and pneumonia (Grade 2 non-serious AE) at the Week 12 visit.

At the Week 24 visit, the participant's mother reported a 1-month history of cough and loss of appetite without shortness of breath, fever, night sweats, or history of weight loss. On physical exam the participant was alert and conscious but was in mild cardio-respiratory distress with required use of accessory muscles of breathing, tachypnoea, wheezing and nasal flaring. The participant was admitted to the hospital for Grade 3 pneumonia and started on amoxicillin and gentamicin. Relevant investigations included: a negative COVID-19 antigen test and a chest x-ray showing patchy infiltrates, enlarged lymph nodes and a mild left sided pleural effusion. GeneXpert was negative for tuberculosis and the participant was eventually discharged from the hospital on oral antibiotics. Given the event of hospitalization, this was considered an SAE. The outcome of the event of pneumonia was recovered/resolved 7 days after developing Grade 3 pneumonia. The Investigator assessed the event as not related to study drug.

Clinical Reviewer's Comment: We agree with the Investigator that the event of pneumonia was not related to study drug, which was received throughout and after the event.

7.2.4 Dropouts and/or Discontinuations Due to Adverse Events (AEs)

Through Week 48, one participant (PID (b) (6)) permanently discontinued study drug Week 36 because of an SAE of DILI (see Section 7.2.3).

7.2.5 Adverse Events of Special Interest

Adverse events of special interest (AESI) have been determined for DTG/ABC/3TC FDC based on the following: nonclinical and/or clinical safety data for DTG (e.g., gastrointestinal disorders, renal disorders, hepatobiliary disorders), ABC (e.g., suspected ABC hypersensitivity), and 3TC; labeling and/or regulatory authority interest for INSTIs and/or the INSTI class (e.g., psychiatric disorders, rhabdomyolysis and myositis, serious rash and/or hypersensitivity); increased incidence of immune reconstitution inflammatory syndrome (IRIS); and/or regulatory authority requirements.

During this study, there were no unexpected safety findings related to the identified DTG/ABC/3TC FDC-related risks of IRIS events, hypersensitivity, and rash (including suspected ABC hypersensitivity), psychiatric disorders, gastrointestinal disorders, and musculoskeletal disorders. Hepatobiliary-related events were consistent with product labeling; there was one case of DILI reported (see Section 7.2.3), but DILI cases have previously been reported in adults. The majority of reported renal-related events were identified following a change from baselines values and were not associated with clinically significant events (see Section 7.4.2).

7.3 Growth

Not included in the study protocol.

7.4 Graded Laboratory abnormalities

Most clinical laboratory findings reported in IMPAACT 2019 are reflective of the pediatric population under study and were also consistent with the laboratory findings described in current product labeling for TRIUMEQ and TRIUMEQ PD. Through Week 24, Week 48, and End of Study, clinical AEs based on laboratory findings were typically Grade 1 or Grade 2. The most common AEs related to laboratory findings were related to changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and eGFR. Throughout the study, there were no SAEs due to a laboratory abnormality.

7.4.1 Hepatic Laboratory Abnormalities

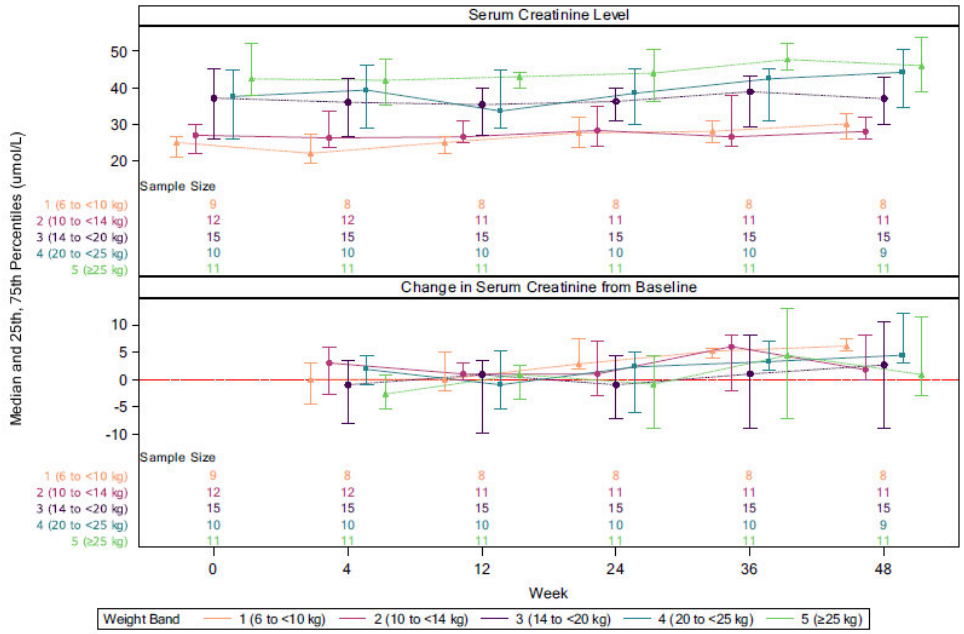
Review of liver chemistries and hepatobiliary-related-findings did not reveal any new patterns of concern. Hepatobiliary-related events were consistent with product labeling. Increases in ALT and AST from baseline were frequently reported, but these were mostly Grade 1 and resolved while receiving continued treatment. Changes seen in the lowest four weight bands were minimal.

Two of the 57 participants experienced ≥Grade 3 increases in liver transaminases. One of the participants was the DILI case from the ≥20 kg to <25 kg weight band described in Section 7.2.3. The second participant was a 3-year-old initially enrolled in the ≥10 kg to <14 kg group, who had advanced to the ≥14 kg to >20 kg prior to the event. The participant had normal ALT and AST levels at screening and experienced Grade 3 ALT and Grade 1 AST increases at Week 48. The participant had Grade 1 increases in ALT and AST noted at various time points between Week 4 and Week 36. Bilirubin remained at baseline throughout the study. At an unscheduled follow-up visit 6 days after the Week 48 visit, ALT improved to Grade 1 and AST was normal. The ALT and AST abnormalities were not associated with clinical signs or symptoms of hepatitis.

7.4.2 Renal Laboratory Parameters

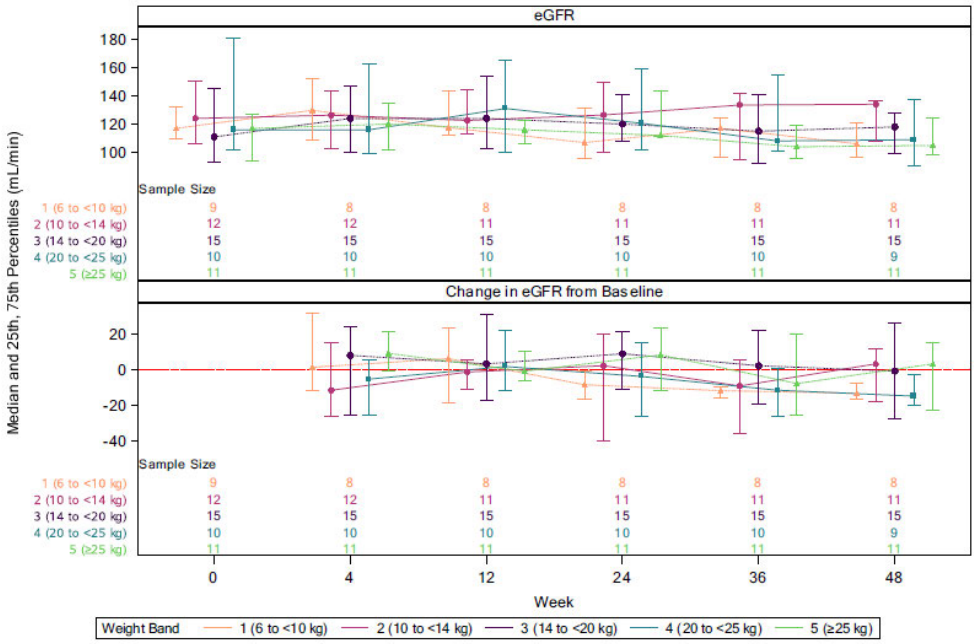
Throughout 48 weeks of treatment, small increases in median serum creatinine values were noted across all weight bands, with small resultant decreases in eGFR noted in most weight bands (See Figures 3 and 4 and Tables 10 and 11 in Appendix A).

Figure 3. Median Serum Creatinine and Change in Serum Creatinine from Baseline by Visit and Weight Band (All Treated Population), IMPAACT 2019 (Study 205860)



Source: Applicant's Clinical Study Report of IMPAACT 2019, Page 240

Figure 4. Median Estimated Glomerular Filtration Rate and Change in Estimated Glomerular Filtration Rate by Visit and Weight Band (All Treated Population), IMPAACT 2019 (Study 205860)



Source: Applicant's Clinical Study Report of IMPAACT 2019, Page 241

Based on DAIDS grading, most changes in creatinine or eGFR had a maximum severity of Grade 2; a small number had ≥Grade 3 increase in creatinine (n=5) and/or ≥Grade 3 decrease in eGFR (n=8). When severity grading was based on actual laboratory-measured values, the values were either normal, Grade 1, or Grade 2. The events were not serious, did not lead to permanent discontinuation of study drug, and were not considered to be associated with any events of clinical significance such as renal failure. Based on current product labeling for DTG-containing regimens, small mean increases in serum creatinine are expected due to non-pathological inhibition of organic cation transporter 2 (OCT2) in the proximal renal tubules, which typically become evident within the first few weeks after initiation of DTG and then remain stable over time. This increase in serum creatinine conversely leads to small decreases in the creatinine-derived eGFR. 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).

Clinical Reviewer's Comment: Changes in creatinine and eGFR were among the most common laboratory findings noted. DTG is known to effect creatine clearance (via inhibition of OCT2, not direct glomerular toxicity), and this is already included in TRIUMEQ and TRIUMEQ PD prescribing information. Review of renal-related laboratory changes did not reveal any new patterns of concern. It is important to recognize that the DAIDS grading table requires grading of creatinine and eGFR values based on both the laboratory-measured values and the change from baseline, with the higher of the two grades assigned. This method of grading could have led to a normal laboratory value being assigned an abnormal severity grade based on a change from baseline. Additionally, it is not unexpected for infants to have variability in observed creatinine values that is within the normal range due to growth and renal maturation. Thus, in addition to any potential OCT2 inhibition from DTG, children may experience larger changes from baseline in creatinine and creatinine-based eGFR over 48 weeks of treatment compared with adults due to their growth and development.

8 Therapeutic Individualization

8.1 Drug Interactions

No new findings relevant to the coadministration of TRIUMEQ or TRIUMEQ PD with other drugs were submitted with these sNDAs.

8.2 Pediatric Populations

This submission was intended to extend labeling of TRIUMEQ PD to pediatric patients aged ≥3 months and weighing 6 kg to <10 kg and to fulfill PMRs 2768-1 (TRIUMEQ NDA 205551) and 4247-1 (TRIUMEQ PD NDA 215413). DAV agrees that the PMRs have been sufficiently addressed and an approval action is warranted.

The review team's conclusions were presented to the Pediatric Review Committee (PeRC) who considered the PMRs fulfilled and the application approvable. The indication will be extended to pediatric patients with HIV-1 infection aged ≥3 months and weighing ≥6 kg to <10 kg for the reasons outlined previously.

8.3 Pregnancy and Lactation

ABC, DTG, and 3TC are present in human milk; however, there is no information on the effects of TRIUMEQ, TRIUMEQ PD, or individual components on the breastfed infant or the effects of the drug on milk production. The Applicant did not propose any labeling changes under the Lactation subsection.

9 Advisory Committee Meeting

An Advisory Committee Meeting was not held for these supplemental NDA applications. No significant issues were raised to warrant a public discussion.

10 Other Relevant Regulatory Issues

10.1 Submission Quality and Integrity

The quality and integrity of the submissions were adequate. From a clinical review perspective, the submissions were well organized and reasonable to navigate.

Upon Agency review of the number of subjects enrolled at each site, as well as the list of protocol deviations and discontinuations due to TEAEs, there were no aberrations identified to warrant any site inspections. No requests were made to the Office of Scientific Investigations (OSI) for site inspections.

10.2 Compliance with Good Clinical Practices

Study 205860 (IMPAACT 2019) was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312)], the European Community Directive 2001/20/EC, and other local legislation.

The appropriate approvals from the independent ethics committee (IEC) or institutional review board (IRB) were secured before study initiation. Protocol amendments and all revisions to the consent form after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

11 Financial Disclosures

The Applicant submitted Form FDA 3454, which certifies that the Applicant did not enter into any financial relationships with principal or sub-investigators. The form included an attachment containing the names of principal investigators and sub-investigators for Study 205860 who have attested to the absence of financial interests or arrangements described in 21 CFR Part 54.4(a)(3). There were 172 total investigators, all of whom certified that they are not ViiV Healthcare employees, received no compensation for conducting the study where the value could be influenced by the outcome of the study, have no proprietary interest in the product, and have no significant equity interest held in the Applicant of the study.

See Appendix B for the Clinical Investigator Financial Disclosure Review Template.

12 Labeling

The USPI (United States Prescribing Information) and PPI (Patient Package Insert) have been agreed to and the main changes are summarized below.

Overall Major Change
Based on the Agency's review of the efficacy results at Week 48 from Study 205860 (IMPAACT 2019), the INDICATION AND USAGE section was revised to include children aged ≥3 months and weighing ≥6 kg.

Section 1 INDICATION AND USAGE
We recommended an age limit in addition to the weight limit for the indication. The age of 3 months was chosen upon agreement with the Applicant, as this is the average age of an infant weighing 6 kg. The new indication statement is as follows: TRIUMEQ and TRIUMEQ PD are a combination of dolutegravir (integrase strand transfer inhibitor [INSTI]), abacavir, and lamivudine (both nucleoside analogue reverse transcriptase inhibitors) indicated for the treatment of HIV-1 infection in adults and in pediatric patients aged ≥3 months and weighing ≥6 kg.
This language was updated in subsection 8.4 *Pediatric Use*; The language states the safety and effectiveness of TRIUMEQ PD have not been established in pediatric patients aged less than 3 months or weighing less than 6 kg.

Section 2 DOSAGE AND ADMINISTRATION
Subsection 2.5 *Recommended Dosage and Administration Instructions for Pediatric Patients Weighing at Least 6 kg*
Updated Table 1 to include dosing for pediatric patients with a body weight of ≥6 kg to 10 kg.

Section 6 ADVERSE REACTIONS
Subsection 6.1 *Clinical Trials Experience*
Updated to include the most common adverse reactions, which were primarily laboratory abnormalities (decreased glomerular filtration rate, increased blood creatinine, and increased ALT). Additional information was also added regarding the two participants who developed Grade 3 or 4 ADRs from the IMPAACT 2019 study, including the participant who discontinued TRIUMEQ after developing DILI (see section 7.2.3).

Section 8 USE IN SPECIFIC POPULATIONS
Subsection 8.6 *Patients with Impaired Renal Function*
Updated with the following language:

- *TRIUMEQ and TRIUMEQ PD are not recommended for patients with creatinine clearance <30 mL/min and pediatric patients with a similar degree of renal impairment based on age-appropriate assessment of renal function because TRIUMEQ and TRIUMEQ PD are fixed-dose combinations, and the dosage of the individual components cannot be adjusted.*
- *Patients with a sustained creatinine clearance between 30 and 49 mL/min or pediatric patients with a similar degree of renal impairment based on age-appropriate assessment of renal function who receive TRIUMEQ or TRIUMEQ PD should be monitored for hematologic toxicities.*

Section 12 CLINICAL PHARMACOLOGY
Subsection 12.4: *Microbiology*
Updated information in the *Resistance in Clinical Subjects* that includes the one case of CVF from the IMPAACT 2019 study (see section 6.2.2).

13 Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No recommendation for a REMS is indicated.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No new PMRs or PMCs are indicated.

14 Recommended Comments to the Applicant

No additional comments need to be communicated to the Applicant at this time.

15 Patient Experience Data

Patient Experience Data are listed in Table 8.

Table 8. Patient Experience Data Relevant to this Application

■	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)	
	□ Performance outcome (PerfO)	

	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	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) Palatability and acceptability of the tablet formulation were assessed in Study 205860 (IMPAACT 2019)	Module 2.5, Section 4.5 Module 5.3.5.2, 205860 CSR, Section 10
x	Patient experience data was not submitted as part of this application.		

Palatability and acceptability of DTG/ABC/3TC DTs and DTG/ABC/3TC Tablets among children <12 years of age at 4, 24 and 48 weeks of treatment was a secondary objective of IMPAACT 2019. The DT and Tablet formulations were considered adequately palatable and administration generally acceptable for the majority of children/caregivers and no major concerns were identified across the weight bands.

Appendix A. Supplemental Tables and Figures

Table 9. Most Common Adverse Events Through Week 48 for All Weight Bands by Maximum Severity, IMPAACT 2019 (Study 205860)

System Organ Class Preferred Term	All Weight Bands (N=57)				
	Grade 1 to 5 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders	**11 (19.3)**	**6 (10.5)**	**3 (5.3)**	**2 (3.5)**	**0 (0.0)**
Anemia	2 (3.5)	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Eosinophilia	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphadenopathy	3 (5.3)	2 (3.5)	1 (1.8)	0 (0.0)	0 (0.0)
Neutropenia	7 (12.3)	4 (7.0)	1 (1.8)	2 (3.5)	0 (0.0)
Secondary thrombocytosis	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Cardiac disorders	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Tachycardia	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Otorrhea	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Conjunctival pallor	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	**8 (14.0)**	**6 (10.5)**	**2 (3.5)**	**0 (0.0)**	**0 (0.0)**
Abdominal discomfort	2 (3.5)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	2 (3.5)	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Abdominal pain upper	2 (3.5)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal tenderness	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Dental caries	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Flatulence	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Gingival swelling	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Vomiting	3 (5.3)	2 (3.5)	1 (1.8)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**8 (14.0)**	**5 (8.8)**	**2 (3.5)**	**1 (1.8)**	**0 (0.0)**
Facial pain	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling hot	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Malaise	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Pyrexia	7 (12.3)	6 (10.5)	0 (0.0)	1 (1.8)	0 (0.0)
Swelling face	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	**2 (3.5)**	**1 (1.8)**	**0 (0.0)**	**1 (1.8)**	**0 (0.0)**
Drug-induced liver injury	1 (1.8)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Hepatomegaly	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	**23 (40.4)**	**12 (21.1)**	**9 (15.8)**	**2 (3.5)**	**0 (0.0)**
Bronchiolitis	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Cellulitis	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Covid-19	4 (7.0)	1 (1.8)	3 (5.3)	0 (0.0)	0 (0.0)
Gastroenteritis	2 (3.5)	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)
Lower respiratory tract infection	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Nasopharyngitis	5 (8.8)	5 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)
Otitis media chronic	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	2 (3.5)	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)
Pneumonia	2 (3.5)	0 (0.0)	1 (1.8)	1 (1.8)	0 (0.0)
Subcutaneous abscess	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)

Tinea capitis	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Tinea faciei	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Tonsillitis	3 (5.3)	1 (1.8)	2 (3.5)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	6 (10.5)	2 (3.5)	4 (7.0)	0 (0.0)	0 (0.0)
Viral upper respiratory tract infection	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**2 (3.5)**	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**
Adverse event following immunization	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Contusion	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Ligament sprain	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Investigations	**48 (84.2)**	**5 (8.8)**	**33 (57.9)**	**10 (17.5)**	**0 (0.0)**
Alanine aminotransferase increased	21 (36.8)	18 (31.6)	1 (1.8)	2 (3.5)	0 (0.0)
Aspartate aminotransferase increased	13 (22.8)	12 (21.1)	0 (0.0)	1 (1.8)	0 (0.0)
Blood alkaline phosphatase increased	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	3 (5.3)	1 (1.8)	2 (3.5)	0 (0.0)	0 (0.0)
Blood cholesterol increased	9 (15.8)	6 (10.5)	3 (5.3)	0 (0.0)	0 (0.0)
Blood creatinine increased	26 (45.6)	4 (7.0)	16 (28.1)	6 (10.5)	0 (0.0)
Blood pressure increased	1 (1.8)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Blood pressure systolic increased	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Blood triglycerides increased	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine renal clearance decreased	3 (5.3)	0 (0.0)	2 (3.5)	1 (1.8)	0 (0.0)
Gamma-glutamyltransferase increased	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Glomerular filtration rate decreased	36 (63.2)	0 (0.0)	29 (50.9)	7 (12.3)	0 (0.0)
Hemoglobin decreased	4 (7.0)	4 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)
Low density lipoprotein increased	5 (8.8)	2 (3.5)	3 (5.3)	0 (0.0)	0 (0.0)
Neutrophil count decreased	4 (7.0)	1 (1.8)	3 (5.3)	0 (0.0)	0 (0.0)
Platelet count decreased	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**11 (19.3)**	**6 (10.5)**	**3 (5.3)**	**2 (3.5)**	**0 (0.0)**
Abnormal loss of weight	1 (1.8)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Decreased appetite	7 (12.3)	6 (10.5)	1 (1.8)	0 (0.0)	0 (0.0)
Malnutrition	2 (3.5)	0 (0.0)	1 (1.8)	1 (1.8)	0 (0.0)
Underweight	6 (10.5)	3 (5.3)	1 (1.8)	2 (3.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Pain in extremity	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	**6 (10.5)**	**6 (10.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Dizziness	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	3 (5.3)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Lethargy	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	2 (3.5)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	**1 (1.8)**	**0 (0.0)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**
Nightmare	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Renal and urinary disorders	**1 (1.8)**	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Dysuria	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**23 (40.4)**	**15 (26.3)**	**8 (14.0)**	**0 (0.0)**	**0 (0.0)**
Childhood asthma	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Cough	20 (35.1)	15 (26.3)	5 (8.8)	0 (0.0)	0 (0.0)
Dyspnoea	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Dyspnoea exertional	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Epistaxis	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal congestion	6 (10.5)	6 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)
Nasal flaring	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Oropharyngeal pain	2 (3.5)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngeal erythema	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)

Productive cough	5 (8.8)	4 (7.0)	1 (1.8)	0 (0.0)	0 (0.0)
Rales	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Respiratory distress	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinorrhoea	13 (22.8)	11 (19.3)	2 (3.5)	0 (0.0)	0 (0.0)
Rhonchi	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Tachypnoea	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Tonsillar exudate	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Tonsillar inflammation	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Upper respiratory tract congestion	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Wheezing	2 (3.5)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**5 (8.8)**	**3 (5.3)**	**2 (3.5)**	**0 (0.0)**	**0 (0.0)**
Hyperhidrosis	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Perioral dermatitis	1 (1.8)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)
Rash	2 (3.5)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Skin plaque	1 (1.8)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
N = Number of all treated population participants in all weight bands.
n (%) = Number (percent) of participants in each subcategory (with respect to the number of all treated population participants in all weight bands)
Participants may have reported more than one event within each PT or SOC.
For each PT or SOC, a participant was only counted for the worst reported grade.
There were no Grade 5 events.
Events listed in descending order.
Grade: 1= Mild, Grade 2= Moderate, Grade 3 = Severe, 4 = Potentially Life-Threatening, 5 = Death

Table 10. Serum Creatinine Change from Baseline by Visit and Weight Band (All Treated Population)

Analysis Visit		Weight Band 1 6 to <10 kg (N=9)	2 10 to <14 kg (N=12)	3 14 to <20 kg (N=15)	4 20 to <25 kg (N=10)	5 ≥25 kg (N=11)	Total (N=57)
Week 4	n	8	12	15	10	11	56
	Mean (SD)	-1.0000 (5.18586)	2 0423 (5.65930)	-1.5933 (10.24611)	1.6956 (4.57668)	-2.8444 (6.50577)	-0.3879 (7.17005)
	Median	0.0000	3.0000	-1 0000	1.8260	-2.6520	-0.9420
	(Q1, Q3)	(-4.5000, 3.0000)	(-2.8260, 6.0000)	(-7.9560, 3.5360)	(-1 0000, 4.4200)	(-5.3040, 0.8840)	(-4.5000, 4 2100)
	(Min, Max)	(-10.000, 5.000)	(-6.188, 12 000)	(-24 000, 18 564)	(-7.072, 9.724)	(-15.912, 7.956)	(-24.000, 18.564)
Week 12	n	8	11	15	10	11	55
	Mean (SD)	0.9130 (3.73141)	0 9724 (3.50246)	-2.5797 (9.54406)	-0.1536 (5.19738)	-0.2345 (6.28683)	-0.4511 (6.44102)
	Median	0.0000	1.0000	0 8840	-1 0000	0.8840	0.8840
	(Q1, Q3)	(-2.0000, 5.0000)	(0 0000, 3.0000)	(-9.7240, 3.5360)	(-5 3040, 5.3040)	(-3.5360, 2.6520)	(-3.5360, 4 0000)
	(Min, Max)	(-4.000, 5.304)	(-6.188, 7.000)	(-27.000, 9.000)	(-6.188, 6.188)	(-10 000, 11.492)	(-27.000, 11.492)
Week 24	n	8	11	15	10	11	55
	Mean (SD)	4.0525 (4 01385)	2.1924 (5.41909)	-2.7952 (11.26653)	0.5840 (7.23077)	-0.9618 (8.35869)	0.1794 (8 23950)
	Median	2.8260	1.0000	-1 0000	2.2680	-0.8840	1.0000
	(Q1, Q3)	(1.8840, 7.5000)	(-3.0000, 7.0000)	(-7.0720, 4.4200)	(-6 0000, 5.0000)	(-9.0000, 4.4200)	(-5.3040, 6 0000)
	(Min, Max)	(-2.000, 10.000)	(-3 536, 13 000)	(-36 000, 12 376)	(-13.260, 9.724)	(-14.144, 13.260)	(-36.000, 13.260)
Week 36	n	8	11	15	10	11	55
	Mean (SD)	4.9510 (1 81917)	3 5982 (5.59465)	0.4579 (9.01024)	4.8216 (4.99895)	4.6415 (10.03444)	3.3696 (7 31714)
	Median	5.1520	6.0000	1 0000	3.2680	4.4200	4.0000
	(Q1, Q3)	(4.0000, 5.6520)	(-2.0000, 8.0000)	(-9.0000, 8.0000)	(1.7680, 7.0000)	(-7.0720, 13.0000)	(-1.0000, 8 0000)
	(Min, Max)	(2.000, 8.000)	(-6.188, 11 000)	(-14.000, 15.912)	(-0 884, 15.912)	(-9 000, 17.680)	(-14.000, 17.680)
Week 48	n	8	11	15	9	11	54
	Mean (SD)	5.9365 (1.94523)	3.1502 (4.56889)	0.3651 (11.49845)	5.7502 (6.45293)	2.7113 (8.18640)	3.1333 (7.92766)
	Median	6 0940	1.7680	2.6520	4.4200	0.8840	3.2680
	(Q1, Q3)	(5.1520, 7.5000)	(0.0000, 8.0000)	(-8.8400, 10.6080)	(3.0000, 12.0000)	(-3 0000, 11.4920)	(-2.6520, 8.0000)
	(Min, Max)	(2.000, 8.000)	(-3 000, 11.000)	(-25.000, 15.912)	(-3.000, 15.028)	(-8.000, 15.912)	(-25.000, 15.912)

Source: Applicant's Clinical Study Report of IMPAACT 2019 (Pages 317, 318)
N = Number of participants in each weight band; n = Number of participants with results in each subcategory in each weight band; Mean (SD) = Mean (Standard Deviation); Q1,Q3 = 25th percentile, 75th percentile; Min, Max = Minimum, Maximum Results obtained through the end of treatment date + 1 day have been included in this analysis

Table 11. Estimated Glomerular Filtration Rate Change from Baseline by Visit and Weight Band (All Treated Population)

	Mean (SD)	-6.2687 (21.28143)	-5.1327 (32.73361)	4.3573 (39.79233)	0.3740 (30.40798)	6.1420 (22.75817)	0.5464 (30.68456)
				Weight Band			
Analysis Visit		1 6 to <10 kg (N=9)	2 10 to <14 kg (N=12)	3 14 to <20 kg (N=15)	4 20 to <25 kg (N=10)	5 ≥25 kg (N=11)	Total (N=57)
Week 4	n	8	12	15	10	11	56
	Mean (SD)	38 0000 (100.28173)	-9.1690 (26.43461)	1 5920 (26.89572)	-7.7990 (19.77012)	8 9802 (19.45011)	4.2615 (44.43319)
	Median	1.1500	-11.7500	7.8000	-5.5000	9.0000	4 0000
	(Q1, Q3)	(-12 0000, 31.5000)	(-26.6000, 15.0500)	(-26 0000, 24.0000)	(-26.0000, 5.0000)	(-1 0000, 21.0000)	(-17.2500, 16.8260)
	(Min, Max)	(-18.000, 280.700)	(-57.200, 24.520)	(-47.000, 36.000)	(-36.000, 26.210)	(-21.000, 51.000)	(-57.200, 280.700)
Week 12	n	8	11	15	10	11	55
	Mean (SD)	5 2088 (26.33105)	-2.6426 (25.62244)	1.6400 (33.54587)	1.6390 (19.13846)	0 5722 (14 86731)	1.0888 (24.71290)
	Median	6.0000	-1.5000	3.0000	1.6000	-1.0000	1 0000
	(Q1, Q3)	(-19 0650, 23.5000)	(-11.0000, 5.0000)	(-17 2000, 31.0000)	(-12.0000, 22.0000)	(-6.7060, 10.0000)	(-16.0000, 21.0000)
	(Min, Max)	(-27.000, 47.800)	(-52.000, 45.500)	(-90.100, 44.000)	(-23.500, 25.100)	(-28.000, 22.000)	(-90.100, 47.800)
Week 24	n	8	11	15	10	11	55
	Median	-8.6250	2.0000	8.7000	-4.0000	8.0000	0.0000
	(Q1, Q3)	(-17 0000, -1.0000)	(-40 0000, 20.0000)	(-10 9400, 21.0000)	(-26.6000, 15.0000)	(-12 0000, 23.0000)	(-16.5600, 20.0000)
	(Min, Max)	(-35.000, 38.100)	(-57.100, 49.800)	(-88.800, 77 000)	(-32.000, 57.900)	(-30.000, 47.000)	(-88.800, 77.000)
Week 36	n	8	11	15	10	11	55
	Mean (SD)	-11.4538 (7.17704)	-11.3390 (29 28825)	-2.6633 (35.03493)	-15.1060 (18.82400)	-4.1880 (24.76562)	-8.2443 (26.08819)
	Median	-12.0000	-9.4000	2.0000	-11.7500	-8.0000	-9.4000
	(Q1, Q3)	(-16.3150, -10.0000)	(-36.0000, 5 0000)	(-19.7000, 22.0000)	(-26.5000, 0.6400)	(-26 0000, 20.0000)	(-22.0000, 6.0000)
	(Min, Max)	(-19.000, 4 000)	(-55.200, 42.500)	(-81.800, 51.600)	(-46 000, 6.000)	(-32.000, 41.932)	(-81.800, 51.600)
Week 48	n	8	11	15	9	11	54
	Mean (SD)	-13.1163 (8.42555)	-7 9645 (28.14290)	-3.9773 (42.66901)	-13.2333 (26.75196)	-1.2289 (19.22594)	-7.1262 (28.97286)
	Median	-13.5000	2.9910	-1.0000	-15 0000	3.0000	-4.0000
	(Q1, Q3)	(-17 0650, -8.0000)	(-18 0000, 11.6000)	(-28 0000, 26.0000)	(-20.0000, -3.0000)	(-23 0000, 15.0000)	(-19.7000, 14.5000)
	(Min, Max)	(-28.000, 0 200)	(-59.700, 23.200)	(-120.700, 44.000)	(-58.300, 27.700)	(-30.000, 22.000)	(-120.700, 44.000)

Source: Applicant's Clinical Study Report of IMPAACT 2019 (Pages 293,294)
N = Number of participants in each weight band; n = Number of participants with results in each subcategory in each weight band; Mean (SD) = Mean (Standard Deviation); Q1,Q3 = 25th percentile, 75th percentile; Min, Max = Minimum, Maximum Results obtained through the end of treatment date + 1 day have been included in this analysis

Appendix B. Financial Disclosure

Clinical Investigator Financial Disclosure Review Template

Application Numbers: NDA 205551 (S-031), NDA 215413 (S-002)

Submission Date(s): December 15, 2022

Applicant: ViiV Healthcare

Product: TRIUMEQ (tablets for oral use); TRIUMEQ PD (tablets for oral suspension)

Reviewer: Timothy Jancel, PharmD, MHS

Date of Review: February 22, 2023

Covered Clinical Study: IMPAACT 2019, Study 205860
Phase I/II Study of the Pharmacokinetics, Safety, and Tolerability of Abacavir/Dolutegravir/Lamivudine Dispersible and Immediate Release Tablets in HIV-1-Infected Children Less than 12 Years of Age

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 172 Total (14 Principal Investigators and 158 Sub-Investigators)		
Number of investigators who are Applicant 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: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in Applicant of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	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:	Yes ☐	No ☐ (Request explanation from applicant)

Assessment:
The Applicant has adequately disclosed financial interests for IMPAACT 2019, Study 205860.

Of the 172 total investigators, all certified that they are not ViiV Healthcare employees, received no compensation for conducting the study where the value could be influenced by the outcome of the study, have no proprietary interest in the product, and have no significant equity interest held in the Applicant of the study.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIRGINIA A LONG
06/14/2023 02:28:50 PM

TIMOTHY J JANCEL
06/14/2023 02:38:53 PM

NATALIE M PICA
06/14/2023 03:41:49 PM

YODIT BELEW
06/14/2023 04:20:52 PM