Clinical Review of Original NDA and Efficacy Supplement

Date	March 4, 2022
From	Amy Bishara, Clinical Reviewer, DAV
Subject	Clinical Review
NDA# and Supplement#	NDA 205551/S-028 (Triumeq®) NDA 215413 (Triumeq PD®)
Applicant	ViiV Healthcare Company
Date of Submission	9/30/2021
PDUFA Goal Date	3/30/2022
Proprietary Name	Triumeq®, Triumeq® PD
Established or Proper Name	abacavir [ABC]/ dolutegravir [DTG]/lamivudine [3TC]
Dosage Form(s)	Triumeq (tablets for oral use): ▪ 600mg ABC, 50mg DTG, and 300mg 3TC Triumeq PD (tablets for oral suspension): ▪ 60mg ABC, 5mg DTG, and 30mg 3TC
Applicant Proposed Indication(s)/Population(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 weighing at least 14 kg. NDA 205551/S-28 **Triumeq**: Treatment of HIV-1 in pediatric patients weighing 25 kg to <40 kg NDA 215413 **Triumeq PD**: Treatment of HIV-1 in pediatric patients weighing 14 kg to <25 kg
Applicant Proposed Dosing Regimen(s)	Weight based dosing (see Section 10 Labeling)
Recommendation on Regulatory Action	*Approval*

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1. Benefit-Risk Assessment

Benefit-Risk Assessment
Triumeq® is a fixed dose combination tablet containing three antiretroviral drugs (ARVs): abacavir 600 mg/dolutegravir 50 mg/lamivudine 300 mg. Triumeq is currently indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing ≥ 40kg. With the current submissions, the Applicant seeks to extend the indication to pediatric patients weighing at least 14 kg to less than 40 kg. As proposed, pediatric patients weighing at least 25 kg would receive the adult tablet formulation and children weighing less than 25 kg would receive a novel dispersible tablet formulation developed for pediatric use, Triumeq PD® (ABC 60 mg/DTG 5 mg/3TC 30 mg). The safety and efficacy of Triumeq and Triumeq PD are supported by the approval of the individual components for children with HIV-1 infection weighing ≥14 to <40 kg: Ziagen® (abacavir, ABC), Tivicay® (dolutegravir, DTG), and Epivir® (lamivudine, 3TC). The results of a bioavailability/bioequivalence study (Study 205894) which compared Triumeq and Triumeq PD confirms that dosing with Triumeq PD yields pharmacokinetic exposures that are associated with efficacy for all three products. No new clinical trial data evaluating patients with HIV-1 infection were included with these applications. Throughout the review of the supplemental New Drug Application (sNDA) and original NDA, no deficiencies that would preclude approval for pediatric patients weighing at least 14 to less than 40 kg were identified. In addition, based on the known safety and efficacy profile and predicted and observed pharmacokinetics of the individual components in pediatric patients weighing at least 10 to <14 kg, the review team concluded that the overall benefit supports extension of the indication to children weighing ≥10 to <14 kg, for whom the individual components are also approved. In conclusion, after review of the prior approvals of ABC, DTG, and 3TC and the pharmacokinetic data from completed and ongoing studies, 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 weighing ≥10 kg to <40 kg.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HIV-1 infection is a life-threatening and serious disease of major public health significance. • Approximately 38 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 150,000 children < 15 years of age acquired HIV in 2020. • 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: o Abacavir/dolutegravir/lamivudine (Triumeq®) o Bictegravir/emtricitabine/tenofovir alafenamide [TAF] (Biktarvy®) o Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (Symtuza®) o Efavirenz/emtricitabine/tenofovir disoproxil fumarate [TDF] (Atripla®) o Elvitegravir/cobicistat/emtricitabine/TDF (Stribild®) o Elvitegravir/cobicistat/emtricitabine/TAF (Genvoya®) o Emtricitabine/rilpivirine/TDF (Complera®) o Emtricitabine/rilpivirine/TAF (Odefsey®) • Fixed-dose combination (FDC) STR treatments are a convenient option for treatment; however, in those weighing less than 25 kg there are fewer fixed dose combination or STR options. Biktarvy is the only INSTI-containing STR approved for children weighing less than 25kg.	• 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	• To support an efficacy claim for the use Triumeq/Triumeq PD for the treatment of HIV-1 infection in children weighing > 14 kg to < 40 kg, the Applicant cites the approval of the individual components (ABC, DTG, and 3TC) for this weight group. • A bioavailability/bioequivalence study (205894) confirms that dosing with Triumeq PD yields pharmacokinetic exposures that are associated with efficacy for all three	• Dosing with Triumeq PD yields pharmacokinetic exposures consistent with those achieved by dosing with the individual components. This information was previously established for Triumeq tablets. Therefore, accurate dosing

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	products. o Another important finding of this study is that Triumeq and Triumeq PD are not interchangeable due to differences in the pharmacokinetic (PK) profile of DTG. • Although the dosage of the individual components does not always align exactly with the approved dosage in every weight band, the proposed doses are expected to achieve exposures comparable to those correlated with efficacy in adult trials. • The efficacy of Triumeq and Triumeq PD for pediatric patients is informed by the clinical trials that supported approval of the components: ARROW (ABC/3TC administered once daily) and IMPAACT P1093 (DTG). o Participants in these trials had virologic and immunologic outcomes similar to adults. • Since the individual components are also approved for children weighing ≥10 to <14 kg, the review team determined that there are sufficient data to provide dosing recommendations for this population.	with Triumeq and Triumeq PD has been established for pediatric patients weighing at least 10 kg. • Each component (ABC, DTG, and 3TC) demonstrated durable virologic suppression in the pediatric population indicating efficacy of the FDC, Triumeq or Triumeq PD, itself. • 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 weigh ≥ 10 to < 40 kg.
Risk and Risk Management	• The safety of Triumeq and Triumeq PD for pediatric patients is informed by the clinical trials that supported approval of the components: ARROW (ABC/3TC administered once daily) and IMPAACT P1093 (DTG). o In ARROW, no new safety issues unique to the pediatric population were identified. There was one report of grade 4 hepatitis in the once-daily cohort considered to be of uncertain causality by the investigator; all other grade 3 and 4 events were considered to be unrelated. o In IMPAACT P1093, the adverse event profile of DTG was found to be similar to adults. No grade 3 or 4 adverse drug reactions were reported. • Of subjects administered Triumeq PD in the ongoing IMPAACT P2019 study, there was one grade 4 hepatotoxicity event determined to likely be drug-related. • Since all three drug components are approved for children weighing ≥ 10 to < 14 kg, the review team concluded that the indication could be extended to this population. Based on available data, no unique safety issues are anticipated for this population.	• The safety profile of the individual drugs contained in Triumeq/Triumeq PD were previously established during the review cycle of the respective NDAs. ABC and 3TC have been approved for decades and have well described pre- and post-marketing safety profiles. • Previously described safety findings for the individual drugs are applicable to the FDC drug product. No unique or new safety signals are anticipated with the FDC. • Continued routine post-marketing pharmacovigilance is recommended with the approval of Triumeq and Triumeq PD for pediatric patients weighing ≥10 to < 14 kg.

- The cup with the suspension should be swirled until no lumps remain and administered within 30 minutes of mixing.

The Applicant proposes the use of Triumeq PD tablets for oral suspension in patients weighing ≥14 to <25 kg and the use of Triumeq tablets in patients weighing ≥25 kg. Triumeq and Triumeq PD are not bioequivalent and therefore not interchangeable on a milligram-per-milligram basis due to pharmacokinetic profile differences of the dolutegravir component. Triumeq PD tablets for oral suspension should thus not be used in patients weighing ≥25 kg and Triumeq tablets should not be used in patients weighing <25 kg. When a pediatric patient is to be transitioned from the tablets for oral suspension form (Triumeq PD) to the tablet form (Triumeq) based upon corresponding weight changes, the dosage form must be adjusted accordingly, as failure to do so may result in under- or overdosing with subsequent changes in efficacy, possible resistance, or potential adverse reactions from varied exposure.

2.2. Summary of Regulatory Activity Related to Submission

Triumeq was approved for the treatment of HIV-1 infection in adults on August 22, 2014 and for pediatric patients weighing ≥ 40kg on November 21, 2017.

Epzicom® (abacavir/lamivudine 600mg/300mg) was approved for adults on August 2, 2004 and for pediatric patients weighing ≥25 kg on September 17, 2015. Epizcom's drug components were previously approved as individual drugs for pediatric patients down to ≥14 kg and ≥3 months: Ziagen® (ABC) was approved as an individual drug for pediatric patients ≥14 kg and ≥3 months on December 17, 1998 and Epivir® (3TC) was approved as an individual drug for pediatric patients ≥14 kg and ≥3 months on November 17, 1995. There have also been tentative approvals for the United States President's Emergency Plan for AIDS Relief (PEPFAR) with dispersible tablets containing ABC 60mg and 3TC 30mg, the same ratio used in Triumeq PD.

Tivicay® (dolutegravir 50mg) was approved for adults on August 12, 2013 and approved for pediatric patients weighing ≥30 kg to <40 kg on June 9, 2016. Tivicay PD, the pediatric formulation, was approved for patients down to ≥4 weeks of age and weighing ≥3kg on June 12, 2020.

2.3. Postmarketing Requirements and Written Requests

The approval of Triumeq (NDA 205551) triggered the issuance of post-marketing requirements (PMRs) under the Pediatric Research Equity Act (PREA). The following three PREA PMRs were issued, summarized below:

2768-1: Conduct a pediatric trial to evaluate PK, safety, and efficacy in HIV-infected pediatric patients 2 to < 6 years of age. The safety and antiviral activity (efficacy) of ABC/DTG/3TC FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks.
Status: trials are ongoing (an efficacy supplement will be submitted when data from the IMPAACT P2019 study are available)

2768-2: Conduct a pediatric trial to evaluate PK, safety, and efficacy in HIV-infected pediatric patients 6 to <12 years of age and in children >12 years of age who weigh < 40 kg. The safety and antiviral activity (efficacy) of ABC/DTG/3TC FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks.
Status: the Applicant seeks to fulfill the PMR with the current submission

2768-3: Evaluate the PK, safety, and efficacy in HIV-infected pediatric subjects 12 years to <18 years of age and weighing ≥ 40 kg. The safety and antiviral activity (efficacy) of ABC/DTG/3TC FDC tablets in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children 12 to <18 years of age and weighing ≥ 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.
Status: Fulfilled

Furthermore, a Pediatric Written Request (WR) was issued on May 16, 2018 and subsequently amended on February 13, 2019. (b) (4)

2.4. Goal of Current Submissions

With the current submissions, the Applicant seeks to extend the indication of treatment of HIV-1 infection to include pediatric subjects weighing at least 14 kg. Use of the adult Triumeq tablet is proposed for children weighing at least 25 kg (NDA 205551/S-028) and a new dispersible tablet, Triumeq PD, has been developed for patients weighing less than 25 kg (original NDA 215413).

As PMR 2768-3 has already been fulfilled, these submissions are intended to fulfill PMR 2768-2. The ongoing IMPAACT P2019 study is being conducted to fulfill PMR 2768-1, and the sponsor is not seeking to fulfill the WR with the current submissions.

2.5. Data to support approval

The mainstay of data used to support this approval is from the previously approved individual and combination products including Ziagen, Epivir, Epzicom, Tivicay, and Triumeq. With the exception of Triumeq, all of these products have already been approved for children weighing 14 to <25 kg, and some for even lower weight bands. Adult and pediatric trials supporting the approvals are summarized below:

Table 1: Trials Supporting Approval of Triumeq

Population	Trial	Trial Arms	Time (wks)
Adults:			
Treatment-Naïve	SINGLE (ING114467) (NCT01263015)	Tivicay + Epzicom (n =414)	144
		efavirenz/emtricitabine/tenofovir (n = 419)	

Population	Trial	Trial Arms	Time (wks)
Treatment-Experienced; INSTI-Naïve	SAILING (ING111762) (NCT01231516)	Tivicay +BR (n=354)	48
		raltegravir + BR (n=361)	
		darunavir/ritonavir +NRTI BR (n=242)	
Pediatrics:			
Treatment-Naive	ARROW (COL105677)	Ziagen or Epivir (as single entities or as FDC Epzicom) given twice daily + a 3rd ARV (n=333)	96
		Ziagen or Epivir (as single entities or as FDC Epzicom) given once daily + a 3rd ARV (n=336)	
Treatment experienced; INSTI-naïve: 6 to <18 years old	IMPAACT P1093 (NCT01302847)	Tivicay or Tivicay PD + BR (n=75 overall, n=23 for 12-18 years old)	48

Source: Triumeq Label Section 14

BR = Background regimen; ARV = antiretroviral drug

Table 2: Trials Supporting Approval of Tivicay or Tivicay PD

Population	Trial	Trial Arms	Time (wks)
Adults:			
Treatment-Naïve	SPRING-2 (ING113086) (NCT01227824)	Tivicay +2NRTIs (n=403)	96
		raltegravir + 2NRTIs (n=405)	
	SINGLE (ING114467) (NCT01263015)	Tivicay +Epzicom (n=414)	144
		efavirenz/emtricitabine/tenofovir (n=419)	
	FLAMINGO (ING 114915) (NCT01449929)	Tivicay + BR (n=243)	24
		darunavir/ritonavir +NRTI BR (n=242)	

Population	Trial	Trial Arms		Time (wks)
Treatment-experienced; INSTI-naïve	SAILING (ING111762) (NCT01231516)	Tivicay +BR (n=354)		48
		raltegravir + BR (n=361)		
INSTI-experienced	VIKING-3 (ING112574) (NCT01328041)	Tivicay + OBT (n=183)		48
Virologically Suppressed	SWORD-1 (NCT02429791) SWORD-2 (NCT02422797)	Pooled presentation		48
		Tivicay + rilpivirine (n=513)	CAR (n=511)	
Pediatrics:				
Treatment naïve and experienced; INSTI-naïve: (4 weeks and older and weighing at least 3 kg)	IMPAACT P1093 (NCT01302847)	Tivicay or Tivicay PD + BR (n=75)		48
HIV-infected children aged less than 18 years	ODYSSEY	Tivicay or Tivicay PD +2 NRTIs		96 weeks

Source: Table 15 Tivicay Label

BR = Background regimen; CAR = Current antiretroviral regimen; OBT = Optimized background therapy

Table 3: Trials Supporting Approval of Epzicom

Population	Trial	Trial Arms	Time (wks)
Adults:			
Treatment-Naïve	CNA 30021	Ziagen (600 mg once daily) + Epivir + efavirenz (n=384)	48
		Ziagen (300mg twice daily) +Epivir + efavirenz (n=386)	
Pediatrics:			
Treatment-Naive	ARROW (COL105677)	Ziagen or Epivir (as single entities or as FDC Epzicom) given twice daily + a 3rd ARV (n=333)	96

Population	Trial	Trial Arms	Time (wks)
		Ziagen or Epivir (as single entities or as FDC Epzicom) given once daily + a 3rd ARV (n=336)	

Source: Epzicom Label Section 14

BR = Background regimen; CAR = Current antiretroviral regimen; OBT = Optimized background therapy; ARV = antiretroviral drug

Table 4: Trials Supporting Approval of Ziagen

Population	Trial	Trial Arms	Time (wks)
Adults:			
Treatment-Naïve	CNA30024	Ziagen (300mg twice daily) + Epivir + efavirenz (n=324)	48
		Epivir + zidovudine + efavirenz (n=325)	
	CNA3005	Ziagen + Epivir/zidovudine (n=262)	48
		indinavir + Epivir/zidovudine (n=265)	
	CNA30021	Ziagen (600 mg once daily) + Epivir + Efavirenz (n=384)	48
		Ziagen (300mg twice daily) +Epivir + efavirenz (n=386)	
Pediatrics:			
Treatment-Experienced	CNA3006 (n = 205)	Ziagen +Epivir +zidovudine	16
		Epivir +zidovudine	
Treatment-Naive	ARROW (COL105677)	Ziagen or Epivir (as single entities or as FDC Epzicom) given twice daily + a 3rd ARV (n=333)	96
		Ziagen or Epivir (as single entities or as FDC Epzicom) given once daily + a 3rd ARV (n=336)	

Source: Ziagen label Section 14

ARV = antiretroviral drug

Table 5: Trials Supporting Approval of Epivir

Population	Trial	Trial Arms	Time (wks)
Adults:			
Treatment-Naive	EPV 20001	Epivir 300mg (once daily) + zidovudine + efavirenz (n=278)	48
		Epivir 150mg (twice daily) + zidovudine + efavirenz (n=276)	
	EPV 40001	Epivir 300 mg once daily + zidovudine + Ziagen (n=54)	48
		Epivir 150 mg (twice daily) + zidovudine + Ziagen (n=52)	
Treatment-Experienced	CAESAR (NUCB3007)	CAR (n=460)	48
		Epivir + CAR (n=896) (zidovudine + didanosine OR zalcitabine)	
		Epivir + CAR + NNRTI (n=460)	
Pediatrics:			
Treatment-Naive	ACTG300	Epivir +zidovudine (n = 236)	36-40
		didanosine (n =235)	
	ARROW (COL105677)	Ziagen or Epivir (as single entities or as FDC Epzicom) given twice daily + a 3rd ARV (n=333)	96

Population	Trial	Trial Arms	Time (wks)
		Ziagen or Epivir (as single entities or as FDC Epzicom) given once daily + a 3rd ARV (n=336)	

Source: Epivir Label Section 14

ARV = antiretroviral drug CAR = Current antiretroviral regimen

Established Pediatric Clinical Trial Data

The clinical data supporting use of Triumeq and Triumeq PD in pediatric patients weighing at least 14 kg are derived from previously conducted pediatric trials evaluating the individual components of Triumeq and Triumeq PD:

- The safety and efficacy of ABC and 3TC administered once-daily were established with a randomized, multicenter trial (ARROW [COL 105677]) in treatment-naïve subjects with HIV-1 infection aged 3 to 17 years. Subjects were treated with a first-line ARV regimen containing ABC and 3TC, administered separately as Epivir with Ziagen, or as Epzicom.

- The safety, PK, and efficacy of DTG were established through an ongoing, open-label, multicenter dose-finding clinical trial (IMPAACT P1093) in which treatment-naïve or treatment-experienced INSTI-naïve subjects aged 4 weeks to 18 years and weighing at least 3 kg were treated with Tivicay or Tivicay PD plus optimized background therapy.

- Additional DTG PK data were evaluated in 2 PK substudies of ODYSSEY, an ongoing, open-label, randomized, non-inferiority trial to evaluate the safety, efficacy, and PK parameters of Tivicay or Tivicay PD + 2 NRTIs (mainly ABC and 3TC) compared with standard of care in pediatric subjects (younger than 18 years) with HIV-1 infection.

For DTG, the proposed Triumeq/Triumeq PD dosing regimens are identical to those approved for Tivicay/Tivicay PD. For ABC and 3TC, the proposed Triumeq/Triumeq PD dosing regimens for the ≥25 kg and 14 to 20 kg weight bands are identical to those approved with individual products. For the ≥20 to <25 kg weight band, the proposed Triumeq PD doses of ABC and 3TC are slightly different but are within the range of the approved ABC and 3TC doses.

New Data

NDA 215413 includes data evaluating the novel pediatric dispersible tablet, Triumeq PD. The new data that have been submitted come from the following three studies:

1. Pivotal Study 205894 is a 2-part, open-label, phase 1, single dose, 3-period crossover relative bioavailability (BA) study that compared the novel pediatric dispersible tablet (Triumeq PD) to Triumeq tablets in healthy adult volunteers.
2. Study 216149 is a randomized, open-label, 2-cohort, 2-period, single dose, crossover clinical study to assess the effect of food on Triumeq PD in healthy adult participants.
3. Study 200402 is a phase 1, single dose, five-period crossover relative bioavailability study of Triumeq PD dispersed and consumed under different dosing conditions compared to a co-dose of Tivicay and Epzicom in healthy subjects.

Other Information Sources
In addition, the Applicant has provided population PK (popPK) based simulation results to support the approval of Triumeq and Triumeq PD for patients weighing ≥14kg (2021N471578). Of note, all popPK models were previously submitted, reviewed, and utilized to support the approval of the individual components of Triumeq.

(b) (4)

3. Discipline Specific Reviews

Chemistry, Manufacturing, and Control (CMC)
A brief synopsis of the pre-marketing CMC reviews for NDA 215413 (Triumeq PD) is provided below. A more streamlined post-marketing review was conducted for sNDA 205551 since the currently marketed formulation of Triumeq tablets would be used for the new indication for patients weighing > 25 kg. Please refer to the individual Product Quality Reviews for further details.

The Product Quality review team determined that the information submitted by the Applicant supports the approval of Triumeq PD. The chemistry, manufacturing, and control information submitted with NDA 215413 assures the identity, strength, purity, and quality of the proposed drug product. The Applicant cross-referenced the CMC information of the three NDAs for the three respective individual drug substances (tablet formulations) and found the information to be adequate to support NDA 215413. Stability data were acceptable. In-use compatibility and dose delivery studies support the 30 minute in-use time after mixing with water and complete cumulative dose delivery of the suspension with the dosing cup following instructions described in the instructions for use (IFU).

The manufacturing and testing facilities for this NDA were also deemed acceptable. All twenty-one facilities, including drug substance (and critical intermediates) and drug product manufacturers, release and stability testing, and packaging site, have compliant status and experience with proposed responsibilities. Therefore, no pre-approval inspection (PAI) request was issued during the review cycle. The Overall Manufacturing Inspection Recommendation was entered into the Panorama platform as “approve” on 2/09/2022.

As a result, this NDA was recommended for approval by the Office of Pharmaceutical Quality (OPQ) from a drug substance, drug product, labeling, manufacturing, and biopharmaceutics perspective.

Clinical Virology
No new virologic data were submitted for review. A brief synopsis of pertinent virologic findings is provided below based upon previously submitted data. Please refer to Dr. Colberg Poley's Clinical Virology Review for further information and details.

Most pediatric subjects from IMPAACT P1093 study, though treatment-experienced, were virologic responders at <50copies/mL (week 24: 62% and week 48: 69%). FDA analyses identified the emergence of known HIV-1 integrase inhibitor resistance-associated substitutions in 3 virologic failure subjects during DTG treatment. Suboptimal adherence appears to have contributed to virologic failure in some pediatric subjects of the IMPAACT P1093 study.

Non-clinical Pharmacology/Toxicology
No new non-clinical pharmacology/toxicology data were submitted. Information pertaining to the non-clinical pharmacology/toxicology assessments can be found in the respective reviews of the data supporting pediatric approvals of Tivicay, Tivicay PD, Epzicom, Epivir, or Ziagen.

4. Clinical Pharmacology

A brief synopsis of the key findings from the three submitted studies, the relevant data from prior approved products, and the results of modeling and simulation to support dosing in pediatric patients weighing ≥ 14 to < 40 kg is provided below as well as use in pediatric patients with renal impairment. Please refer to Dr. Yang Zhao's clinical pharmacology review further details.

Study 205894, 216149, and 200402 Results
Study 205894 demonstrated that the area under the curve (AUC) and maximum serum concentration (C_{max}) for DTG following administration of Triumeq PD as a dispersion were ~70% higher than those observed after administration of Triumeq tablet at the same dose. The magnitude of difference in exposure between Triumeq PD and Triumeq were found to be similar to those observed between Tivicay PD and Tivicay. Therefore, it can be concluded that comparable exposure of DTG can be established between Triumeq PD and Tivicay PD. For ABC and 3TC, AUC and C_{max} following administration of Triumeq PD dispersible tablets were similar to those observed after administration of Triumeq tablet at the same dose. Because comparable relative bioavailability has been previously established between Triumeq and Epzicom, it can also be concluded that comparable exposure of ABC and 3TC can be established between Triumeq PD and Epzicom.

Study 216149 demonstrated that the AUC for DTG, ABC, and 3TC following administration of Triumeq PD with a high fat meal was similar to the AUC achieved following administration in a fasted condition; however, the C_{max} for DTG, ABC, and 3TC was lower when Triumeq PD was given in the fed versus fasted condition.

For multiple reasons outlined in further depth in the clinical pharmacology review, the review team did not consider the lower C_{max} of ABC and 3TC when Triumeq PD is taken under fed conditions to have clinical relevance. Furthermore, the lower C_{max} of ABC and 3TC appears to be universal across various products when taken with high fat meals and the lower C_{max} values were not considered to be clinically relevant in respective reviews. In conclusion, comparable plasma exposures of DTG, ABC, and 3TC were achieved following administration of Triumeq PD under fed and fasting conditions and thus Triumeq PD may be taken with or without food.

Study 200402 demonstrated that the PK of DTG, ABC, and 3TC following a single dose oral administration of Triumeq dispersible tablets after dispersion with high mineral content water were similar to dispersion with purified water. It also demonstrated that withholding the dispersion for 30 minutes vs. immediate consumption produced similar PK profiles for DTG, ABC, and 3TC.

Conclusions for DTG dosing:
The proposed DTG dosing for patients is identical to the approved dosing for Tivicay PD or Tivicay. The simulated DTG exposure AUC_{0-24} and the concentration at 24 hours (C24) in pediatric patients with the proposed Triumeq PD and Triumeq tablet dosing are comparable to historical DTG exposure in pediatric and adult patients. Given the fact that Triumeq tablet vs. Tivicay tablet, or Triumeq PD vs. Tivicay PD at the same dose levels produced similar DTG exposure, the proposed DTG doses are considered acceptable for all weight bands.

Conclusions for ABC dosing:
The proposed ABC dosing are identical to the approved dosing for the Ziagen tablet in pediatric patients weighing ≥14 to <20 kg and ≥25 to <40 kg. Since the Triumeq tablet, Triumeq PD and Ziagen tablet at the same dose levels produced similar ABC exposure, the proposed ABC dosing for Triumeq PD and Triumeq tablets are acceptable.

For pediatric patients weighing ≥20 to <25 kg, the proposed ABC dosing (360 mg in Triumeq PD) is lower than the approved dosing for the Ziagen tablet (450 mg) but within the approved dose range for the Ziagen solution (320–400 mg). The simulated ABC AUC at the proposed doses across different weight bands is comparable to historically observed ABC exposure in pediatrics and adults. The proposed ABC dosing is therefore considered acceptable for all weight bands.

Conclusions for 3TC dosing:
The proposed 3TC dosing for pediatric patients weighing ≥14 to <20 kg and ≥25 to <40 kg are identical to the approved dosing for the Epivir tablet. Since the Triumeq tablet, Triumeq PD, and Epivir tablet at the same dose levels produced similar 3TC exposure, the proposed 3TC dosing for Triumeq PD and Triumeq tablets are acceptable.

For pediatric patients weighing ≥20 to <25 kg, the proposed 3TC dosing (180 mg of Triumeq PD) is lower than the approved dose of Epivir tablet (225 mg) or Epivir solution (200–250 mg); however, the simulated AUC at the proposed 180 mg dose for pediatric patients weighing ≥20 to <25 kg (8.50 µg·hr/mL) is comparable to the simulated exposure at other weight bands (8.81−10.70 µg·hr/mL). The simulated 3TC AUC_{0-24} for the proposed doses are comparable to the historically observed exposures in 3TC in pediatrics and adults. The proposed 3TC dosing is therefore considered acceptable for all weight bands.

Reviewer's Comment: The Applicant is also currently evaluating Triumeq and Triumeq PD at the proposed dosing regimens in the aforementioned ongoing IMPAACT P2019 (Study 205860) for once daily dosing in pediatric patients <12 years of age and submitted an interim report summarizing noncompartmental PK analysis (NCA) parameters for DTG, ABC, and 3TC at different weight bands (b) (4) (b) (4)

Use in Patients with Renal Impairment

3TC (which is renally excreted) has higher exposures in subjects with renal impairment (i.e. lower creatinine clearance (CrCl)) and a dose adjustment is recommended in its label for subjects with CrCl 30 to <50mL/min (to 150mg once daily). Triumeq's current labeling, however, states that use is not recommended in patients with CrCl <30mL/min since it is a FDC and the individual components cannot be adjusted accordingly. The allowance for use of Triumeq by patients with CrCl >30 to < 50 mL/min was based on a review of multiple data sources; ultimately, the review team concluded that there was a signal for increased risk of hematological toxicity with increased 3TC exposure. The benefits of a convenient STR for this population, however, outweighed the small and monitorable risk of hematological toxicity for patients with CrCl 30 to < 50 mL/min. Please see Dr. Stephanie Troy's clinical review of Triumeq 205551/S-25 for further information.

The Applicant originally proposed the following guidelines for usage in patients with renal insufficiency according to weight:

(b) (4)

The Agency requested further information from the Applicant on 2/15/2022 to justify their proposal to have different cut-offs by weight. DAV asked them to consider using CrCl of <30mL/min as the minimum cutoff for all children and requested the Applicant provide support for their respective agreement or disagreement with the proposed cutoff. Despite the anticipated higher 3TC exposures in subjects with CrCl 30 to <50 mL/min, the Agency believed a CrCl of <30mL/min cutoff was justified based upon the known safety risks of elevated 3TC exposures (monitorable bone marrow suppression) and ranges of doses/exposures evaluated in children and adults.

The Applicant responded on 3/1/2022 stating that, "due to a lack of clinical safety observation in children with moderate renal impairment (CrCl of 30-49mL/min) weighing <25 kg, the threshold for 3TC dose modification could not be amended from 50mL/min to 30mL/min as part of this Triumeq PD submission" and that this is what led "to non-aligned advice on 3TC dose modification in the event of moderate renal impairment in children above versus below 25kg."

They agreed, however, upon the Agency's proposed minimum CrCl cutoff of <30mL/min and provided the following data to support their decision:

- Predicted 3TC exposures in children (across relevant weight bands) with renal impairment (CrCl of 30 to 49 mL/min) that demonstrated overall lower exposure than those observed in adults with renal impairment.

- 2 participants in the ODYSSEY PK substudies and IMPAACT P1093 (in the 6 to <10 and 3 to <6 kg weight bands) with renal impairment (CrCl of 30 to 49 and thus requiring dose adjustments) that had improved renal function while on Triumeq-based treatment.

Reviewer's comment: Since children with HIV-1 infection and moderate renal impairment are a very small population and may be excluded from clinical trials (or dose-adjusted), there are no systematic safety observations in this scenario. Conducting studies in this very small population would be difficult and data to guide the use of Triumeq/Triumeq PD for children with renal insufficiency are therefore unlikely to become available in the foreseeable future. For the reasons previously stated, access to potent, well tolerated STRs is important because these simplified regimens greatly facilitate treatment adherence, thereby improving outcomes. Based upon review of the relevant data and extensive experience with 3TC in children, we agree that the 30mL/min cutoff for the use of Triumeq in children across all approved weight bands is appropriate. Monitoring for hematologic toxicity is part of routine clinical management for children living with HIV-1 infection. Labeling will explicitly state that no data are available from children with renal insufficiency and the potential concerns associated with increased 3TC exposures will be available in Section 8.6. With this information, providers will have the flexibility to determine whether the FDC is the most suitable treatment option for an individual patient. Please refer to the full review by Yang Zhao and Su-Young Choi, Clinical Pharmacology, for further details.

5. Clinical Efficacy

Approach to efficacy review

The mainstay of data used to support approval of Triumeq/Triumeq PD for children weighing ≥ 14 kg to <40 kg is from the previously approved individual and combination products including Ziagen, Epivir, Epzicom, Tivicay, and Triumeq. The efficacy of the individual drug products of Triumeq was evaluated in pediatric patients enrolled in the IMPAACT P1093 trial (NCT01302847) and the ARROW trial (NCT02028676).

The totality of the pharmacokinetic and antiviral activity (HIV-1 RNA) data were used to establish the efficacy of the individual ARVs for treatment of HIV-1 infection in children.

Pharmacokinetic data provide the pivotal data to support approval of ARVs for pediatric patients. Virologic and immunologic outcomes are evaluated to ensure that these traditional efficacy outcomes are comparable between children and adults. The latter clinical outcomes are summarized in this section. Data presented below are not restrictive to pediatric patients weighing 14 to 40 kg but are reflective of all cohorts studied in these trials.

ABC and 3TC

ARROW was a multicenter, randomized study in treatment-naïve patients aged 3 months to 17 years with HIV-1 infection. After a minimum of 36 weeks of treatment with a first line regimen containing 3TC and ABC dosed twice daily according to the World Health Organization (WHO) recommendations, subjects were given the option to be randomized to continue twice-daily dosing or transition to once-daily dosing of 3TC and ABC, in combination with a third antiretroviral drug, for an additional 96 weeks (Randomization 3). Of note, virologic suppression was not a requirement for participation for Randomization 3.

Of the 1,206 original ARROW subjects, 669 participated in Randomization 3; 75% of subjects in the twice-daily cohort (n=333) were virologically suppressed at baseline compared with 71% of subjects in the once-daily cohort (n=336). The median age (interquartile range) was 5.1 years (3.6 to 8.3) and 5.9 years (3.8 to 8.6) for the twice daily and once daily cohort, respectively. The percentage of subjects with HIV-1 RNA less than 80 copies/mL through 96 weeks was 70% in the twice-daily cohort compared to 67% in the once-daily cohort. Sensitivity analyses were performed to determine whether virologic outcomes varied by age or weight band and no statistically significant differences were found. Most study participants had normal CD4 cell counts at baseline in Randomization 3 and no notable changes in CD4 count were noted in either cohort over the 96-week study period; this was not surprising, given that subjects had already received a median 1.8 years of ART before entering Randomization 3 and experienced substantial gains in CD4 percentage during that period of time.

DTG

IMPAACT P1093 was a multicenter, open-label dose-finding study in treatment-experienced, INSTI-naïve subjects with HIV-1 infection aged 4 weeks - 17 years of age. Subjects were stratified by 5 age cohorts: Cohort 1, aged 12 to <18 years; Cohort 2A, aged 6 to < 12 years; Cohort 3, aged 2 to < 6 years; Cohort 4, aged 6 months to < 2 years; and Cohort 5, aged 4 weeks to < 6 months. Median age (range) was 27 months (1 to 214).

Subjects who received either Tivicay tablets or Tivicay PD tablets for oral suspension as per the dosing recommendations for their weight band were included in the efficacy analysis. Of the 42 subjects who had reached Week 48, 69% of subjects had HIV-1 RNA < 50 copies/mL and the median CD4 count increase from baseline to Week 48 was 141 cells per mm^3 (7% increase).

Reviewer's Comment: Adequate virologic and immunological response within these two trials in combination with pharmacokinetic exposures within acceptable ranges supported the efficacy of the individual components of Triumeq for the pediatric populations studied and therefore of the FDC, Triumeq, itself. Extrapolation of these results to the Triumeq PD formulation is supported by Study 205894, which demonstrated that the exposures obtained from Triumeq PD are comparable to those obtained from the individual components.

6. Safety

Approach to safety review

The safety of Triumeq and Triumeq PD for children weighing ≥ 14 kg to 40 kg can be assessed by looking at the relevant data supporting the previous approvals of Triumeq, Tivicay, Epzicom, Ziagen, and Epivir in children and adults. This assessment is also informed by interim data from the ongoing clinical study IMPAACT P2019. PK and modeling played a limited role by predicting exposures that could potentially prompt safety concerns (of which none were identified).

Summary of Safety Results from Pediatric Trials Supporting Approval of ABC, 3TC, and DTG administered once daily

ABC and 3TC

The safety of once-daily compared with twice-daily dosing of ABC and 3TC, administered as either single products or as the FDC Epzicom, was assessed in Randomization 3 of the ARROW trial (n = 336). Unlike many HIV clinical trials that are performed for regulatory purposes, the ARROW study was conducted to inform best practices for treatment of HIV-1 infection in children in resource-limited settings. Since the safety profile of twice-daily ABC and 3TC were already well established, the goal was to identify adverse events that may be caused by the higher maximal concentration of ABC and 3TC that result from once-daily dosing. The primary safety assessment was based on grade 3 and 4 adverse events. Once-daily dosing was not associated with an increase in SAEs, Grade 3 or 4 AEs, or laboratory abnormalities compared to twice-daily dosing. One event of grade 4 hepatitis in the once-daily cohort was considered as uncertain causality by the investigator and all other grade 3 or 4 adverse events were considered not related by the investigator. There were no discontinuations due to AEs. No additional safety issues were identified in pediatric subjects compared with historical data in adults and children.

DTG

The safety of Tivicay and Tivicay PD in pediatric subjects aged at least 4 weeks and weighing at least 3 kg was evaluated in the IMPAACT P1093 trial; data from 2 weight-band-based PK substudies of the ODYSSEY trial provided supportive safety data. The safety analysis through week 24 of the IMPAACT P1093 trial included 30 subjects from cohorts I (age 12 to <18 years, n=19), IIA (age 6 to < 12 years, n=5), and III (age 2 to < 6 years, n=6) weighing at least 14 kg at enrollment who received the recommended dose and formulation. Safety data were available from an additional 45 subjects weighing less than 14 kg. The ODYSSEY trial provided safety data from an additional 97 subjects (81 of whom weighed 14-40 kg), but these data were considered supportive due to a lack of standardized coding and incomplete collection of adverse events.

Overall, the safety data from the IMPAACT P1093 and ODYSSEY trials were similar to those seen in adults. Overall, 13 subjects (17%) experienced adverse drug reactions; all were Grade 1 or Grade 2. Adverse drug reactions reported in more than 1 subject were decreased blood bicarbonate (n=3), decreased hemoglobin (n=2), decreased neutrophil count (n=4), and IRIS (n=2). There were no grade 3 or 4 drug-related adverse events reported and no adverse events

leading to discontinuation. Grade 3-4 laboratory toxicities that occurred in more than 1 participant were decreased neutrophils (n=11), decreased bicarbonate (n=4), decreased hemoglobin (n=3), increased lipase (n=2), and increased potassium (n=2). Following review, the events deemed drug-related occurred at a frequency consistent with that observed in the adult population.

IMPAACT P2019: Ongoing Study

IMPAACT 2019 is an open-label, multicenter study evaluating Triumeq dispersible tablets (subjects weighing < 25 kg) or immediate release tablets (subjects weighing ≥ 25 kg) in treatment-experienced and treatment-naïve children less than 12 years of age. The study is evaluating the PK of the three drugs (with a focus on DTG) as well as the safety and tolerability over 48 weeks of treatment. Enrollment is complete but the study is ongoing.

Limited safety data have been submitted to date (b) (4) while the findings have been generally reassuring, one report of Grade 4 drug-induced liver injury merits further discussion in this review.

The 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 ART regimen prior to study enrollment was ZDV/3TC (300/150mg) ½ tablet PO q12 hours and LPV/r 2.5 mL q 12h which he took for several months prior to study participation. After he 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 (for which he was treated with a bronchodilator syrup terbutaline sulfate 1.5 mg plus glyceryl guiacolate 66.6 mg PO daily for 2 days). His physical exam revealed rhinorrhea with pale conjunctivae, but no jaundice was noted. Laboratory results were notable for markedly elevated hepatic enzymes, as shown in Table 6 below. The study agent was held according to the protocol due to elevated LFTs and permanently discontinued the following day due to concern for drug induced liver injury (DILI). The event was considered drug-related by the clinical investigator and the study sponsor. One month later, the study site considered the drug-induced liver injury event resolved and the patient was re-initiated on the same ART regimen he was receiving prior to enrollment, with doses adjusted for growth. The subjects' relevant labs are summarized in Table 6 below:

Table 6 : Summary of Laboratory Results for IMPAACT P2019 DILI Case

Test name	**Results**				
	Week 24	**Week 36**	**Week 41**	**Week 42**	**Week 44**
Total bilirubin	0.61 mg/dL	0.62 mg/dL		0.87 mg/dL	0.67 mg/dL
Direct bilirubin	0.14 mg/dL	0.31 mg/dL		0.33 mg/dL	0.32 mg/dL
Alanine transferase (ALT)	33 U/L	272 U/L (Grade 4)	225 U/L (Grade 3)	110 U/L (Grade 2)	32 U/L (Grade 1)

Aspartate transaminase (AST)	40 U/L	275 U/L (Grade 3)	196 U/L (Grade 3)	115 U/L (Grade 2)	43 U/L (normal)

Source: Safety report submitted to (b) (4)/SDNs 26 & 27.

Reviewer's Comment: We agree that the elevated hepatic transaminases are likely related to the study drug, Triumeq. Although the timing relative to the study drug is unusual (i.e. 36 weeks), drug-induced liver injury may still occur at this time. There is a known potential of ABC and DTG to cause hepatoxicity. Clinical trials in adults of DTG + ABC/3TC demonstrated grade 3 to 4 hepatic AEs in 1% of the population. In pediatric trials of DTG, no subjects had grade 3 or 4 hepatic AEs; however, one patient in the ARROW trial who received ABC/3TC had grade 3 to 4 hepatoxicity of unknown causality. Furthermore, no alternate etiology was identified, and the patient's transaminases normalized once Triumeq was discontinued. It is therefore likely the elevated LFTs were related to the ABC or DTG components specifically. Although the Triumeq label mentions the potential for hepatoxicity in adults, labeling will be adjusted to be more inclusive and reflective of past and ongoing study results in children.

Reviewer's Comment- Safety Summary: The safety of the individual drugs contained in Triumeq were previously established during the review cycle of the respective NDAs. In addition. abacavir and lamivudine have well described pre- and post-marketing safety profiles. Therefore, previously described safety findings for the individual drugs are applicable to the FDC drug product. No unique or new safety signals are expected to arise for Triumeq that were not observed for the individual components. Although the proposed labeling for Triumeq sufficiently describes the AE profiles for ABC/DTG/3TC, additions/changes will be considered for further clarification and to be all inclusive of the case mentioned above (labeling negotiations are ongoing at this time). Continued routine post-marketing pharmacovigilance is recommended with the approval of the FDC formulation.

7. Expansion of indication to patients weighing ≥ 10 to <14 kg

Given that ABC/DTG/3TC is a priority regimen, both in the US and globally, DAV sought to be as inclusive as possible with this action. Since the individual products are approved for children weighing ≥10 to <14 kg, the Agency contacted the Applicant to see if there were additional supportive data to inform dosing recommendations of Triumeq PD for this population.

In their 02/14/2022 response to the Information Request from the Agency dated 01/14/2022, the Applicant proposed expansion of the indication for Triumeq PD dosing down to patients weighing ≥10 kg based upon the following data:

- Simulations were conducted using the WHO ARV weight band focusing on AUC_{0-24}, C_{max}, and C_{24} for DTG, ABC, and 3TC.
- DTG population PK modeling was developed based upon data from IMPAACT P1093 (ING 112578) and ODYSSEY PK sub-studies (201296).

- ABC population PK modeling was developed based on the data from studies of ARROW PK substudy part 1, PENTA 13, PENTA 15, ARROW PK substudy Part 2, CNAA1001, and CNAA1013 (ACTG330).
- 3TC population PK modeling was developed with the data from pediatric studies ARROW PK substudy part 1, PENTA 13, PENTA 15, ARROW PK substudy part 2, and historical studies NUCA2002, and NUCA2005.

The Sponsor's proposed dose for the ≥10 to <14 kg weight band is 4 tablets of Triumeq PD: 240 mg ABC, 20 mg DTG, and 120 mg 3TC.

Conclusions for DTG dosing:
Triumeq tablet vs. Tivicay tablet, or Triumeq PD vs. Tivicay PD at the same dose levels produced similar DTG exposures. Therefore, it is appropriate to use the same dose of DTG approved for Tivicay PD in Triumeq PD for children weighing ≥10 to less than 14 kg.

Conclusions for ABC dosing:
For patients weighing ≥10 to <14 kg, the proposed ABC dosing (240 mg from Triumeq PD) is higher than the approved dosing for Ziagen solution (224 mg); however, the simulated AUC at the proposed 240 mg dose for ≥10 to < 14 kg (16.45 μg·hr/mL) is comparable to the simulated exposure at other weight bands (14.85−18.37 μg·hr/mL).

Conclusions for 3TC dosing:
3TC population PK modeling accounted for a higher bioavailability estimate for the solid dosage forms (tablet and capsule) than for the oral solution in pediatric participants. For pediatric patients weighing ≥10 to <14 kg, the proposed 3TC dosing (120 mg of Triumeq PD) is within the approved dose range from Epivir solution (100−140 mg).

Reviewer's Comment: For pediatric patients weighing ≥10 to <14 kg, the proposed DTG dosing of 20 mg, ABC dosing of 240 mg, and 3TC dosing of 120 mg for Triumeq PD are considered acceptable based upon the conclusions stated above. Please see the clinical pharmacology review for further details.

8. Pediatrics

This submission was intended to extend labeling of Triumeq to pediatric patients weighing ≥ 14 to <40kg and to fulfill PMR 2768-2. DAV agrees that the PMR has 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 PMR fulfilled and the application approvable. The indication will be extended to pediatric patients weighing10-14kg for the reasons outlined previously. PMR-2768-1 remains outstanding and will be fulfilled upon submission of the IMPAACT P2019 final results.

The Pediatric Written Request also remains outstanding at this time.

Reviewer's Comment: Due to similar dosing recommendations for Triumeq and individual drug components in subjects weighing at least 14 kg, data from individual drug components can be used to support the approval of Triumeq for children weighing 14 to <25 kg, thereby fulfilling the corresponding PREA PMR. Despite the absence of a dedicated clinical trial of Triumeq PD in children 6 to 12 years of age, the current submissions do fulfill PMR 2768-2. As the FDA and ViiV discussed previously in the dolutegravir development program in an email correspondence on December 18, 2018, a dedicated clinical trial(s) is not necessary to fulfill the required PREA-PMR(s) for Triumeq as is stated under 2768-3. This statement is applicable to both PMR 2768-2 and 2768-1.

9. Other Relevant Regulatory Issues

9.1. Submission Quality and Integrity

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

9.2. Compliance with Good Clinical Practices

No concerns.

9.3. Financial Disclosures

ViiV has submitted FDA Form 3454 which certifies that they (Applicant) did not enter any financial relationships with principal or sub-investigators. This form included an attachment containing the names of principal investigators and sub-investigators for studies 206894 and 216149 who have attested to the absence of financial interests or arrangements described in 21 CFR Part 54.4(a)(3)). There was a total of 6 investigators (1 Principal Investigator and 5 Sub-Investigators) in study 205894; and a total of 3 investigators (1 Principal investigator and 2 sub-investigators) in study 216149; all of whom certified that they have no disclosable financial interests. None of the investigators are ViiV employees. See Appendix 1 for the Clinical Investigator Financial Disclosure Review.

9.4. Advisory Committee Meeting

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

10. Labeling

Revisions to the USPI (United States Prescribing Information) and PPI (Patient Package Insert) were ongoing at the time this review was finalized. In brief, the labeling has been updated to reflect changes in the indication, extending the population to pediatric patients weighing at least 10 kg to less than 25 kg for Triumeq PD tablets for oral suspension and patients weighing at least 25 kg for Triumeq tablets.

The changes with this efficacy supplement and original NDA primarily affected the following sections of the USPI: Indications and Usage [1], Dosage and Administration [2], Dosage Forms and Strengths [3], Warnings and Precautions [5], Adverse Reactions [6], Use in Specific

Populations [8], Description [11], Clinical Pharmacology [12], Clinical Studies [14], and How Supplied/Storage and Handling [16]. Corresponding revisions will be made to the PPI.

11. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
No recommendation for a REMS is indicated.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
This review did not raise any new concerns that would warrant additional PMRs or PMCs.

12. Recommended Comments to the Applicant

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

Appendix 1

Clinical Investigator Financial Disclosure Review

Application Number: 215413

Submission Date(s): 9/30/2021

Applicant: ViiV Healthcare

Product: Triumeq and Triumeq PD

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: There were a total of 6 investigators (1 Principal Investigator and 5 Sub-Investigators) in study 205894; and a total of 3 investigators (1 Principal investigator and 2 sub-investigators) in study 216149		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
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)

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/

AMY C BISHARA
03/05/2022 12:39:28 PM

PRABHA VISWANATHAN
03/05/2022 12:40:54 PM