Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology and Division Director Review

Date	3/10/2025
From	Antigone Kraft, MD Kimberly Struble, PharmD Jenny Zheng, PhD Kunyi Wu, PharmD Yun Wang, PhD Jiajun Liu, PharmD, MSc
Subject	Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology Review
NDA/BLA # and Supplement#	NDA 205395/S-028
Applicant	Janssen Products
Date of Submission	May 29, 2024
PDUFA Goal Date	March 29, 2025
Proprietary Name	Prezcobix
Established or Proper Name	Darunavir (DRV) and cobicistat (COBI)
Dosage Form(s)	Oral fixed-dose combination tablet
Applicant Proposed Indication(s)/Population(s)	Treatment of HIV-1 in treatment-naïve and treatment-experienced pediatric patients weighing at least 25 kg with no DRV resistance-associated substitutions
Applicant Proposed Dosing Regimen(s)	Fixed-dose-combination tablet of 675 mg darunavir/150 mg cobicistat taken once daily with food
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed above
Recommended Dosing Regimen(s) (if applicable)	Same as proposed: Fixed-dose-combination tablet of 675 mg darunavir/150 mg cobicistat taken once daily with food

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

PREZCOBIX (darunavir/cobicistat; DRV/COBI) is a fixed dose combination (FDC) product approved for the treatment of HIV-1 infection in treatment-naïve and treatment experienced adults and pediatric patients weighing at least 40 kg who are on a stable antiretroviral regimen with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V). The Applicant, Janssen Products, submitted a supplemental New Drug Application (sNDA) to update the prescribing information to include use in pediatric patients age ≥ 6 years and weighing ≥ 25 to < 40 kg by providing a new FDC tablet of 675 mg darunavir (DRV)/150 mg cobicistat (COBI) for use in pediatric patients in this age and weight band.

Global UNAIDS estimates that 39.9 million people were living with HIV in 2023 and that 1.4 million were children (age 0-14 years). The goal of HIV treatment is to maintain virologic suppression defined as plasma HIV-1 RNA < 50 copies/mL, preserve and restore the immune system, and reduce HIV-associated morbidity. Additionally, viral suppression will prevent further disease transmission. With proper antiviral treatment, children with HIV can live long and healthy lives with undetectable HIV-1 RNA.

The safety and efficacy data submitted in this supplemental New Drug Application (sNDA) support approval of Prezcobix® 675/150 mg for the treatment of HIV-1 infection in children weighing at least 25 kg to less than 40 kg with no darunavir resistance-associated substitutions.

Throughout the review cycle, no deficiencies were identified that would preclude approval of this sNDA. The basis for approval for this sNDA was primarily supported by trial GS-US-216-0128, a Phase 2/3 multicenter, multicohort study to evaluate the safety and efficacy in children living with HIV-1 receiving COBI boosted atazanavir (ATV) or COBI boosted darunavir (DRV) each in combination with two nucleotide reverse transcriptase inhibitors (NRTIs) or emtricitabine and tenofovir alafenamide (F/TAF). Virological suppression was defined as HIV-1 RNA <50 copies/mL. The study was conducted at a total of 5 centers; South Africa (1), United States (3) and Zimbabwe (1).

For the purpose of this review, Cohort 2 was reviewed, specifically only those who received a DRV/COBI based regimen. The primary endpoints were the pharmacokinetic (PK) parameters for DRV (AUCtau – Ctau and Cmax were secondary endpoints) and the incident of treatment emergent adverse events (AEs) and treatment-emergent laboratory abnormalities. A total of 8 participants were enrolled in the DRV/COBI cohort. Participants were given COBI 150 mg-tablets orally once daily in combination with DRV (in addition to a background antiretroviral regimen). This review summarizes the safety and efficacy data through week 48.

The DRV exposures, safety and efficacy were similar to those seen in adults. Because the trial is not powered for statistical analyses of safety or efficacy, the results are presented as descriptive statistics. The COBI exposures are approximately 2-fold and 1.5-fold higher in participants at least 6 years of age and at

least 25 to < 40 kg compared to adults and pediatric participants weighing at least 40 kg, for AUC and Cmax, respectively. The safety data from these pediatric participants is acceptable and consistent with the safety profile seen in adults and adolescents. Therefore, the increased exposures are not considered clinically significant. In addition, the exposure of COBI when administered as a component of PREZCOBIX is similar to the observed COBI exposure for GENVOYA® in pediatric participants aged 6 to < 12 years who were enrolled in the clinical trial that evaluated GENVOYA. (https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/elvitegravir and http://www.sciencedirect.com/science/article/pii/S2352464217300093?via%3Dihub). Letter of Cross-Reference from 3/6/2025: link

The safety data submitted with this supplemental NDA demonstrates an overall favorable safety profile and no new safety signals were observed. No participant experienced loss of virologic response (HIV-1 RNA > 50 copies/mL). The most commonly observed treatment emergent adverse events (AEs) were Grade 1 or 2 in severity and similar to those previously seen in adult studies and consistent with the current labeling in the US Prescribing Information (USPI). There were no deaths, SAEs, or discontinuations due to AEs.

DRV and COBI administration as a scored FDC tablet (DRV/COBI 675/150 mg) was bioequivalent to the coadministration of the separate available tablet formulations (DRV 1×600-mg and 1×75-mg tablet and COBI 1×150-mg tablet) under fed conditions.

In conclusion, the review team recommends approval for the FDC tablet (DRV/COBI 675/150 mg) taken once daily with food in children age weighing ≥ 25 to < 40 kg.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Global UNAIDS estimates that 39.9 million people were living with HIV in 2023, and that 1.4 million were children (0-14 years). • The goal of HIV treatment is to achieve and maintain HIV-1 RNA < 50 copies/mL to reduce the risk of disease transmission and maximize the individual's health.	If untreated, HIV is a life-threatening condition. If individuals do not maintain HIV-1 RNA < 50 copies/mL, there is an increased risk of transmission to future partners as well as vertical transmission in future pregnancies. HIV is a significant public health concern.
Current Treatment Options	• DHHS recommends that pediatric antiretroviral therapy (ART) be determined based on patient age, weight, and available dosing formulations • The Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV recommends children initiate ART with three drugs: two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) plus an integrase inhibitor • In some cases, an ART regimen with two NRTIs plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or boosted protease inhibitor may be indicated • Palatability and patient ability to swallow pills remain factors in establishing	The HIV treatment armamentarium for pediatric patients would benefit from another fixed dose combination oral option that is well tolerated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	a successful ART regimen	
Benefit	• The PK of DRV when combined with COBI in pediatric participants age ≥ 6 years and weighing ≥ 25 to < 40 kg were similar to adults. • The data to support the use of Prezcobix® in pediatric patients with HIV-1 were from study GS-US-216-0128. Eight participants were given DRV and COBI in addition to two NRTIs. All participants maintained virologic suppression throughout Week 48.	The PK assessment is reasonable and shows similar exposures between pediatric participants and adults therefore the efficacy observed from the adult trials can be extrapolated to the pediatric population. Additionally in study GS-US-216-0128 the pediatric participants were able to maintain virologic suppression with COBI-boosted DRV and no participants experienced any loss of virologic response through 48 weeks.
Risk and Risk Management	• The most common adverse events (AEs) observed were vomiting and nasal congestion (3 participants each, 37.5%). No AEs led to study discontinuation. There were no deaths or SAEs in the study.	The frequency of reported AEs in Trial GS-US-216-0128 were generally mild and consistent with the current product labeling. No additional safety labeling changes are proposed based on the already established safety profile. No Risk Evaluation and Mitigation Strategy (REMS) is recommended at this time.

2. Background

Regulatory History and Data Reviewed

Prezcobix (darunavir and cobicistat, DRV and COBI) is a fixed dose combination tablet (FDC) containing one active antiretroviral drug (DRV) and a cytochrome P450 (CYP) 3A inhibitor (COBI) that increases the systemic exposure of DRV. Prezcobix, originally approved in 2015 for use in adults for the treatment of human immunodeficiency virus (HIV-1) infection, was expanded in July 2020 to include in treatment-naïve and treatment-experienced pediatric patients weighing at least 40 kg with no darunavir resistance-associated substitutions. The data submitted in this supplemental NDA (sNDA) are to support the use of a new scored DRV/COBI 675/150 mg film coated FDC tablet in pediatric patients with HIV-1 infection weighing at least 25 kg to less than 40kg.

During the initial review cycle, three PREA PMRs were issued to study the pediatric population. One (2845-3 for adolescents 12 to < 18 years of age) has been fulfilled. This supplemental application partially addresses one of the remaining, unfulfilled PREA PMRs (PMR 2845-2):

> PMR 2845-2 (submitted): Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir and cobicistat fixed dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 6 years to less than 12 years of age and weighing at least 15 kg. The safety and antiviral activity (efficacy) of darunavir and cobicistat FDC age-appropriate formulation in pediatric subjects should be evaluated for a minimum of 24 weeks. A clinical trial in children ages 6 years to less than 12 years may not be required if the dosing recommendation for the FDC age-appropriate formulation can be supported by pediatric trials already conducted with the individual drug products and if the age-appropriate FDC produces similar exposures as the individual components.

As referenced in the PREA PMR, a dedicated clinical trial in children ages 6 years to less than 12 years evaluating the FDC may not be required if the dosing recommendation for the FDC age-appropriate formulation can be supported by pediatric trials already conducted with the individual drug products and if the age-appropriate FDC produces similar exposures as the individual components. The Applicant has not performed studies in pediatric participants with the scored FDC tablet.

This sNDA review summarizes the data from pediatric Study GS-US-216-0128, along with a bioequivalence study comparing the scored DRV/c 675/150 mg FDC table to the single agents of DRV (600 mg and 75 mg tablet) and COBI (150 mg) administered concomitantly.

The Week 48 Clinical Study Report and associated data sets for study GS-US-216-0128: A Phase 2/3, Multicenter, Open-label, Multicohort Study Evaluating Pharmacokinetics (PK), Safety, and Efficacy of Cobicistat (COBI)-boosted Atazanavir (ATV/COBI) or Cobicistat-

boosted Darunavir (DRV/COBI) and Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1–Infected, Virologically Suppressed Pediatric Participants were provided to support the labeling changes to expand treatment to pediatric patients aged 6 years and older weighing at least 25 kg.

3. Product Quality

Please refer to the CMC review for details on the new scored FDC tablet (DVR/COBI 675/150 mg). In summary, the product quality review team concluded the new scored FDC tablet meets acceptance criteria and recommended approval.

4. Nonclinical Pharmacology/Toxicology

No new pharm/tox data were submitted in this supplement. Please see the original Prezcobix review for any pharm/tox details.

5. Clinical Pharmacology

Executive Summary

The DRV/COBI 800/150 mg film-coated FDC tablet is currently approved for the same indication in adults and in pediatric patients weighing at least 40 kg as one tablet once daily (QD). This Clinical Pharmacology review evaluates whether the DRV exposures of the proposed dosage regimen for the proposed pediatric population is comparable to the exposure of adults and pediatric patients weighing at least 40 kg under the approved dosage regimen. The Clinical Pharmacology review team supports approval of DRV/COBI 675/150mg FDC taken orally QD for treatment of HIV-1 in pediatric patients aged ≥6 years and weighing ≥25 kg to <40 kg.

The Applicant submitted the following studies to support the use of an oral 675/150 mg film-coated FDC tablet formulation of DRV/COBI as one tablet once daily for the treatment of HIV-1 in pediatric population aged ≥6 years and weighing ≥25 kg to <40 kg.

- A bioequivalence (BE) study (TMC114IFD1004) in healthy adults comparing the 675/150-mg FDC drug product to coadministration of the approved separate agents, COBI 150-mg tablet with DRV 600-mg and DRV 75-mg film-coated tablets, under fed conditions.
- A pediatric study (GS-US-216-0128) assessing the PK, safety, and efficacy of COBI-boosted DRV (dosed based on body weight), administered as separate agents, in HIV-1 infected children and adolescents.
- A population PK analysis to: 1) characterize DRV disposition, 2) derive Bayesian posterior predicted DRV exposures in the target pediatric patients, 3) simulate DRV exposures at the proposed dosing regimen (steady-state $AUC_{0\text{-}24h}$ and C_{0h}) in children ≥6 years to <12 years old and weighing ≥25 kg to <40 kg, and 4) compare derived exposures of pediatric patients against reference exposures.

BE Study (Study TMC114IFD1004)

Study Design

This was a Phase 1, randomized, open label, 2-panel, 2-way crossover, single-center study to evaluate the BE of a single-dose of DRV/COBI 675/150 mg FDC tablet (Treatment A) compared to the coadministration of the separate available tablet formulations (COBI 150-mg tablet with DRV 600-mg and DRV 75-mg film-coated tablets, Treatment B) in fed (standardized high-fat breakfast) conditions. There was a washout period of at least 7 days between doses. A total of 22 healthy participants were assigned to one of two treatment sequences (AB or BA), and all completed the study.

PK samples were collected pre-dose and up to 72 hours post-dose. Bioanalytical method validation and performance are deemed acceptable and are summarized in the Appendix.

Results

Table 1: PK of DRV After Administration as a Scored FDC Tablet (DRV/COBI 675/150 mg) Compared to the Coadministration as the Separate Available Tablet Formulations (DRV 1×600 mg and 1×75 mg tablet and COBI 1×150 mg tablet), under Fed Conditions (TMC114IFD1004)

Parameter	Mean (SD); t_{max}: Median (Range)		GMR Ratio (Test/Reference)	90% CI
	Treatment A (Test)	Treatment B (Reference)		
N	22	22	-	-
C_{max} (ng/mL)	7,157 (1,772)	7,561 (1,566)	94.07	88.29-100.22
t_{max} (h)	4.00 (1.50-5.02)	4.00 (1.51-5.00)	-	-
AUC_{last} (ng.h/mL)	82,049 (24,678)	84,952 (26,230)	96.24	90.46-102.39
AUC_{∞} (ng.h/mL)	82,254 (24,705)	85,161 (26,232)	96.23	90.47-102.36
$t_{1/2}$ (h)	6.4 (1.2)	6.1 (1.3)	-	-

AUC_{∞}=area under the plasma concentration-time curve from time of intake until infinity; AUC_{last}=area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration; CI=confidence interval; C_{max}=maximum plasma concentration; COBI=cobicistat; DRV=darunavir; FDC=fixed-dose combination; GMR=geometric mean ratio; N=number of participants; PK=pharmacokinetic(s); SD=standard deviation; $t_{1/2}$=elimination half-life; t_{max}=time to reach maximum plasma concentration.

Treatment A: a single oral dose of DRV 675 mg and COBI 150 mg as 1×scored FDC tablet under fed conditions.

Treatment B: a single oral dose of DRV as 1×600 mg and 1×75 mg tablet and COBI as 1×150 mg tablet under fed conditions.

Source: Applicant's Summary of Clinical Pharmacology, Table 3

Table 2: PK of COBI After Administration as a Scored FDC Tablet (DRV/COBI 675/150 mg) Compared to the Coadministration as the Separate Available Tablet Formulations (DRV 1×600 mg and 1×75 mg tablet and COBI 1×150 mg tablet), under Fed Conditions (TMC114IFD1004)

Parameter	Mean (SD); t_{max}: Median (Range)		GMR Ratio (Test/Reference)	90% CI
	Treatment A (Test)	Treatment B (Reference)		
N	22	22	-	-
C_{max} (ng/mL)	807 (236)	861 (199)	92.27	85.33-99.78
t_{max} (h)	4.00 (2.00-5.00)	3.00 (1.51-5.00)	-	-
AUC_{last} (ng.h/mL)	6,499 (2,475)	6,931 (2,520)	92.70	87.41-98.32
AUC_{∞} (ng.h/mL)	6,613 (2,525)	7,027 (2,539)	92.93	87.55-98.66
$t_{1/2}$ (h)	3.6 (0.6)	3.7 (0.5)	-	-

AUC_{∞}=area under the plasma concentration-time curve from time of intake until infinity; AUC_{last}=area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration; CI=confidence interval; C_{max}=maximum plasma concentration; COBI=cobicistat; DRV=darunavir; FDC=fixed-dose combination; GMR=geometric mean ratio; N=number of participants; PK=pharmacokinetic(s); $t_{1/2}$=elimination half-life; t_{max}=time to reach maximum plasma concentration.

Treatment A: a single oral dose of DRV 675 mg and COBI 150 mg as 1×scored FDC tablet under fed conditions.

Treatment B: a single oral dose of DRV as 1×600 mg and 1×75 mg tablet and COBI as 1×150 mg tablet under fed conditions.

Source: Applicant's Summary of Clinical Pharmacology, Table 4

Reviewer's Note:

The study was conducted under fed conditions because Prezcobix® is to be taken with food.

Conclusion

The results of this study showed that DRV and COBI administration as a scored FDC tablet (DRV/COBI 675/150 mg; Treatment A) was bioequivalent to the coadministration of the separate available tablet formulations (DRV 1×600-mg and 1×75-mg tablet and COBI 1×150-mg tablet; Treatment B) under fed conditions. For both analytes, the 90% CIs of the GMRs for the primary PK parameters (Cmax, AUClast, and AUC∞) were contained within the BE limits of 80.00% to 125.00%.

Phase 2/3 Study GS-US-216-0128

This study evaluates PK, safety, and efficacy of COBI-boosted ATV, COBI-boosted DRV, and 2 NRTIs in HIV-1 infected children and adolescents aged ≥4 weeks to <18 years under 5 cohorts, which are defined as follows (per most recent Protocol Amendment 9 dated 07 September 2022). The use of F/TAF as the 2 NRTIs is only applicable to participants in cohorts 2 and 3 enrolled after implementation of Protocol Amendment 7. Otherwise, participants could receive any 2 NRTIs.

- Cohort 1: adolescents aged ≥12 to <18 years and weighing ≥25 kg
- Cohort 2: children aged ≥6 years and weighing ≥25 kg
- Cohort 3: children aged ≥2 years and weighing ≥14 to <25 kg
- Cohort 4: children aged ≥4 weeks and weighing ≥3 to <25 kg
- Cohort 5: children aged ≥4 weeks and weighing ≥3 to <14 kg

The approved DRV 75 mg, 600 mg, and 400 mg tablets were used in the study. The recommended daily dosage of DRV was based on body weight according to the approved product labeling for PREZISTA®.

- Body weight ≥15 to <30 kg: 600 mg
- Body weight ≥30 to <40 kg: 675 mg
- Body weight ≥40 kg: 800 mg

In Cohort 2, participants received DRV in combination with COBI 150 mg (2 x 75 mg tablets).

An intensive PK evaluation for DRV and COBI occurred during either the Week 2 or the Week 4 visit or within 7 days after the completion of Week 2 or the Week 4 visit. Trough plasma PK sample was collected predose at Weeks 8, 24, and 36. Timed PK samples were taken at Weeks 12, 16, and 48.

Intensive PK (IPK) results for DRV

In Cohort 2, 8 participants were enrolled under different protocol amendments with different weight criteria (ie, Protocol Amendments 4 [n=4] and 6 [n=1]: ≥25 kg [Group 1] and ≥15 to <25 kg [Group 2]; Protocol Amendments 7 [n=2] and 8 [n=1]: ≥25 to <35 kg). Table 3: Data availability for 8 participants in Study 0128 Cohort 2 shows the body weight, dosing and IPK information for 8 participants in Cohort 2.

As shown in Table 3, only 3 participants within 25 kg to <40 kg were administered DRV/COBI 675 mg/150 mg contributed full intensive PK data. For Participant (b) (6), the date and time of the Day 10 dose instead of the IPK visit dose (i.e., Day 14) was reported. Therefore, PK parameters were not derived for this participant. Participant (b) (6) who was supposed to receive DRV/COBI 675 mg/150 mg (body weight of 38.7 kg) received DRV/COBI 600 mg/150 mg, which is considered as an important protocol deviation. There were 3 subjects in Cohort 2 who weighed between 25 kg to 30 kg and received 600 mg DRV and 1 subject in Cohort 2 who weighed above 40 kg and received 800 mg DRV.

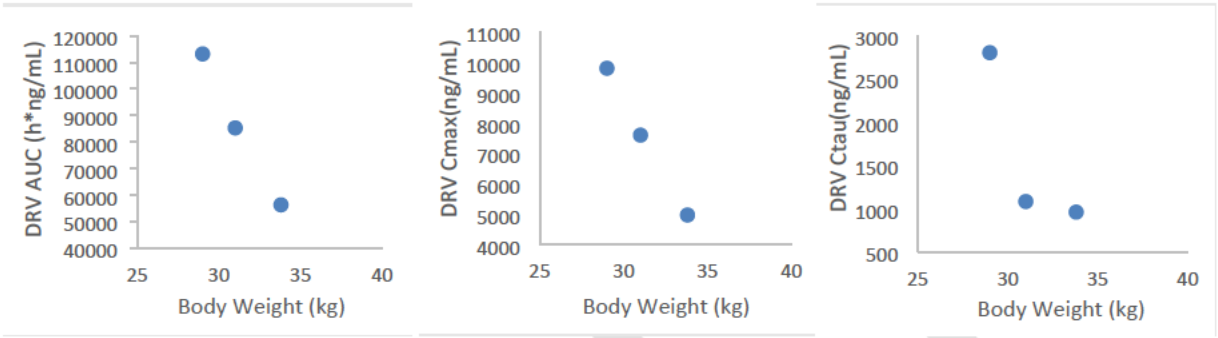
Table 3: Data availability for 8 participants in Study 0128 Cohort 2

Participants	Body Weight	DRV Dosing	IPK available? (Yes/No)	Note:
(b) (6)	27.6	600	No	
	29	675	Yes	Used for IPK analysis
	29.2	600	Yes	
	31	675	Yes	Used for IPK analysis
	32.4	675	No	
	33.8	675	Yes	Used for IPK analysis
	38.7	600	Yes	
	45.4	800	No	

Source: Reviewer generated table.

The IPK data show a trend of decreasing DRV exposures (i.e., AUC, Cmax and Ctau) with increasing body weight (Figure 1); however, the interpretation of the IPK results is inconclusive in the setting of limited pediatric sample size and different dosages administered to the pediatric IPK subgroup.

Figure 1: Body Weight dependent DRV Exposure following DRV/COBI 675 mg/150 mg (Intensive PK Data from Study 0128)



Source: Reviewer generated figure.

Intensive PK (IPK) results for COBI:

The steady-state PK parameters for COBI in Cohort 2, if available, are presented in Table 4. The AUC and Cmax of COBI in Cohort 2 are approximately 2-fold and 1.5-fold higher than adults and pediatric participants weighing at least 40 kg, respectively.

Table 4: Cobicistat Plasma PK Parameters (Intensive PK Analysis Set for Cobicistat; Study 0128, Cohort 2)

	Cohort 2: Age 6 to < 12 Years and Weight ≥ 25 kg (N = 8)	
COBI PK Parameter	**N**	**Mean (%CV)[a]**
AUC_{tau} (h•ng/mL)	5	16,103.0 (35.0)
C_{max} (ng/mL)	7	1510 (21.9)
C_{tau} (ng/mL)	5	86.3 (95.9)
T_{max} (h)	7	4.0 (4.0, 5.0)
$t_{1/2}$ (h)	4	4.7 (3.6, 5.9)
CL_{ss}/F (mL/h)	5	10,313.7 (35.2)
V_z/F (mL)	4	63,236.3 (30.5)

%CV = percentage coefficient of variation; COBI = cobicistat; PK = pharmacokinetics; Q1 = first quartile; Q3 = third quartile
a Median (Q1, Q3) for T_{max} and $t_{1/2}$
Source: Applicant's Study 0128 Report, Table 16

Reviewer's Comment: With the limited number of participants (and limited IPK data) administered with the proposed DRV/COBI 675/150 mg, the PK parameters for DRV cannot be accurately estimated based on IPK data. The PK parameters for DRV were derived using

popPK approach for the labeling. The COBI exposures are approximately 2-fold and 1.5-fold higher than adults and pediatric participants weighing at least 40 kg, for AUC and Cmax, respectively. The safety data in pediatric participants aged 6 to < 12 years and weighing at least 25 kg to less than 40 kg are acceptable and consistent with the safety profile seen in adults and adolescents (see safety section below). Therefore, the increased exposures are not considered clinically significant. In addition, the exposure of COBI when administered as a component of PREZCOBIX is similar to the observed COBI exposure for GENVOYA® in pediatric participants aged 6 to < 12 years who were enrolled in the clinical trial that evaluated GENVOYA. (https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/elvitegravir and http://www.sciencedirect.com/science/article/pii/S2352464217300093?via%3Dihub). Link to letter of cross-reference can be found here:link.

Population PK Analysis and Simulation

The Applicant submitted an updated population PK (PopPK) model to characterize the PK of DRV in adults and HIV-1 infected pediatric patients of ≥6 years of age and weighing ≥25 kg. The reviewer considers the Applicant's PopPK model adequate in characterizing DRV PK and supporting the proposed 675/150 mg DRV/COBI QD as one tablet once daily for the treatment of HIV-1 in pediatric population aged ≥6 years and weighing ≥25 kg to <40 kg. Using the final PopPK model, the Applicant conducted simulations to predict DRV exposure using proposed dose for the indicated population. The simulation results suggest that the DRV exposures ($AUC_{0\text{-}24h}$ and C_{0h}) of patients weighing ≥ 25 kg to <40 kg at a dosage of 675/150 mg QD are comparable to those of the reference adult population with HIV-1 infection. See Pharmacometric Assessment in Section 15.2 for details.

6. Clinical Virology

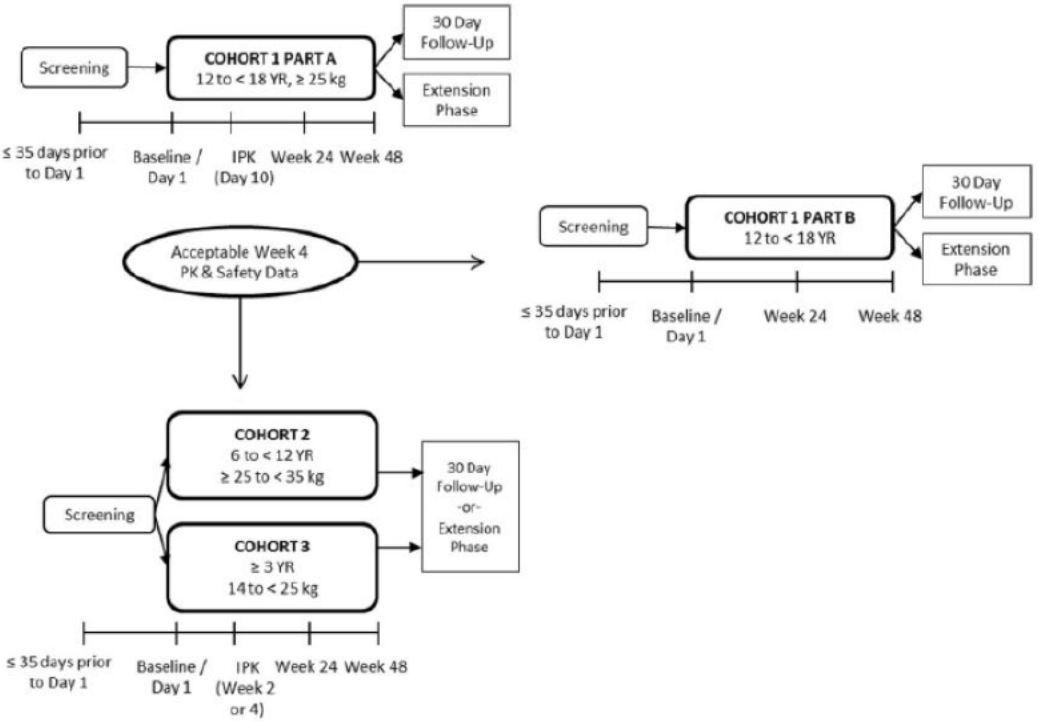
All pediatric participants maintained HIV-1 RNA < 50 copies/mL. Please refer to the clinical virology review for more details.

7. Clinical – Descriptive Analysis of Results (Efficacy)

Study Design

Study GS-US-216-0128 is an ongoing, Phase 2/3, multicenter, open-label, multicohort study evaluating PK, safety, and efficacy of COBI-boosted ATV, COBI-boosted DRV, and 2 NRTIs in children and adolescents with HIV-1 infection aged ≥4 weeks to <18 years in 5 cohorts (Figure 2). The use of F/TAF as the 2 NRTIs is only applicable to participants in cohorts 2 and 3 enrolled after implementation of Protocol Amendment 7. Otherwise, participants could receive any 2 NRTIs. Data presented in this review is from the interim analysis provided by the Applicant. Please refer to the clinical pharmacology section of this review for a more in-depth analysis of the overall study design.

Figure 2: Study Schema



IPK = intensive PK; PK = pharmacokinetic(s); YR = years

Enrollment Criteria

Eligibility criteria for Cohort 2 included participants who were virologically suppressed study.

- In order to be included in the study, participants with HIV-1 needed to meet the following criteria:
  - Age 6 years to < 12 years
  - Weight ≥ 25 to < 35 kg
    - Note: in the original protocol, the lower weight limit was ≥15 kg but it was adjusted through different protocol amendments
  - Stable antiretroviral regimen for a minimum of 3 months prior to the screening visit
    - Prior to Protocol Amendment 7, the stable regimen was defined as 2 NRTIs and RTV-boosted ATV (ATV/r) once daily or RTV-boosted DRV (DRV/r) once daily or twice daily. After Protocol Amendment 7, the stable regimen was defined as 2 NRTIs plus a third agent per local prescribing guidelines. This third agent was switched to DRV (or ATV for other cohorts) on Day 1 of the study.
  - Documented plasma HIV-1 RNA for ≥ 3 months prior to the screening visit.
    - Prior to Protocol Amendment 7: HIV-1 RNA at an undetectable level according to the assay being used, but not more than 75 copies/mL
    - After Protocol Amendment 7: HIV-1 RNA < 50 copies/mL

    - After Protocol Amendment 8: virologically suppressed for ≥ 3 months with HIV-1 RNA < 50 copies/mL or viremic with HIV-1 RNA ≥ 50 copies/mL and on a stable regimen.
- Participants were excluded from the study if they met any of the following criteria:
    - CD4 cell count < 200 cells/mm^3
    - Active hepatitis C virus (HCV) infection
    - An opportunistic illness indicative of Stage 3 HIV diagnosed within 30 days prior to screening
    - Hepatis B virus (HBV) surface antigen (HBsAg) positive or evidence of HBV infection

Study Endpoints

Primary Endpoints for Cohort 2:

- PK parameters of AUCtau for: ATV (Cohorts 2 and 3); DRV (Cohorts 2 and 3); TAF (Cohorts 2 and 3 taking F/TAF)
- The incidence of treatment-emergent adverse events (AEs) and treatment-emergent laboratory abnormalities through Week 24

Secondary Endpoints for Cohort 2:

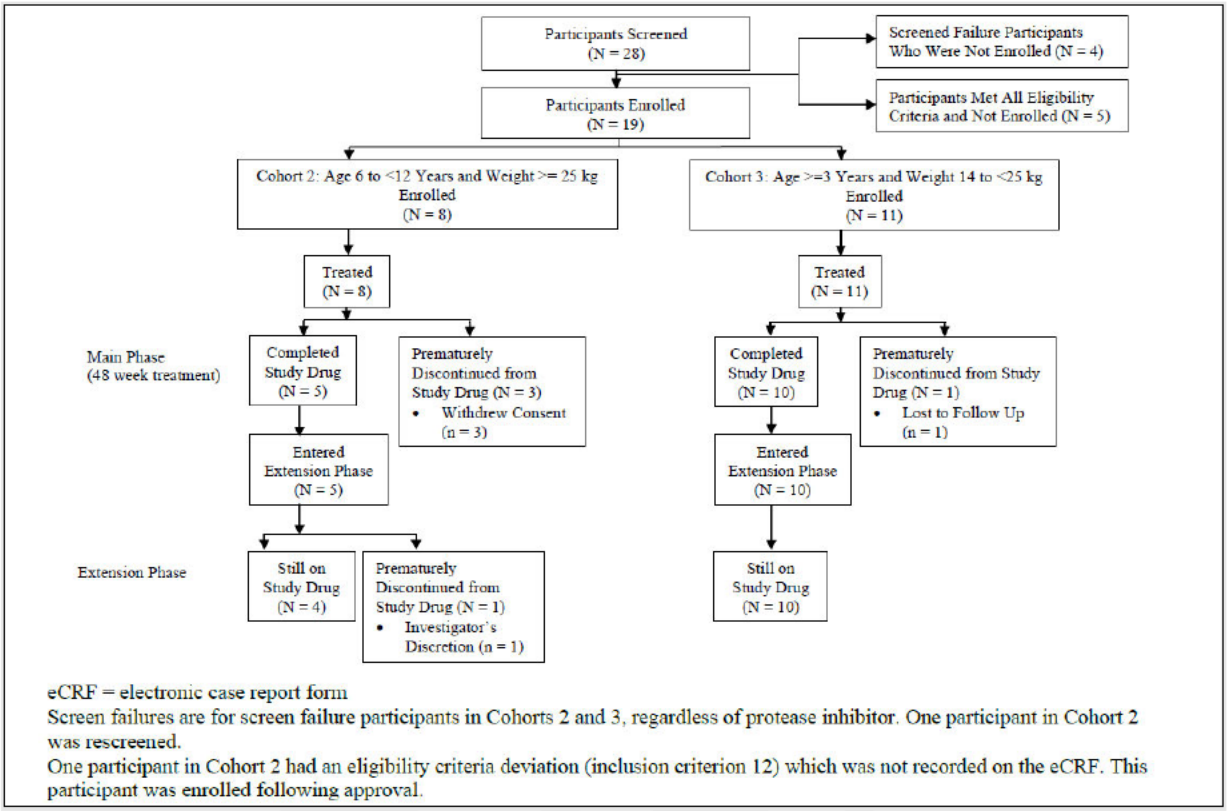
- PK parameters of:
    - Ctau, Cmax, and CL/F for ATV and DRV
    - AUCtau, Ctau, Cmax, CL/F, and Vz/F for cobicistat (COBI)
    - Cmax, Clast, CL/F, and Vz/F for TAF
    - AUCtau, Cmax, and Ctau for emtricitabine (FTC) and TFV
- The incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities through Week 48
- The percentage of participants with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US Food and Drug Administration (FDA)-defined snapshot algorithm
- The change from baseline in CD4 cell counts (cells/µL), and CD4 percentage at Weeks 24 and 48

Disposition

As previously mentioned, this review focuses on Cohort 2 and those participants receiving DRV/COBI based regimen. Of the 28 screened participants, 8 were enrolled into Cohort 2 and received at least 1 dose of study drug (DRV/COBI based regimen). Participants were enrolled at 5 study centers in 3 countries (1 participant in South Africa, 5 participants in the US, and 2 participants in Zimbabwe).

At the data cutoff date, 62.5% (5 of 8) or participants had completed study drug in the main, 48-week treatment phase, and had entered the extension phase. Three participants discontinued the study drug due to withdrawn consent during the Week 48 window. Eighty percent (4 of 5) of participants continued study drug in the extension phase, one participant from the cohort discontinued the study in the extension phase due to the investigator's discretion.

Figure 3: Disposition of All Participants



eCRF = electronic case report form
Screen failures are for screen failure participants in Cohorts 2 and 3, regardless of protease inhibitor. One participant in Cohort 2 was rescreened.
One participant in Cohort 2 had an eligibility criteria deviation (inclusion criterion 12) which was not recorded on the eCRF. This participant was enrolled following approval.

Baseline Demographics

Table 5 displays the baseline demographics and disease characteristics. All participants tested negative for HBV surface antigen and HCV antibody negative. The mode of HIV infection in the majority of participants was vertical transmission (87.5%) although one participant had reportedly unknown transmission. In this cohort, most participants were female (75%, 6 of 8). The median age was 10 (range 7-11) years, and 87.5% (7 of 8) participants were Black.

Table 5: Baseline Demographics and Disease Characteristics for Cohort 2

	Cohort 2 (n=8)
Age (years)	
Median	10
Range	7-11
Sex, n (%)	
Male	2 (25%)
Female	6 (75%)
Race	
Black	7 (87.5%)
Other	1 (12.5%)
Baseline Weight, kg	
Median (range)	31.7 (27.6-45.4)
Baseline HIV RNA, n (%)	
< 50 copies/mL	8 (100%)
≥ 50 copies/mL	0
CD4 Cell Count (cells/mm^3)	
Median (range)	998 (439-1113)
HIV Disease Status	
Asymptomatic	8 (100%)
Symptomatic	0

All participants were to be on a stable, 3-drug antiviral regimen prior to the study. Three subjects were enrolled after Protocol 7, which stated the use of F/TAF as the required two NRTIs. The other participants who enrolled prior to this amendment received 2 NRTIs as well as ritonavir-boosted darunavir (DRV). NRTIs used by participants in Cohort 2 were: Abacavir, Lamivudine, Didanosine, Emtricitabine, and Zidovudine.

Among the 8 participants in the cohort, 2 weighed between 30 and <40 kg. These participants received 600 mg QD of DRV. The other 6 participants received per 675 mg per protocol. This deviation did not affect the overall safety and efficacy, and all participants were included in the analysis of safety and efficacy.

Results

The proportion of Cohort 2 participants with HIV-I RNA <50 copies/mL at Weeks 24 and 48 as determined using the US FDA-defined snapshot algorithm were as follows:

- Week 24: 100% (8 of 8 participants)
- Week 48: 100% (8 of 8 participants)

Mean (SD) baseline and changes from baseline in CD4 cell count were as follows (Tables 6 and 7).

- Baseline: 894 (240.2) cells/μL
- Week 24: −9 (179.7) cells/μL
- Week 48: −55 (198.7) cells/μL

Table 6: CD4 Change from Baseline

Participant	CD4 Baseline (cells/μL)	CD4 Week 24 (change from baseline)	CD4 Week 48 (change from baseline)
(b) (6)	660	800 (+140)	643 (-17)
	804	457 (-347)	782 (-22)
	1063	1161 (+98)	1146 (+83)
	1078	1202 (+124)	1150 (+72)
	1113	1016 (-97)	795 (-318)
	439	625 (+186)	684 (+245)
	967	843 (-124)	653 (-314)
	1029	981 (-48)	862 (-167)
Mean	**894**	**885 (-9)**	**839 (-55)**
Median	**998**	**+25**	**-20**

Table 7: CD4% Change from Baseline

Participant	CD4% Baseline	CD4% Week 24 (change from baseline)	CD4% Week 48 (change from baseline)
(b) (6)	35.4	33.4 (-2)	30 (-5.4)
	37.2	40.5 (-3.3)	38.8 (+1.6)
	34.5	35.1 (-0.6)	35.4 (+0.9)
	44.6	43.9 (-0.7)	45.2 (+0.6)
	48.5	46 (-2.5)	47.9 (-0.6)
	29.1	28.8 (-0.3)	30.4 (+1.3)
	43.9	43.5 (-0.4)	32.5 (11.4)
	42.7	45.7 (+3)	45.9 (+3.2)
Mean	**39.49%**	**39.62% (+0.12%)**	**38.26 (-1.23%)**
Median	**40**	**-0.65%**	**0.75%**

Reviewer note: Because the trial is not powered for statistical analysis of efficacy, only descriptive statistics are presented in this review and in product labeling. Overall, there were no concerning patterns noted in CD4 count during the 48-week analysis. The CD4 fluctuations over time and likely due to the small sample size and not deemed clinically significant.

Conclusions

No participants experienced loss of virologic response at Week 24 or Week 48. The HIV-1 RNA and CD4 cell count results will be included in product labeling to support the use of DRV/COBI in children > 6 years of age and weighing at least 25 kg.

8. Safety

8.1 Methods

All DRV/COBI participants from Cohort 2 are included in the safety review and the safety data through Week 48 are summarized below. The AdaM datasets were used to evaluate key safety results, including adverse drug reactions, serious adverse events, discontinuations due to AEs, significant AEs and laboratory abnormalities. Adverse events were coded using MedDRA Version 26.0. Severity grades were defined by the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities. Due to the limited sample size of this cohort, safety analyses by subgroups (age, sex, and race) were not performed. Overall, the safety findings are consistent with those of the applicant, and we did not identify any new significant safety issues.

8.2 Major Safety Results

8.2.1 Deaths

There were no deaths in this cohort during this interim analysis.

8.2.2 Serious Adverse Events

No serious adverse events were reported during this interim analysis.

8.2.3 Discontinuations due to AEs

There were no AEs that led to premature study drug discontinuation during this interim analysis. Three participants prematurely discontinued from the study drug prior to Week 48 due to withdrawal of consent.

8.2.4 Significant AEs

No grade 3-4 AEs were reported during this interim analysis.

8.2.5 Common AEs

Common AEs: Overall, all participants from this cohort had at least one AE, all of which were Grade 1 or 2 in severity. Table 8 provides a summary of all treatment-emergent adverse events during this interim analysis separated by Grade as reported according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

Table 8: Summary of TEAEs by Maximum Severity/Toxicity Through Week 48

System Organ Class	Cohort 2 N = 8	
	Grade 1 n (%)	Grade 2 n (%)
Any AE	3 (37.5)	5 (62.5)
Respiratory, thoracic and mediastinal disorders	5 (62.5)	0 (0.0)
Infections and infestations	4 (50.0)	2 (25.0)
Nervous system disorders	3 (37.5)	0 (0.0)
Eye disorders	2 (25.0)	0 (0.0)
Gastrointestinal disorders	2 (25.0)	2 (25.0)
Psychiatric disorders	2 (25.0)	0 (0.0)
Blood and lymphatic system disorders	1 (12.5)	0 (0.0)
Ear and labyrinth disorders	1 (12.5)	1 (12.5)
General disorders and administration site conditions	1 (12.5)	0 (0.0)
Injury, poisoning and procedural complications	1 (12.5)	2 (25.0)
Musculoskeletal and connective tissue disorders	1 (12.5)	0 (0.0)
Product issues	1 (12.5)	0 (0.0)
Investigations	0 (0.0)	1 (12.5)
Reproductive system and breast disorders	0 (0.0)	1 (12.5)

Source: OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table.
Filters: COHORT = "Cohort 2" and SAFFL = "Y" (Cohort 2); TRTEMFL = "Y" and AETOXGRN = ("Grade 1" or "Grade 2") (Adverse Events).

The most common reported adverse events were nasal congestion and vomiting, both reported in 37.5% (3 of 8 participants). The most commonly reported AEs by system organ class were categorized as "infections and infestations" (62.5%) or "respiratory, thoracic, and mediastinal disorders" (62.5%), and further reported as abdominal pain, cerumen impaction, cough, headache, influenza, and upper respiratory tract infection (all occurred in 2 of 8 participants, 25%). Most events were considered not related to the study drug.

The adverse drug reactions (adverse events considered related to the study drug) were reported in 2 of 8 (25%) participants and included vomiting, with severity grading of 1 and 2. One additional participant reported "product taste abnormal" and "product size issue" that were deemed related to the study drug as well.

8.2.5 AEs of Special Interest

Prezcobix is not recommended to be used in combination with tenofovir disoproxil fumarate (TDF) in patients with severely impaired renal function (CrCl <70) due to the effect of cobicistat on inhibition of tubular secretion of creatinine and decreasing estimate creatinine clearance. It is recommended that creatinine clearance be estimated before using these two drugs combined. Therefore, renal events were reviewed in detail. Overall, no AEs relating to abnormal renal function were reported or noted.

8.3 Supportive Safety Results

8.3.1 Laboratory Findings

Clinical laboratory measurements were collected at different time points throughout the study; in general, there were no new or unexpected safety findings in the study population. The sections below discuss the week 48 (post baseline) reported laboratory graded abnormalities. A change in Absolute Neutrophile Count was observed in half of the participants, though not at notable levels. There were no graded increases in serum creatinine.

There were no clinically relevant changes from baseline in median values of serum creatinine through the data cutoff date in this cohort. A gradual increase from baseline in serum creatinine was observed after week 4, and a decrease from baseline in eGFR was noted from week 4 onwards, but this was not considered clinically significant. There were no Grade 4 abnormalities observed.

There were no laboratory abnormalities in AST, ALT, or total bilirubin in this cohort. One participant had an elevation in alkaline phosphatase that was graded as Grade 1 (Table 9). No cases of Hy's Lab were identified.

Table 9: Proportion of Participants with Graded Laboratory Abnormalities Above Baseline through week 48 – Chemistry

Parameter	**N= 8 (%)**
Alkaline Phosphatase	
Grade 1	1 (12.5%)
Amylase	
Grade 1	1 (12.5%)
Grade 2	2 (25%)
Bicarbonate	
Grade 1	1 (12.5%)
Calcium Corrected for Albumin - Hypercalcemia	
Grade 1	2 (25%)
Calcium Corrected for Albumin - Hypocalcemia	
Grade 1	1 (12.5%)
Cholesterol - Hypercholesterolemia	
Grade 1	1 (12.5%)
Grade 2	3 (37.5%)
LDL Cholesterol (Fasting)	
Grade 1	3 (37.5%)

Grade 2	1 (12.5%)
Magnesium - Hypomagnesemia	
Grade 1	
Grade 2	1 (12.5%)
Potassium - Hyperkalemia	
Grade 1	1 (12.5%)
Proteinuria	
Grade 1	2 (25%)

Table 10: Proportion of Participants with Graded Laboratory Abnormalities through week 48 – Hematology

Parameter	**N = 8 (%)**
Absolute Neutrophil Count	
Grade 1	4 (50%)
Grade 2	1 (12.5%)
Hematuria	1 (12.5%)
Grade 1	

On further review of data that extended past week 48, two participants were noted to have Grade 3 hematuria. An IR was submitted to the Sponsor, and narratives for each participant. Overall, these Grade 3 hematuria events were related to menses and not study drug related

- Participant (b) (6) experienced Grade 3 (increase from 0) hematuria (150 RBC) at week 144, which was resolved at week 156. The Sponsor noted that this finding coincided with the patient's menstrual cycle and was not felt to be related to the study drug.
- Participant (b) (6) experienced Grade 3 (increase from 0) hematuria (3+ occult blood) at week 216. Which was resolved at week 228. The Sponsor also noted that this finding co-incided with the patient's menstrual cycle and was not felt to be related to the study drug.

8.3.2 Vital Sign Monitoring
No clinically relevant changes in vital signs were observed through Week 48

Overall Assessment of Safety

No new or unexpected safety findings were noted in the study participants and the adverse event profile and laboratory abnormalities were similar to those observed in adults and adolescents. The DRV exposures in pediatric participants at least 6 years of age and weighing

at least 25 kg to < 40 kg is similar to adults. The COBI exposures were 1.5 to 2-fold higher in this pediatric population; however, these exposures were deemed not clinically significant. As noted above, the safety profile in these pediatric participants was consistent with the safety profile seen in adults and adolescents. In addition, the exposure of COBI when administered as a component of PREZCOBIX is similar to the observed COBI exposure for GENVOYA® in pediatric participants aged 6 to < 12 years who were enrolled in the clinical trial that evaluated GENVOYA. (https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/elvitegravir and http://www.sciencedirect.com/science/article/pii/S2352464217300093?via%3Dihub). Letter of cross-reference can be found at this link. .

8.4 Safety Assessment from Adult Bioequivalence Study

8.4.1 Study TMC114IFD1004: A Single-dose, Open-label, Randomized, Crossover Pivotal Bioequivalence Study in Healthy Participants to Assess the Bioequivalence of Darunavir 675 mg in the Presence of 150 mg Cobicistat When Administered as a Fixed Dose Combination (Darunavir/Cobicistat) Compared to the Co-administration of the Separate Agents (Darunavir and Cobicistat) Under Fed Conditions.

The primary objective of this study was to evaluate single-dose PK and bioequivalence (BE) of DRV 675 mg in the presence of COBI 150 mg when administered as a scored FDC tablet compared to the separate formulations to support the development of the FDC PREZCOBIX tablet for children ≥ 6 to <12 years and/or weighing ≥ 25 kg. Twenty-two healthy adult participants were enrolled and completed the study as planned per protocol. Please refer to the clinical pharmacology section of this review for details and results of this BE study.

The study was comprised of 22 healthy adults who were assigned to 2 treatment sequences, 11 per treatment sequence (AB or BA). Treatments are defined as follows:

- Treatment A (test): a single oral dose of DRV 675 mg and COBI 150 mg as a scored FDC tablet
- Treatment B (reference): a single oral dose of DRV as 1 x 600-mg and 1 x 75-mg tablet and COBI as a x 150-mg tablet

The demographics were comparable between the 2 sequences. Most of the participants were female (15/22 total, 8 in sequence AB and 7 in sequence BA). All participants were white, except for one participant who was reported as multiracial. Overall, age range was from 18 to 51 years with a median of 43 years in sequence AB (range 20-51 years) and 30 years in sequence BA (range18-45 years).

Safety analysis from this study showed no AEs leading to study discontinuation, SAEs or deaths related to the study. The most common reported TEAEs were classified as nervous system disorders (4 participants, 18.2%), gastrointestinal disorders (3 participants, 13.6%), and musculoskeletal/connective tissue disorders (3 participants, 13.6%). The most frequently reported TEAE was headache, which was reported in 4 participants (18.2%). All AEs were Grade 1 in severity with the exception of one participant who had a headache that was graded as Grade 2. The headache occurred after the onset of treatment and an analgesic was administered for the adverse event.

Two (9.1%) participants in this study experienced study drug related TEAEs. Both of participants experienced Grade 1 headache on Day 1 of the study.

Laboratory findings were notable for multiple laboratory values outside of the reference ranges. No laboratory abnormalities were reported as TEAEs by the investigator, and no new safety signals were identified. All abnormalities were Grade 1 or 2 in severity. Most common laboratory abnormalities were increased cholesterol and triglyceride values. The most frequently reported treatment-emergent non-graded laboratory abnormalities were low protein (7 participants, 31.8%), low erythrocyte mean corpuscular hemoglobin concentration (12 participants, 54.5%), low hematocrit (4 participants, 18.1%) and high monocyte/leukocyte ratio (5 participants, 22.7%). These non-graded laboratory abnormalities were deemed not clinically significant.

Overall Conclusions: The BE study did not identify any new or unexpected safety findings

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

Not applicable

11. Other Relevant Regulatory Issues

This section may include discussion on other issues (if not addressed in previous sections):

- Application Integrity Policy (AIP)
- Exclusivity or patent issues of concern
- Financial disclosures
- Other Good Clinical Practice (GCP) issues
- Office of Scientific Investigations (OSI) audits
- Any other outstanding regulatory issues

12. Labeling

Prescribing Information
The major labeling changes are described in this section.

- Section 1 – INDICATIONS AND USAGE
  - Indications changed to include pediatric patients weighing at least 25 kg
- Section 2 – DOSAGE AND ADMINISTRATION
  - A new table is included showing the recommended dosage of PREZCOBIX based on age and weight for the new pediatric population as follows: The

recommended dose (taken once daily with food) for pediatric patients 6 years and older and weighing at least 25 kg to less than 40 kg is 675 mg darunavir/150 mg cobicistat.
    - For pediatric patients who are unable to swallow the tablet whole, the labeling includes recommendations to split the scored tablet into two pieces.
- Section 3 – DOSAGE AND STRENGTH
    - Addition of a new dosage from:
    - The 675 mg darunavir/150 mg cobicistat is a green to dark green oval-shaped scored film-coated tablet debossed with "675" on one side and "TG" on the other side
- Section 6 – ADVERSE REACTIONS
    - Section 6.1, Clinical Trials Experience
        - Addition of reference to and pediatric patients 6 to less than 12 years of age (Cohort 2, virologically suppressed, N=8 with weight ≥25 kg. No specific safety data from Cohort 2 was included because the safety analyses of this trial in these pediatric participants did not identify new safety concerns compared to the known safety profile in adult participants
- Section 8 – USE IN SPECIFIC POPULATIONS
    - Section 8.2: Lactation
        - Labeling updated to include language that is consistent with other recently revised HIV labeling, specifically to highlight that there is no data on the presence of DRV or COBI in human milk
    - Section 8.4: Pediatric Use
        - This section was updated to reflect the inclusion of pediatric patients weighing at least 25 kg and who are at least 6 years of age.
- Section 11 – DESCRIPTION
    - A description of the new 675 mg darunavir/150 mg cobicistat tablets: inactive ingredients such as colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are coated with a coating of iron oxide black, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
- Section 12 – CLINICALA PHARMACOLOGY
    - Section 12.3: Pharmacokinetics
        - Section describes the bioequivalence data between PREZCOBIX (675 mg/150 mg) and darunavir (675 mg) co-administered with cobicistat (15mg) mg as single entities
        - The PK estimates for DRV AUC_{0-24} and C_{0h} from participants Aged ≥ 6 to < 12 Years and Weighing ≥ 25 to < 40 kg were included in Table 4 of the USPI. Text was added to state COBI exposures were similar between adults and adolescents but higher in children aged 6 to less than 12 years, weighing at least 25 kg. The difference observed in children for COBI is not considered clinically relevant
- Section 14 – CLINICAL STUDIES
    - Section 14.2: Clinical Trial Results in Pediatric Subjects with HIV-1 Infection

- Cohort 2 of Study GS-US-216-0128 is included to support the updated labeling. Labeling highlights that all subjects remained virally suppressed at Week 48 and shows that the median CD4 change from baseline and CD4+% at Week 48 was -20 cells/mm3 (range -318 to 245) and 0.75% (-11.40 to 3.20), respectively.

13. Postmarketing Recommendations

None

14. Recommended Comments to the Applicant

None

15. Appendices

15.1 Bioanalytical Method Validation and Performance

For DRV and COBI, a combined method was validated at (b) (4). For both DRV and COBI, a stable isotope-labeled internal standard was used for quantification of plasma concentrations using LC-MS/MS with a LLOQ of 5.00 ng/mL for both DRV and COBI. The samples were analyzed within the storage stability. The validation method and the analytical reports have been reviewed and deemed acceptable (See Tables 11 and 12).

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of darunavir and cobicistat at (b) (4) for Study GS-US-216-0128. There are no concerns with the analytical site. The clinical and analytical inspection request for bioequivalence study TMC114IFD1004 was declined by OSIS because the requested clinical and analytical sites have recently been inspected, and inspection is not needed for this study.

Table 11: Bioanalytical Method Validation Summary

Validation Report #	BA 10833 (for Study TMC114IFD104)	(b) (4) 42-0902, (b) (4) 60-1343 (for Study GS-US-216-0128)
Drug Analytes	DRV, COBI	DRV, COBI
CRO	(b) (4)	(b) (4)
Method of Detection	LC-MS/MS	LC-MS/MS
Biological Matrix	Human plasma	Human Plasma
Anticoagulant	Ethylenediaminetetraacetic acid (EDTA)	K_3EDTA
Calibration standard Range (ng/mL)	DRV: 5.0 to 10000 COBI: 5.0 to 5000	DRV: 20 to 10000 COBI: 5 to 2500
Calibration Accuracy (RE%)	DRV: -7.4 to 8.6 COBI: -3.0 to 5.5	DRV: -3.7 to 4.0 COBI: -1.8 to 4.4
Quality Control (QC) Levels (ng/mL)	DRV: 15, 500, 5000, and 8000 COBI: 15, 500, 1500, and 4000	DRV: 20, 60, 800, 5000 and 9000 COBI: 5, 15, 100, 1000, and 2000
QC Inter-day Accuracy (RE%)	DRV: 2.1 to 8.7 COBI: -0.9 to2.8	DRV: -2.2 to 3.8 COBI: -3.0 to 2.0
QC Inter-day Precision (%CV)	DRV: ≤1.7 COBI: ≤3.6	DRV: ≤6.3 COBI: ≤5.7
Storage Stability	DRV and COBI (n the absence of FTC and TAF) are stable in human plasma stored at -20˚C and -70˚C for 530 days. DRV and COBI are stable for at least 222 days at -20˚C and -70˚C in the presence of emtricitabine and tenofovir alafenamide.	DRV: 1635 days at -20˚C and -70˚C COBI: 121 days at -20˚C and 1297 days at -70˚C

Source: Collated by the Reviewer

Table 12: Bioanalytical Method Performance Summary

Study number	TMC114IFD104	GS-US-216-0128 (Cohort 2&3)
Bioanalytical Report #	(b) (4) 2026B-2026BX-A	(b) (4) 60-1384B; (b) (4) 60-1384C
Method of Detection	LC-MS/MS	LC-MS/MS
Method reproducibility (passing rate)	DRV: 98.1% COBI: 98.6%	DRV: 100% COBI: 85%
Calibration standard Inter-day Accuracy (RE%)	DRV: -8.5 to 5.0 COBI: -4.3 to 2.8	DRV: -1.8 to 1.0 COBI: -2.2 to 2.0
QC Levels (µg/mL)	DRV: 15, 500, 4500, and 7500 COBI: 15, 500, 2250, and 3750	DRV: 20, 60, 800, 5000 and 9000 COBI: 5, 15, 100, 1000, and 2000
QC Inter-day Accuracy (RE%)	DRV: -7.1 to 4.7 COBI: 1.3 to 7.3	DRV: -2.2 to 3.8 COBI: -3.0 to 2.0
QC Inter-day Precision (%CV)	DRV: ≤5.6 COBI: ≤7.3	DRV: ≤3.8 COBI: ≤5.7

Source: Collated by the Reviewer

15.2. Pharmacometrics Assessment

15.2.1. Review Summary

In general, the Applicant's PopPK analysis is considered acceptable for the purpose of characterizing the PK of DRV in the target HIV-1 infected pediatric patients of ≥6 years of age and weighing ≥25 kg to <40 kg and performing simulations to derive exposure metrics for exposure comparison. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. More specifically, the model was used to support the current submission as outlined in **Table 13**.

Table 13. Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	Proposed labeling change to include pediatric patients at least 25 kg to less than 40 kg; addition of pharmacokinetic exposure comparison in Table 4 of the label.	Available pharmacokinetic data for the different components of PREZCOBIX indicate that there were no clinically relevant differences in darunavir exposure between adults and adolescents or children weighing at least 25 kg. The reviewer agrees with the proposed language in the label.
	Extrinsic factor	N/A	N/A

15.2.2. Population PK Analysis

15.2.2.1. Introduction

Based on the indicated pediatric population in this submission, the objectives of the PopPK analysis were to:

- compare individual DRV $AUC_{0\text{-}24h}$ and C_{0h} for pediatric participants enrolled in Cohort 2 of Study 216-0128 with reference adult exposures
- assess whether the proposed DRV dose of 675 mg QD (in combination with COBI 150 mg QD) for pediatric patients weighing ≥25 kg to <40 kg result in comparable DRV $AUC_{0\text{-}24h}$ and C_{0h} as compared to those in reference adults based on PopPK simulations in virtual populations

15.2.2.2 Model Development

Data

A total of 347 DRV plasma concentrations were available from 27 HIV-1 infected pediatric participants who received DRV in combination with COBI (with or without F/TAF) in Cohorts 1 to 3 in Study 216-0128. A brief description of the studies included for popPK analysis is presented in **Table 14**. **Table 15** provides the summary statistics of the baseline demographic covariates in the analysis dataset.

Table 14. Summary of Studies with PK Sampling Included in Population PK Analysis

Study Number	Study Title & Design	Number of Participants	Dosing Regimen[a]	PK Assessments
GS-US-216-0128	A Phase 2/3, Multicenter, Open-label, Multicohort Study Evaluating PK, Safety, and Efficacy of ATV/co or DRV/co and F/TAF in HIV-1 Infected, Virologically Suppressed Pediatric Participants	Cohort 1 (Part A): 8 participants (DRV+COBI) Cohort 2: 8 participants (DRV+COBI)[b] Cohort 3: 11 participants (DRV+COBI+F/TAF)	Cohort 1 (Part A): participants aged ≥12 to <18 years weighing ≥25 kg receiving DRV (ie, 600 mg qd for ≥25 to <30 kg, 675 mg qd for ≥30 to <40 kg, and 800 mg qd for ≥40 kg) in combination with COBI 150 mg qd. Cohort 2: participants aged ≥6 to <12 years weighing ≥25 kg, receiving DRV (ie, 600 mg qd for ≥25 to <30 kg, 675 mg qd for ≥30 to <40 kg, and 800 mg qd for ≥40 kg) in combination with COBI 150 mg qd[b]. Cohort 3: participants aged ≥3 years weighing ≥14 to <25 kg receiving DRV 600 mg in combination with COBI 90 mg and F/TAF 120/15 mg qd.	Cohort 1 Part A: predose PK sample at D1, W12, 24, and 48; intensive PK sampling on D10 (predose, 1, 2, 3, 4, 5, 8, and 12 hours postdose). Cohort 2: predose PK sample at W8, W24, and W36; timed PK sample at W12, W16, and W48; intensive PK sampling at either W2 or W4 (predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, and 24 hours postdose). Cohort 3: predose PK sample at W8, W24, and W36; timed PK sample at W12, W16, and W48; intensive PK sampling within 7 days after either the W2 or W4 visit (predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, and 24 hours postdose).

ARV=antiretroviral; ATV=atazanavir; /co=boosted with cobicistat; COBI=cobicistat; D=day; DRV=darunavir; HIV-1=human immunodeficiency virus type 1; F/TAF=emtricitabine/tenofovir alafenamide; PK=pharmacokinetic; qd=once daily; W=week.

[a] The recommended daily dosage of DRV based on body weight according to the local Prescribing Information was to be given and was not to exceed the recommended adult dosage.

[b] Participants enrolled in Cohort 2 after implementation of Protocol Amendment 7 also received F/TAF 200/25 mg once daily as third agent.

Source: Table 1 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 Infection in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128), EDMS-RIM-1148316, 2.0

Nonlinear mixed effect modeling of concentration-time data was performed using NONMEM (Version 7.4). First-order conditional estimation approximation with the INTERACTION was used. Postprocessing of NONMEM analysis (e.g., diagnostics) results were carried out using the R software (version 3.6.2 or higher).

Table 15. Summary of Baseline Demographic Covariates for Analysis

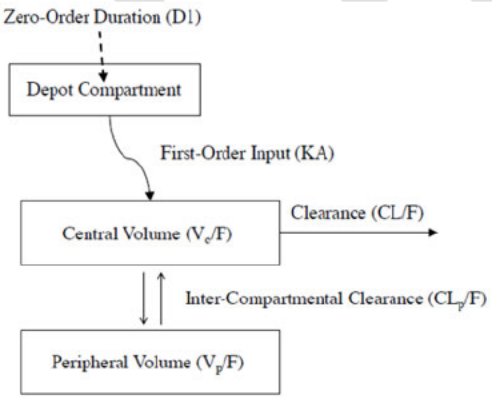
Variable	Value	Cohort 1	Cohort 2	Cohort 3	All participants
Number of participants	n	8	8	11	27
Age (years)	Mean (SD)	14.1 (1.5)	9.5 (1.7)	4.9 (1.7)	9.0 (4.2)
	Median	14.5	10.0	4.0	9
	Range	(12; 16)	(7; 11)	(3; 7)	(3; 16)
Weight (kg)	Mean (SD)	55.0 (13.2)	33.4 (6.0)	17.4 (2.3)	33.2 (17.6)
	Median	53.7	31.7	16.8	29.2
	Range	(37.2; 78.0)	(27.6; 45.4)	(14.7; 22.0)	(14.7; 78.0)
Creatinine clearance (mL/min)[a]	Mean (SD)	146 (23.1)	149 (17.3)	158 (25.9)	152 (22.5)
	Median	150	150	154	154
	Range	(108; 178)	(114; 172)	(121; 209)	(108; 209)
Sex, n (%)	Male	4 (50.0)	2 (25.0)	5 (45.4)	11 (40.7)
	Female	4 (50.0)	6 (75.0)	6 (54.6)	16 (59.3)
Race, n (%)	White	3 (37.5)	0 (0)	0 (0)	3 (11.1)
	Black or African American	3 (37.5)	7 (87.5)	11 (100%)	21 (77.8)
	Other	2 (25.0)	1 (12.5)	0 (0)	3 (11.1)

[a] *Based on Schwartz formula.*
n=number of participants; SD=standard deviation.
Source: Table 2 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 Infection in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128), EDMS-RIM-1148316, 2.0

Base model

A PopPK model has been previously developed from PK data collected in Phase 1 and 2 adult studies where DRV was administered in combination with RTV (ritonavir), as well as Phase 3 adult Studies 216-0130, FD2HTX3001 and IFD3013 where DRV was administered in combination with COBI (PopPK Report 2017). The PopPK model comprised a 2-compartment disposition model with a sequential zero-order input into the depot compartment followed by a first-order absorption from the depot to the central compartment. The model structure is shown in **Figure 4**. An external evaluation of the previously developed PopPK model was initially performed using data collected in Study 216-0128. However, this model was not suitable to describe current data, as suggested by trends in the residuals versus predictions and time at both population and individual levels, as well as pcVPC (not shown for base model; refer to Applicant's PopPK report for details). The model was then adapted to describe the data from the current analysis dataset.

Figure 4. Schematic Overview of DRV PopPK Model



CL/F=apparent clearance; CLp/F=intercompartmental clearance; D1=zero-order duration; DRV=darunavir; ka=firstorder; absorption rate constant; PopPK=population pharmacokinetics; Vc/F=apparent volume of distribution of the central compartment; Vp/F=apparent volume of distribution of the peripheral compartment.

Source: Figure 1, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 Infection in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128), EDMS-RIM-1148316, 2.0

Covariate analysis

A formal covariate analysis on current data set was not conducted given the prior knowledge of parameter-covariate relationship of previous developed popPK model. The correlations between individual random effects and the covariates of interest (e.g., age, body weight, creatinine clearance, alpha-1-acid glycoprotein or AAG, sex, and race) were explored graphically. In addition, a normally distributed additive error model on the natural logarithm of the data was first investigated, keeping all other parameters fixed to the adult values (run 205, objective function value or OFV was 214.534). Then, based on the findings from the exploratory analysis, the effect of body weight on CL/F and Q/F (with fixed coefficient of 0.75) and on Vc/F and Vp/F (with fixed coefficient of 1) were added, and after this CL/F and D1 were re-estimated (run 213, OFV was -109.362). Population and individual level goodness-of-fit (GOF) and residual plots for run 213 show that the data were well described at both population and individual level, with no major trends in the residuals. Therefore, the Applicant selected run 213 as the final PopPK model for DRV.

15.2.2.3 Final Model

The parameter estimates for the final covariate model are listed in Table 16. The model described the observed data adequately, as seen in the GOF plots (**Figure 5**). The diagnostic plots and summary tables below refer to the DRV component unless otherwise specified.

Table 16. Parameter estimates of the final PopPK model

Parameter (unit)	Estimate (RSE%)
CL/F (L/h, typical value[b])	69.2 (6.43%)
V_c/F (L, typical value[c])	88.3 (fixed[i])
Q/F (L/h, typical value[d])	24.0 (fixed[i])
V_p/F (L, typical value[e])	90.0 (fixed[i])
k_a (h^{-1})	0.393 (fixed[i])
F1[a]	1.18 (fixed[i])
D_1 (h)	2.02 (10.9%)
Effect of body weight on CL/F[b] and Q/F[d]	0.75 (fixed[j])
Effect of body weight on V_c/F[c] and V_p/F[e]	1 (fixed[j])
Effect of TDD on CL/F[b]	0.388 (fixed[i])
Effect of AAG on CL/F[b]	0.0304 (fixed[i])
IIV on CL/F[f]	0.0517 (fixed[i]) (CV=23.0%) (shr=3.92%)
IIV on V_c/F[f]	0.0244 (fixed[i]) (CV=15.7%) (shr=79.4%)
IIV on Q/F[f]	0.260 (fixed[i]) (CV=54.5%) (shr=85.5%)
IIV on V_p/F[f]	0.310 (fixed[i]) (CV=60.3%) (shr=28.6%)
IIV on D_1[g]	0.782 (fixed[i]) (CV=108%) (shr=38.0%)
RUV[h]	0.387 (16.9%) (CV=68.7%)
OFV	105.172

AAG=alpha-1-acid glycoprotein; CL/F=apparent clearance; CV=coefficient of variation; D1=zero-order duration; DRV=darunavir; ETA=random effect; F1=apparent bioavailability; IIV=interindividual variability;

ka=first-order absorption rate constant; OFV=objective function value; PK=pharmacokinetic; PopPK=population pharmacokinetics; Q/F=apparent intercompartmental clearance; RSE=relative standard error; RUV=residual unexplained variability; shr=shrinkage; TDD=total daily dose; Vc/F=apparent volume of distribution of the central compartment; Vp/F=apparent volume of distribution of the peripheral compartment; WT=body weight.

[a] For DRV single agent commercial formulation relative to tablet used in previous clinical studies (F_{rel}).

[b] Implemented as $CL/F=69.2\times(1/(1+0.0304\times AAG))\times(TDD/1200)^{0.388}\times(WT/70)^{0.75}$; where TDD=800 mg and AAG=94.2 mg/dL.

[c] Implemented as $Vc/F=88.3\times(WT/70)^{1}$.

[d] Implemented as $Q/F=24.0\times(WT/70)^{0.75}$.

[e] Implemented as $Vp/F=90.0\times(WT/70)^{1}$.

[f] Estimate (RSE%) represents the OMEGA point estimate and its associated RSE. CV represents the coefficient of variation for a lognormal distribution, calculated as sqrt(exp(OMEGA)-1)×100. Shrinkage calculated as (1-sd(ETA)/sqrt(OMEGA))×100, where sd(ETA) is the sample standard deviation of the random effects.

[g] Implemented on the logit scale, CV% not evaluable.

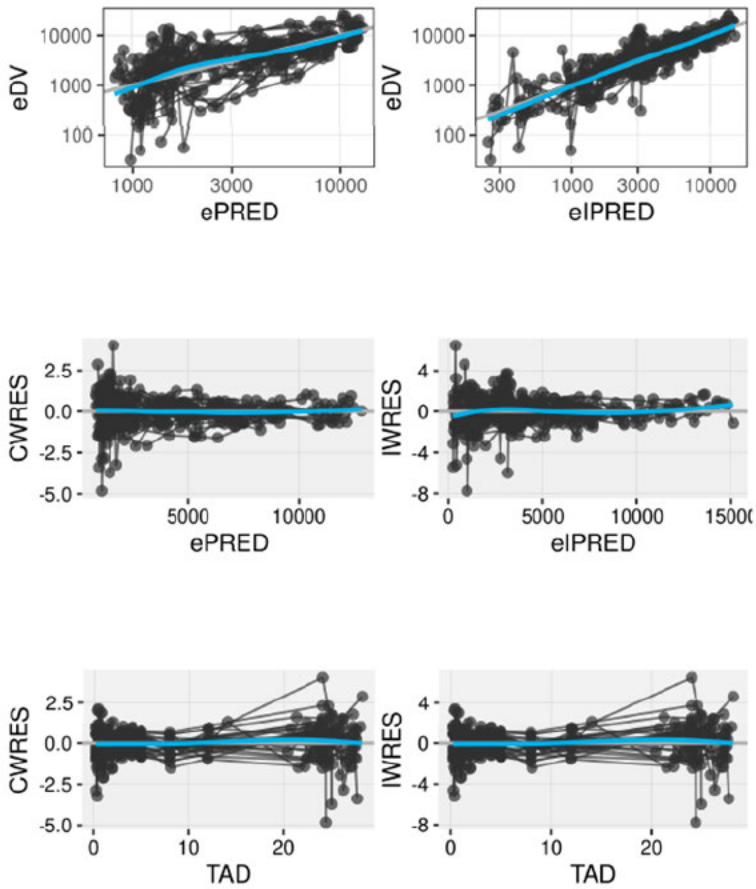
[h] Estimate (RSE%) represents the SIGMA point estimate and its associated RSE. CV represents the coefficient of variation for a lognormal distribution, calculated as sqrt(exp(SIGMA)-1)×100.

[i] Fixed to value from previous PopPK model developed in adults.

[j] Fixed to standard allometric coefficient.

Source: Table 5, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 Infection in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128), EDMS-RIM-1148316, 2.0

Figure 5. Goodness-of-Fit Plots for final PopPK model

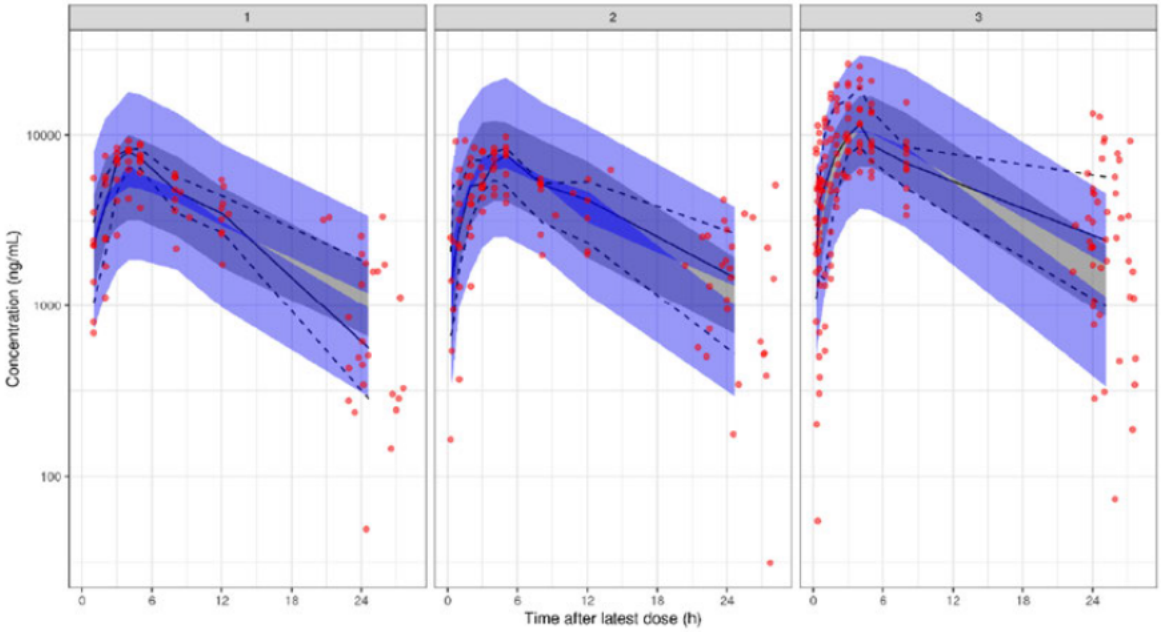


CWRES=conditional weighted residuals; eDV=observations on linear scale; eIPRED=individual predictions on linear scale; ePRED=model predictions on linear scale; IWRES=individual weighted residuals; PopPK=population pharmacokinetics; TAD=time after latest dose.

Source: Attachment 6 GOF plots for Run 213 (Final) PopPK model, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 Infection in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128), EDMS-RIM-1148316, 2.0

A prediction-corrected visual predictive check (pcVPC) was performed to ensure that the model has maintained fidelity with the observed DRV PK data. Model based simulations of 1000 replicates of the analysis data set were performed. Simulated and observed distributions were compared by calculating the median, 5th, and 95th percentiles for each time interval (**Figure 6**).

Figure 6. Prediction-corrected VPC Plot for Final PopPK Model Stratified by Study Cohorts



CI=confidence interval; pcVPC=prediction-corrected visual predictive check; PopPK=population pharmacokinetics. The black solid line and gray shaded area represent, respectively, the median of prediction-corrected observations (red circles) and its associated 95% CI based on the simulations. The black dashed lines and blue shaded areas represent, respectively, the 5th and 95th percentiles of the prediction-corrected observations and their associated 95 CIs based on the simulations.

Source: Attachment 13 pcVPC stratified by cohort for Run 213 (final) PopPK model, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 Infection in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128), EDMS-RIM-1148316, 2.0

Reviewer comments: The reviewer was able to reproduce and verify the Applicant's final popPK model, and no discordance was identified. The model parameters were estimated with

reasonable precision (RSE% for estimated parameters were <10.9%). The shrinkages for IIV ranged from 3.92% (for CL/F) to 85.5% (Q/F); however, the IIVs were fixed to the previously developed popPK model (refer to base model section above). Based on the observed vs. individual and population predicted GOF plots, the data points randomly scatter around the line of unity with no significant trends identified. The conditional weighted residual (i.e., CWRES) plots also demonstrate no bias or misspecification of the final popPK model. The pcVPC plots stratified by study cohorts showed over-predictions and under-predictions at the end of the dosing interval for Cohort 1 and Cohort 3, respectively; however, the review emphasis is only placed on Cohort 2 as this is the indicated patient population of interest (i.e., pediatric population aged ≥6 years and weighing ≥25 kg to <40 kg), the reviewer considers that the final popPK model have reasonably captured the central tendency of the observed concentration-time profile. Overall, the final popPK model is adequate in describing DRV PK and supports model-based simulations for exposure comparison, and ultimately, dosing recommendation for the target pediatric population.

15.2.2.4 PK Simulations and Exposure Comparison

The Applicant proposed dosage is slightly different from the dosages administered in Study 216-0128 (See Section 5 Clinical Pharmacology). Based on the proposed dosage of 675/150 mg QD for the indicated pediatric patients (i.e., ≥6 year-old and weighing ≥25 kg to <40 kg), model-predicted exposures were derived for Cohort 2 using the final PopPK model. Arithmetic means, geometric means along with geometric mean ratios (GMR) of individual $AUC_{0\text{-}24h}$ and C_{0h} between pediatric patients and reference adults are summarized in **Table 17**. The GMR (90% confidence interval or CI) for DRV $AUC_{0\text{-}24h}$ is 1.048 (0.936, 1.173), suggesting similar exposure. For DRV C_{0h}, the GMR (90% CI) is relatively low at 0.695 (0.522, 0.926) when compared to reference adult group but is numerically higher compared to Cohort 1 (12 to <18 years) in the same study with the label recommended dose The overall results may have limited interpretation considering: 1) the relatively small sample size of 8 subjects in Cohort 2 of Study 0128, and 2) the relatively wide spread in the distribution of the corresponding C_{0h} (i.e., coefficient of variation, 43.8%) in Cohort 2 of Study 0128.

Table 17. Comparison of $AUC_{0\text{-}24h}$ and C_{0h} for Participants in Study 216-0128 Assuming the Proposed DRV/COBI Dosing Regimen in Pediatric Participants VS Adult DRV Studies

Exposure Metrics	GS-US-216-0128 (25 to <40 kg); DRV/COBI 675/150 mg (N=8)[a]	Reference Adults: Study FD2HTX3001; DRV/COBI/FTC/TAF 800/150/200/10 mg (N=356)
$AUC_{0\text{-}24h}$ (ng*h/mL)		
Mean (SD)	92052 (17254)	87909 (20232)[b]
Geometric mean	90007	85877

GMR (90% CI)	-	1.048 (0.936, 1.173)
C_{0h} (ng/mL)		
Mean (SD)	1345 (569)	1899 (759)
Geometric mean	1230	1769
GMR (90% CI)	-	0.695 (0.522, 0.926)

$AUC_{0\text{-}24h}$=area under the concentration-time curve over a 24-hour dosing interval at steady-state; C_{0h}=plasma concentration at the end of a 24-hour dosing interval at steady-state; COBI=cobicistat; DRV=darunavir; FTC=emtricitabine; N=number of participants; QD=once daily; TAF=tenofovir alafenamide; GMR, geometric mean ratio; 90% CI, 90% confidence interval; SD, standard deviation

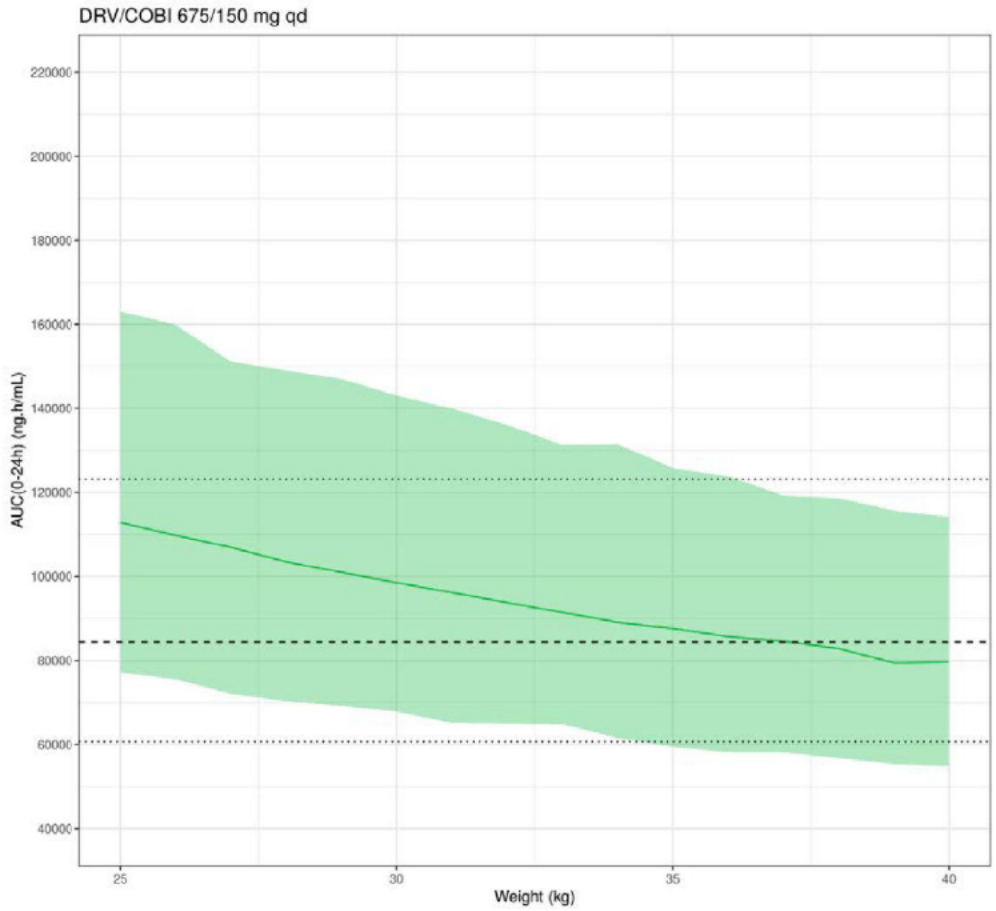
[a]Subject (b) (6) in Cohort 2 has body weight 45.4 kg and is excluded from this analysis. Subject (b) (6) in cohort 1 has body weight 37.2 kg and is included in this analysis

[b]N=355

Source: adapted from Table 9 and Attachment 16, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 Infection in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128), EDMS-RIM-1148316, 2.0

Subsequently, simulations were conducted in 1000 virtual pediatric subjects with body weight ranging from 14 to 70 kg at 1-kg increments. The 90% prediction interval (PI) of the simulated pediatric exposures (based on proposed dosage) were compared to the 90% PI of the reference adult exposures (i.e., individual exposures) from Study FD2HTX3001. Simulated $AUC_{0\text{-}24h}$ and C_{0h} are illustrated in **Figure 7** and **Figure 8**, respectively, for the target pediatric weight range of ≥25 kg to <40 kg. Based on the simulation findings, the proposed DRV/COBI 675/150 mg QD dosing regimen for the target pediatric patient population (i.e., ≥6 year-old and weighing ≥25 kg to <40 kg) results in similar or higher (up to 34% higher at 25 kg) DRV $AUC_{0\text{-}24h}$ and similar or lower (up to 33% lower at 39 kg) DRV C_{0h} compared with those of the reference adults. Overall, the simulation findings support the proposed DRV/COBI 675/150 mg QD dosing regimen for pediatric patients aged ≥6 and weighing ≥25 kg to <40 kg.

Figure 7. Distribution of DRV $AUC_{0\text{-}24h}$ in Pediatric Patients 25 to <40 kg (Proposed Dosing Regimen) compared to Adults (Study FD2HTX3001)

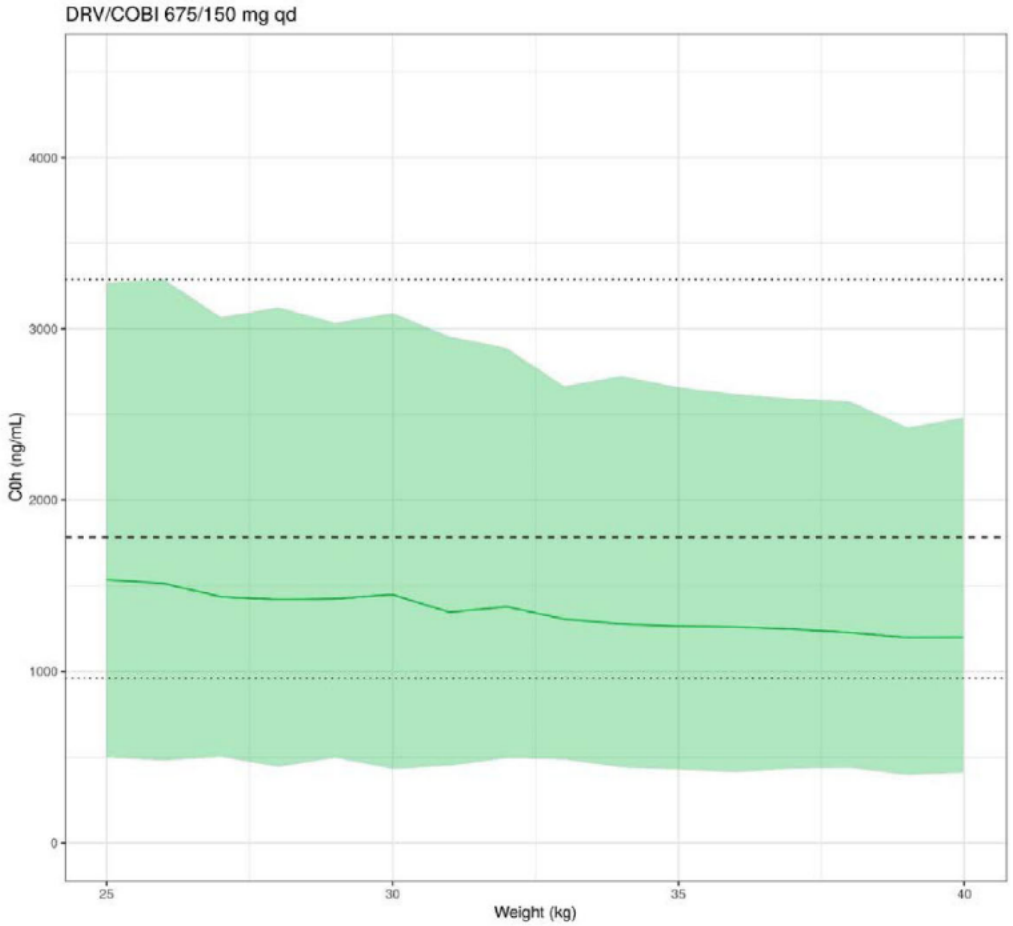


$AUC_{0\text{-}24h}$=area under the plasma concentration-time curve over a 24-hour dosing interval at steady-state; COBI=cobicistat; DRV=darunavir; PI=prediction interval; qd=once daily.

Note: The colored lines and shaded areas represent the median and 90% PI for $AUC_{0\text{-}24h}$ for each DRV/COBI dosing regimen. The black lines represent the adult median (dashed line), 5th and 95th percentiles of the 90% PI (dotted lines) of individual predicted $AUC_{0\text{-}24h}$ in Study FD2HTX3001.

*$AUC_{0\text{-}24h}$ 5th to 95th percentiles, 60667 to 123130 ng*h/mL;*
Source: Appendix 3, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 Infection in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128), EDMS-RIM-1148316, 2.0

Figure 8. Distribution of DRV C_{0h} in Pediatric Patients 25 to <40 kg (Proposed Dosing Regimen) compared to Adults (Study FD2HTX3001)



C_{0h}=plasma concentration at the end of a 24-hour dosing interval at steady-state; COBI=cobicistat; DRV=darunavir; PI=prediction interval; qd=once daily.

Note: The colored lines and shaded areas represent the median and 90% PI for C_{0h} for each DRV/COBI dosing regimen. The black lines represent the adult median (dashed line), 5th and 95th percentiles of the 90% PI (dotted lines) of individual predicted C_{0h} in Study FD2HTX3001.

C_{0h} 5th to 95th percentiles, 960 to 3288 ng/mL;
Source: Appendix 3, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 Infection in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128), EDMS-RIM-1148316, 2.0

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