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

Date	February 17, 2026
From	Sarita Boyd, PharmD Kimberly Struble, PharmD Jenny Zheng, PhD Kunyi Wu, PharmD Yun Wang, PhD Justin Earp, PhD
Subject	Division Director, CDTL, Clinical, and Clinical Pharmacology Review
Application Type	NDA 220092
NDA/BLA # and Supplement#	NDA 205395-S29
Applicant	Janssen
Date of Submission	April 30, 2025 May 7, 2025 (supplement)
PDUFA Goal Date	February 28, 2026 March 7, 2026 (supplement)
Proprietary Name	Prezcobix PED Prezcobix
Established or Proper Name	Darunavir (DRV) and cobicistat (COBI)
Dosage Form(s)	Tablets for oral suspension (Prezcobix PED) Tablets (Prezcobix)
Applicant Proposed Indication(s)/Population(s)	PREZCOBIX and PREZCOBIX PED are indicated in combination with other antiretroviral agents for the treatment of human immunodeficiency virus (HIV-1) in treatment-naïve and treatment-experienced adults and pediatric patients 3 years of age and older weighing at least 15 kg with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V).
Applicant Proposed Dosing Regimen(s)	Pediatric patients aged 3 years and older weighing at least 15 kg to less than 25 kg: One Prezcobix PED 600 mg darunavir/90 mg cobicistat tablet for oral suspension
Recommendation on Regulatory Action	Approve new tablet for oral suspension formulation and Approve (supplement) to align labeling
Recommended Indication(s)/Population(s)	Same as proposed
Recommended Dosing Regimen	Same as proposed
Cross-Reference	Letters of cross-reference were provided by Gilead Sciences for the following applications: • NDA 203094 (Tybost: cobicistat [COBI] tablets)

	• NDA 207561 (Genvoya: elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide, or E/C/F/TAF) • NDA 203100 (Stribild: elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate, or E/C/F/TDF)

1. Executive Summary

The Chemistry, Manufacturing, and Controls (CMC) data and results from the bioequivalence Study TMC114FD1HTX1004 support the approval of Prezcobix PED tablet for oral suspension, a new dosage formulation of a fixed-dose combination of darunavir (DRV) 600 mg and cobicistat (COBI) 90 mg for use in pediatric patients aged ≥3 years and weighing ≥15 kg to <25 kg. The pharmacokinetics, safety, and efficacy data for DRV and COBI coadministered as separate agents in pediatric patients with HIV-1 aged ≥3 years and weighing ≥15 kg to <25 kg were previously reviewed and approved under NDA 203094/S-18 (Tybost [COBI]). Please refer to NDA 203094/S-18 for details. This submission fulfills PREA PMR 2845-1, which was issued at the time of NDA 205395 (Prezcobix [DRV/COBI]) approval on January 29, 2015.

2. Background

Prezcobix (darunavir and cobicistat, DRV/COBI) is a fixed dose combination (FDC) tablet containing an HIV-1 protease inhibitor (DRV) as the active antiretroviral drug and a cytochrome P450 (CYP) 3A inhibitor (COBI) that increases the systemic exposure of DRV. Prezcobix is currently indicated, for once daily use, in combination with other antiretroviral agents for the treatment of HIV-1 in treatment-naïve and treatment-experienced adults and pediatric patients weighing at least 25 kg with no darunavir resistance-associated substitutions (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V). The recommended dosages of Prezcobix for the current approved indication are as follows:

Patient Population	Dose (once daily with food)
Adult Patients	One 800 mg darunavir/150 mg cobicistat tablet
Pediatric Patients weighing at least 40 kg	
Pediatric Patients weighing at least 25 kg to less than 40 kg	One 675 mg darunavir/150 mg cobicistat tablet

Prezcobix (DRV/COBI 800 mg/150 mg tablet) was originally approved in adults in January 2015 and was expanded in July 2020 to include use in pediatric patients weighing ≥40 kg. In March 2025, the pediatric indication was further expanded to include use in pediatric patients weighing ≥25 kg to <40 kg using a lower strength, scored tablet (DRV/COBI 675 mg/150 mg tablet).

In April 2025, the Applicant submitted an original NDA for Prezcobix PED (DRV/COBI 600 mg/90 mg tablet for oral suspension), a new age-appropriate dosage formulation, for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced pediatric patients aged ≥3 years and weighing ≥15 kg to <25 kg. The proposed dosage and administration is one tablet for oral suspension dispersed in water once daily with food. In May 2025, the Applicant submitted an efficacy supplement to the Prezcobix NDA to revise the Prezcobix labeling in alignment with the proposed Prezcobix PED labeling. This review pertains to both 2025 submissions.

Of note, in June 2025, the pediatric indication for the separate component COBI (Tybost, NDA 203094) was expanded as a CYP3A inhibitor to increase systemic exposure of DRV once daily in combination with other antiretroviral agents in the treatment of HIV-1 infection in treatment-naïve and treatment-experienced pediatric patients weighing ≥15 kg. The recommended dosage in pediatric patients weighing ≥15 kg to <25 kg is COBI 90 mg coadministered with DRV 600 mg. This approval was based on data from Study GS-US-216-0128 (hereafter referred to as Study 128), an ongoing Phase 2/3, open-label study evaluating the pharmacokinetics (PK), safety, and efficacy of DRV and COBI coadministered as separate agents along with two nucleoside reverse transcriptase inhibitors (NRTIs) in children and adolescents with HIV-1 aged ≥3 years to < 18 years across multiple cohorts.

To allow for extrapolation of Study 128 data for DRV and COBI administered as separate agents to the FDC tablets for oral suspension (Prezcobix PED), the Sponsor conducted a bioequivalence study (TMC114FD1HTX1004) in healthy adults to compare DRV and COBI exposures between Prezcobix PED (600 mg/90 mg) and DRV and COBI coadministered as separate agents (Prezista suspension at a dose of 600 mg and Tybost 90-mg tablet). In addition, the final population PK (PopPK) model for Study 128 simulated DRV and COBI exposures for pediatric patients in the weight band of ≥15 kg to <25 kg, further allowing for the extrapolation of established clinical efficacy and safety profile of DRV and COBI from adults to this pediatric population.

3. Product Quality

Prezcobix tablets (DRV/COBI 800 mg/150 mg and 675 mg/150 mg) are already approved, and no new Chemistry, Manufacturing, and Controls (CMC) information was submitted as part of the sNDA for this dosage formulation.

Prezcobix PED tablet for oral suspension (DRV 600 mg/90 mg) is a new dosage formulation for the newly proposed patient population. The Office of Product Quality (OPQ) team concluded that the CMC information submitted for Prezcobix PED is adequate. (b) (4) [redacted]. The Applicant provided data showing that (b) (4) levels exceeded the maximum acceptable level after (b) (4) months of storage. To address this, the Applicant proposed a control strategy that includes a specification limit for (b) (4) in the drug product specification of not more than (NMT) (b) (4), equivalent to (b) (4) ng/day for a maximum daily dose of 90 mg cobicistat. This

limit is lower than the FDA's recommended Acceptable Intake (AI) limit of (b) (4) ng/day and was therefore found to be acceptable. Please refer to the CMC review for complete details.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted.

5. Clinical Pharmacology

Executive Summary

The Clinical Pharmacology review team supports approval of DRV/COBI 600/90-mg dispersible FDC oral tablets once daily (QD) for treatment of HIV-1 in pediatric patients aged ≥3 years and weighing ≥15 kg to <25 kg.

The current approved DRV/COBI regimens for oral use include:

- 800/150-mg FDC once daily (QD) for adults and pediatric patients ≥40 kg
- 675/150-mg FDC QD for pediatric patients ≥25 to <40 kg

The applicant developed DRV/COBI 600/90-mg FDC tablets, to be taken orally after dispersion in water, for QD use in children aged ≥3 years and weighing ≥15 to <25 kg.

The objective of this review is to evaluate whether DRV and COBI exposures from the proposed 600/90 mg dispersible tablet in children aged ≥3 years weighing 15 to <25 kg are comparable to exposures in adults and pediatric patients ≥25 kg using approved dosage regimens.

The Applicant submitted the following studies to support the proposed indication:

- A BE study (TMC114FD1HTX1004) in healthy adults comparing the FDC drug product to coadministration of the separate agents, under fed conditions.
- A Phase 2/3 study (GS-US-216-0128) assessing the PK, safety, and efficacy of COBI-boosted DRV, administered as separate agents, in children and adolescents living with HIV-1.
- A PopPK analysis to simulate DRV exposures (C_{0h} and AUC_{0-24h}) in pediatric patients weighing ≥15 to <25 kg (600/90 mg QD dose) relative to adults.
- Additional supportive PopPK analyses for COBI in children weighing ≥15 kg at the proposed doses.

DRV PK data for pediatric patients ≥25 kg (Cohorts 1 and 2 of Study GS-US-216-0128) were previously evaluated under NDA 205395, S-016 and S-028. Intensive PK data for DRV and COBI in pediatrics ≥15 kg (Cohorts 2 and 3) have been reviewed recently under NDA 203094, S-17 and S-28. The following dosing regimens are recommended in the Tybost® (cobicistat) package insert:

Body Weight	Darunavir Dosage	TYBOST Dosage
Weighing at least 15 kg to less than 25 kg	600 mg orally once daily	90 mg orally once daily
Weighing at least 25 kg to less than 30 kg	600 mg orally once daily	150 mg orally once daily
Weighing at least 30 kg to less than 40 kg	675 mg orally once daily	
Weighing at least 40 kg	800 mg orally once daily	

This review focuses on PK data from BE study TMC114FD1HTX1004 and population PK analyses for DRV and COBI.

BE study (Study TMC114FD1HTX1004)

Study Design

This was a Phase 1, randomized, open-label, 2-way crossover study to evaluate the bioequivalence of a single dose of DRV 600 mg in the presence of COBI 90 mg as an FDC tablet dispersed in water compared to the co-administration of the separate available formulations (darunavir 100 mg/ml suspension at a dose of 600 mg and cobicistat 90 mg tablet), under fed (standardized high-fat breakfast) conditions. There was a washout period of at least 7 days between doses. A total of 32 healthy participants were assigned to one of two treatment sequences (AB or BA), and 30 participants 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. Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Darunavir After Administration of a Single Oral Dose of DRV 600 mg and COBI 90 mg as 1 × FDC tablet Dispersed in Water Under Fed Conditions (Treatment A, Test) and of DRV 600 mg as 100 mg/mL Suspension and COBI as 1 × 90 mg Tablet, Under Fed Conditions (Treatment B, Reference); Pharmacokinetics Data Statistical Main Analysis Set (TMC114FD1HTX1004)

	Geometric Mean			Test vs reference		
Pharmacokinetic Parameter	n	Treatment A (test)	Treatment B (reference)	GMR (%)	90% CI (%)	Intra participant CV (%)
C_{max} (ng/mL)	30	4,760	4,914	96.85	88.94 - 105.47	19.6
AUC_{last} (ng.h/mL)	30	47,444	48,305	98.22	92.46 - 104.33	13.8
AUC_{∞} (ng.h/mL)	29	47,254	47,926	98.60	92.66 - 104.91	13.9

GMR: Geometric mean ratio, CI: confidence interval, CV: coefficient of variation

Table 2. Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Cobicistat After Administration of a Single Oral Dose of DRV 600 mg and COBI 90 mg as 1 × FDC tablet Dispersed in Water Under Fed Conditions (Treatment A, Test) and of DRV 600 mg as 100

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mg/mL Suspension and COBI as 1 × 90 mg Tablet, Under Fed Conditions (Treatment B, Reference); Pharmacokinetics Data Statistical Main Analysis Set (TMC114FD1HTX1004)

	Geometric Mean			Test vs reference		
Pharmacokinetic Parameter	n	Treatment A (test)	Treatment B (reference)	GMR (%)	90% CI (%)	Intra participant CV (%)
C_{max} (ng/mL)	30	204	274	74.18	66.68 - 82.53	24.6
AUC_{last} (ng.h/mL)	30	1,429	1,677	85.23	77.72 - 93.47	21.2
AUC_{∞} (ng.h/mL)	28	1,500	1,772	84.68	77.05 - 93.08	21.0

GMR: Geometric mean ratio, CI: confidence interval, CV: coefficient of variation

Conclusion

- The FDC tablet dispersed in water (DRV/COBI 600/90mg) was bioequivalent to the coadministration of the separate available formulations (DRV 100 mg/mL suspension at a dose of 600 mg and COBI 1 x 90 mg tablet) for DRV exposure.
- COBI exposure from the FDC tablet dispersed in water (DRV/COBI 600/90mg) was 15% lower for AUC and 26% lower for Cmax versus separate formulations, but this did not affect DRV pharmacokinetics, which met bioequivalence criteria.

Reviewer's Note

- The study was conducted under fed conditions because Prezcobix® is to be taken with food.
- The PK data for COBI presented in Section 12.3 of the US Package Insert need to reflect the COBI PK difference observed between FDC and COBI coadministered with DRV as a separated formulation.

Population PK Analysis

The Applicant submitted an updated population PK (PopPK) model to characterize the PK of DRV in adults and pediatric patients with HIV-1 aged ≥3 years weighing 15 to <25 kg. The reviewer considers the Applicant's PopPK model adequate in characterizing DRV PK and supporting the proposed 600/90 mg DRV/COBI as dispersible FDC tablet once daily for the treatment of HIV-1 in pediatric population aged ≥3 years weighing 15 to <25 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 15 to <25 kg at a dosage of 600/90 mg QD are comparable to those of the reference adult population with HIV-1 infection (**Table 3**). See Section 15.2.2 Pharmacometrics Assessment for details.

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Table 3. Comparison of PK between adults and pediatric subjects under label proposed dose

Study		GS-US-216-0128		GS-US-216-0130 Week 48	TMC114FD2HTX3001	TMC114IFD3013	TMC114-C228 Week 24 (qd Substudy)	TMC114-C230 Week 48
Population	Pediatric BW ≥40 kg	BW ≥25 to <40 kg	BW ≥14 to <25 kg	Adult	Adult	Adult	Pediatric 3 to <6 years	Pediatric 12 to <18 years
Regimen	DRV/COBI 800/150 mg	DRV/COBI 675/150 mg	DRV/COBI 600/90 mg	DRV/COBI 800/150 mg	D/C/F/TAF 800/150/200/10 mg (Ackaert 2021)	D/C/F/TAF 800/150/200/10 mg (Ackaert 2021)	DRV 40 mg/kg +rtv 7 mg/kg (BW <15 kg) or DRV 600 mg/rtv 100 mg (BW ≥15 kg)	DRV/rtv 800/100 mg
N	8	8	11	298	355	750	10	12
Mean (SD) $AUC_{0\text{-}24h}$ (ng.h/mL)	69,474 (10,359)	92,052 (17,254)	146,477 (40,055)	101,711 (33,066)	87,909 (20,232)	85,972 (22,413)	120,000 (40,600)	84,400 (23,600)
Mean (SD) C_{0h} (ng/mL)	938 (445)	1,345 (569)	2,265 (1,293)	2,151 (1,322.5)	1,899 (759)	1,813 (859)	3,371 (1,715)	2,141 (865)

$AUC_{0\text{-}24h}$=area under the concentration-time curve over a 24-hour dosing interval at steady-state; BW=body weight; C_{0h}=plasma concentration at the end of a 24-hour dosing interval at steady-state; COBI=cobicistat; DRV=darunavir; N=number of participants; qd=once daily; rtv=ritonavir; SD=standard deviation; TAF=tenofovir alafenamide.
Source: Table 9 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128) (Mar 18, 2025)

6. Clinical Virology

No new virology data were submitted.

7. Clinical/Statistical – Efficacy

The pivotal data to support approval of DRV/COBI tablets for oral suspension for the proposed indication are the PK and PopPK data discussed in Section 5 (Clinical Pharmacology) and Section 15 (Appendix) of this review rather than efficacy data.

Extrapolation of efficacy for antiretroviral drugs such as DRV/COBI can be made based on the presumption that the course of HIV disease and the effects of the drugs are sufficiently similar in adult and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c). Under this regulatory framework, both DRV (Prezista; with ritonavir) and COBI (Tybost; with DRV) were previously approved in pediatric patients ≥3 years and weighing ≥15 kg to <25 kg at the proposed dosages based on PK and safety data. Efficacy data from pediatric studies to support these approvals were considered supportive. Please refer to NDA 203094/S-18 for the clinical review of supportive efficacy data from Study 128 for DRV and COBI (administered as separate agents with two NRTIs) in this pediatric population.

Under the aforementioned regulatory framework, the efficacy of DRV/COBI tablets for oral suspension is based on (1) whether DRV and COBI exposures are comparable when administered as the FDC tablet for oral suspension (Prezcobix PED) versus the approved individual pediatric products (Prezista suspension coadministered with Tybost), and (2) whether COBI adequately and safely increases DRV exposures when administered as the FDC tablet for oral suspension (Prezcobix PED) in the proposed pediatric population, consistent with the exposures previously established in adults. Based on the PK and PopPK analyses

described in Sections 5 (Clinical Pharmacology) and 15 (Appendix) of this review, these criteria have been met. Therefore, the review team recommends approval of the DRV/COBI tablets for oral suspension.

8. Safety

Please refer to NDA 203094/S-18 for the clinical safety review of Study 128 for DRV and COBI (administered as separate agents with two NRTIs) in pediatric patients with HIV-1 aged ≥3 years and weighing ≥15 kg to <25 kg. The safety data from this study supported the approval of COBI (Tybost) administered with DRV as separate agents in this pediatric population.

Extrapolation of safety data from pediatric patients weighing ≥15 kg to <25 kg in Study 128 and ultimately from adults in the DRV registrational trials to DRV/COBI tablets for oral suspension (Prezcobix PED) is supported by the PK and PopPK analyses described in Sections 5 (Clinical Pharmacology) and 15 (Appendix) of this review.

9. Advisory Committee Meeting

An advisory committee meeting was not held.

10. Pediatrics

These submissions are in response to PREA PMR 2845-1, which was issued at the time of NDA 205395 approval on January 29, 2015. The original final report submission date was December 31, 2021; however, FDA granted a deferral extension in April 2024 with a final report submission date of May 2025.

2845-1	Evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of darunavir and cobicistat fixed dose combination (FDC) age-appropriate formulation in HIV-infected pediatric subjects 3 years to less than 6 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 3 years to less than 6 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.

With these submissions, the PREA PMR is considered fulfilled.

11. Other Relevant Regulatory Issues

- *Other Good Clinical Practice (GCP) issues*

Not applicable

- *Office of Scientific Investigations (OSI) audits*

Not applicable

- *Office of Study Integrity and Surveillance (OSIS) audits*

Please refer to Section 15.1.1 (Bioanalytical Method Validation and Performance) in the Appendix for details.

12. Labeling

Prezcobix PED was added throughout relevant sections of the USPI. Specific sections were updated as follows:

INDICATIONS AND USAGE (1)

- The population within the indication was broadened to include pediatric patients 3 years of age and older weighing at least 15 kg.

DOSAGE AND ADMINISTRATION (2)

- An overview of the two different dosage forms was added.
- The following information was added to the recommended dosage table: total daily dose for pediatric patients aged 3 years and older weighing at least 15 kg to less than 25 kg is one Prezcobix PED 600 mg darunavir/90 mg cobicistat tablet for oral suspension.
- Preparation and administration instructions for Prezcobix PED was added, including specific instructions for dispersement in drinking water prior to administration with food.

DOSAGE FORMS AND STRENGTHS (3)

- Prezcobix PED tablets for oral suspension was added as a new dosage form.

ADVERSE REACTIONS, Clinical Trials Experience (6.1)

- Under clinical trials in pediatrics, the description of cohorts in Study 128 was updated to include pediatric participants aged ≥3 years with weight ≥15 kg to <25 kg (Cohort 3, N=11).

USE IN SPECIAL POPULATIONS, Pediatric Use (8.4)

- This section was edited to reflect the inclusion of pediatric patients 3 years of age and older weighing at least 15 kg in Study 128.

DESCRIPTION (11)

- A description of Prezcobix PED formulation was added, including the list of inactive ingredients.

CLINICAL PHARMACOLOGY, Pharmacokinetics (12.3)

- The following results were added: No clinically significant difference was observed between Prezcobix PED (600 mg/90 mg) and darunavir suspension (100 mg/mL) at a dose of 600 mg co-administered with cobicistat 90 mg as single entities under fed conditions in healthy adults.

- The pediatric subsection was updated to include the PK estimates from Study 128 for DRV 600 mg/COBI 90 mg in pediatric participants aged ≥3 years and weighing ≥15 kg to <25 kg (Cohort 3, N=11).

CLINICAL STUDIES, Clinical Trial Results in Pediatrics with HIV-1 (14.2)

- Study 128 results for DRV and COBI were updated with results from pediatric participants aged ≥3 years and weighing ≥15 kg to <25 kg (Cohort 3). Baseline demographics and disease characteristics as well as Week 48 efficacy results were included.

HOW SUPPLIED/STORAGE AND HANDLING (16)

- The supply information and storage and handling instructions for Prezcobix PED tablets for oral suspension were added.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No postmarketing risk management activities are required for this application.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No addition PMRs or PMCs are recommended at this time.

14. References

None

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15. Appendix

15.1 Additional Information and Assessment

15.1.1 Bioanalytical Method Validation and Performance

For DRV and COBI, a combined method was validated at (b) (4). The validation method used for Study TMC114IFD1HTX1004 (BA10833) was previously reviewed for NDA205395, S-28, and was deemed acceptable. 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 PK samples were analyzed within the storage stability. The bioanalytical report for Study TMC114IFD1HTX1004 has been reviewed and deemed acceptable (See Table 3).

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical and a clinical site inspection for Study TMC114IFD1HTX1004. There are no concerns with the clinical site. The analytical site inspection at (b) (4) identified that the method validation studies only evaluated method specificity in the presence of paracetamol. However, subjects in the study also received the following co-administered medications:
- Cetirizine
- Desogestrel
- Ethinyl estradiol
- Drospirenone
- Ethinylestradiol betadex clathrate
- Levonorgestrel
- Medroxyprogesterone acetate

Additionally, interference was observed in predose samples from 43.8% of subjects who received concomitant medications, with peak area responses ranging from 0.4% to 9.2% for darunavir and 0% to 7.0% for cobicistat.

Form 483 was issued. (b) (4) indicated that the molecular weights of all the concomitant medications are more than 150 atomic mass unit (amu) less than darunavir and cobicistat (molecular weight <397.7 g/mol), so the possibility of interference or lack of specificity for the quantification of darunavir and cobicistat using LC-MS/MS is low. In addition, the darunavir and cobicistat methods use deuterated internal standards, such that the internal standards co-elute with the analyte of interest, to avoid any potential matrix interference concerns. The response is acceptable.

Table 4. Bioanalytical Method Performance Summary

Study number	TMC114IFD1HTX1004
Bioanalytical Report #	(b) (4)-NL-SML-2338
Method of Detection	LC-MS/MS

Method reproducibility (passing rate)	DRV: 81.8% COBI: 81.8%
Calibration range (ng/mL)	DRV: 5.00-10,000 COBI: 5.00-5,000
Calibration standard Inter-day Accuracy (%bias)	DRV: -6.6 to 3.6 COBI: -3.6 to 4.4
Calibration standard Inter-day precision (%CV)	DRV: ≤3.2 COBI: ≤6.3%
QC Levels (µg/mL)	DRV: 15, 500, 4500, and 7500 COBI: 15, 500, 2250, and 3750
QC Inter-day Accuracy (%bias)	DRV: -2.3 to 5.6 COBI: -4.8 to -0.8
QC Inter-day Precision (%CV)	DRV: ≤7.0 COBI: ≤6.5

15.1.2 Pharmacometrics Assessment

15.1.2.1 Population PK Analysis

15.1.2.1.1 Review Summary

In general, the applicant's population PK (PopPK) analysis is considered acceptable for the purpose of characterizing the PK profile of darunavir in pediatric patients 3 years of age and older weighing at least 15 kg to less than 25 kg. The DRV/COBI 800/150-mg filmcoated fixed-dose combination (FDC) tablet (Prezcobix®) was approved for use in adults and pediatric patients aged 12 years and older weighing at least 40 kg in 2015, and a DRV/COBI 675/150-mg FDC tablet developed for children living with HIV-1 aged ≥6 years and weighing ≥25 to <40 kg was approved in 2024. The current application proposed 600/90-mg dispersible FDC tablet once daily dose for children aged ≥3 years weighing 15 to <25 kg. The PK exposure is considered comparable between pediatric and adults under label proposed dose. The PopPK results are acceptable**.**

Table 5. 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**	Change in current supplement: (b) (4)	No change was proposed regarding to statements related to intrinsic factor. The reviewer verified the PK exposure listed in labeling Table 4, which is calculated based on final PopPK model.
	Extrinsic factor	Change in current supplement: *PREZCOBIX or PREZCOBIX PED should be taken with food.*	Acceptable

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15.1.2.1.2 Introduction

The primary objectives of applicant's analysis were to:

- To compare DRV $AUC_{0\text{-}24h}$ and C_{0h} for pediatric participants enrolled in Cohorts 2 and 3 of Study216-0128 with reference exposures from (i) adult Studies 216-0130, FD2HTX3001, and IFD3013, (ii) Cohort 1 (Part A) of Study 216-0128, and (iii) pediatric Studies C228 and C230.
- To assess whether a unique DRV dose of 675 mg qd (in combination with COBI 150 mg qd) for pediatric patients weighing ≥25 to <40 kg and a DRV dose of 600 mg qd (in combination with 90 mg qd COBI) for pediatric patients weighing ≥14 to <25 kg result in comparable DRV $AUC_{0\text{-}24h}$ and C_{0h} with respect to adults, using model-based PopPK simulations.

15.1.2.1.3 Model development

Data

PopPK analysis was performed using HIV-1 infected pediatric participants in Study 216-0128 receiving DRV in combination with COBI (with or without F/TAF) in Cohorts 1 to 3, which include 347 DRV plasma concentrations from 27 participants. Brief descriptions of the studies included are presented in Table 6.

Table 6. 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 in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128) (Mar 18, 2025)

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PopPK analysis was conducted via nonlinear mixed effects modelling with a qualified installation of the nonlinear mixed effects modelling (NONMEM) software, (Version 7.4) (ICON plc, Ellicott City, MD). First-order conditional estimation with interaction (FOCEI) was used as estimation method. Graphical and all other statistical analyses, including evaluation of NONMEM outputs, were performed with R version 3.6.2 or higher.

Table 7 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 7. 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)

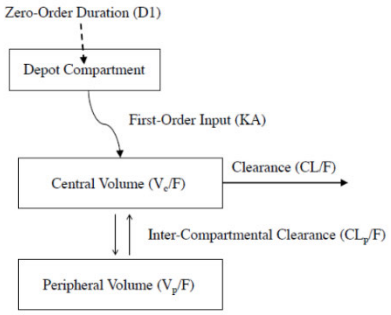
n=number of participants; SD=standard deviation.
[a]: Based on Schwartz formula.

Source: Table 2 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128) (Mar 18, 2025)

Base model

The previous developed PopPK model for darunavir was used as the starting point for model development. It is a two-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 (Figure 1).

Figure 1. Schematic Overview of Previously Developed DRV PopPK Model



CL/F=apparent clearance; CL_p/F=intercompartmental clearance; D_1=zero-order duration; DRV=darunavir; k_a=first order absorption rate constant; PopPK=population pharmacokinetics; V_c/F=apparent volume of distribution of the central compartment; V_p/F=apparent volume of distribution of the peripheral compartment.

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Source: Figure 1 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128) (Mar 18, 2025)

Covariate analysis

The applicant did not conduct a formal covariate analysis on the current analysis dataset due to the prior knowledge of parameter-covariate relationships already included in the previously developed PopPK model. However, the correlations between individual random effects and the covariates of interest (age, body weight, creatinine clearance, AAG, sex, and race) were explored graphically. There were no evident correlations among random effects and baseline demographics and participant characteristics after accounting for the effect of body weight on CL/F, Vc/F, Q/F, and Vp/F in final popPK model. No new covariate was included in the model.

15.1.2.1.4 Final Model

The parameter estimates for the final covariate model are listed in Table 8. The model described the observed data adequately, as seen in the goodness-of fit plots (Figure 2). Prediction-corrected visual predictive check (pcVPCs) plots show that the final PopPK model adequately captured the central tendency and variability of the data, which the observed 20th, 50th, and 80th percentiles of the data has agreement with the respective 95% CIs obtained from the simulations (Figure 3).

Table 88. 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

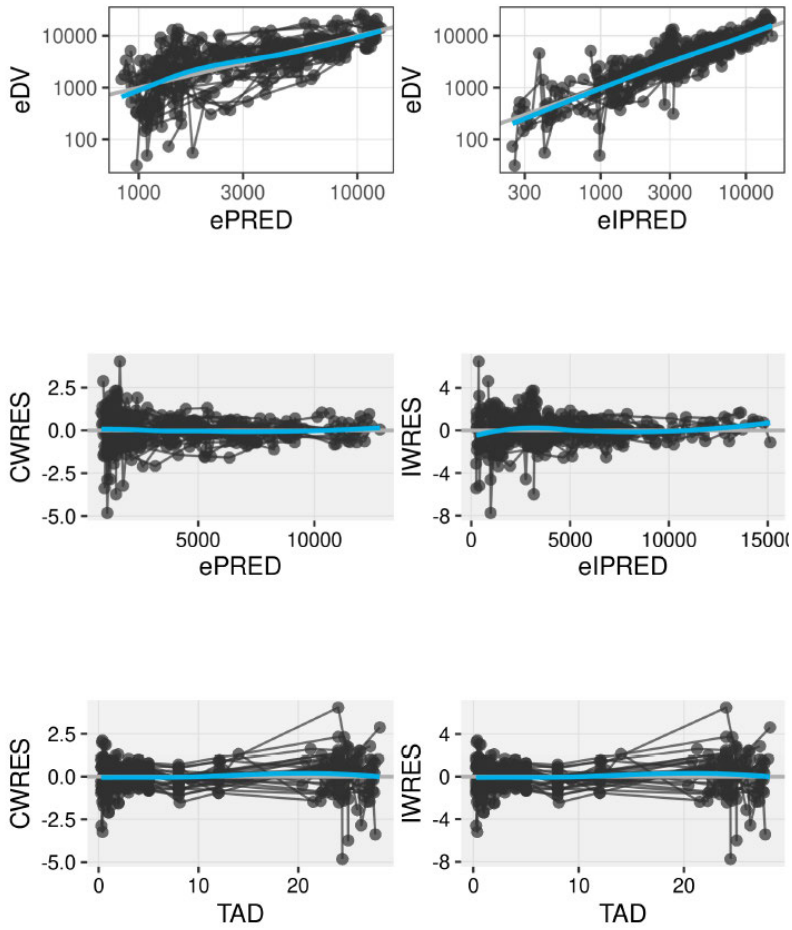
AAG=alpha-1-acid glycoprotein; CL/F=apparent clearance; CV=coefficient of variation; D1=zero-order duration;
DRV=darunavir; ETA=random effect; exp=exponential; F1=apparent bioavailability; IIV=interindividual variability; ka=first-order absorption rate constant; PopPK=population pharmacokinetics; OFV=objective function value; Q/F=apparent intercompartmental clearance; RSE=relative standard error; RUV=residual unexplained variability; sd=standard deviation; shr=shrinkage; sqrt=square root; TDD=total daily dose; Vc/F=apparent volume of distribution of the central compartment; Vp/F=apparent volume of distribution of the

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peripheral compartment; WT=body weight.[a] For DRV single agent commercial formulation relative to tablet used in previous clinical studies (Frel).
[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 sd 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 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128) (Mar 18, 2025)

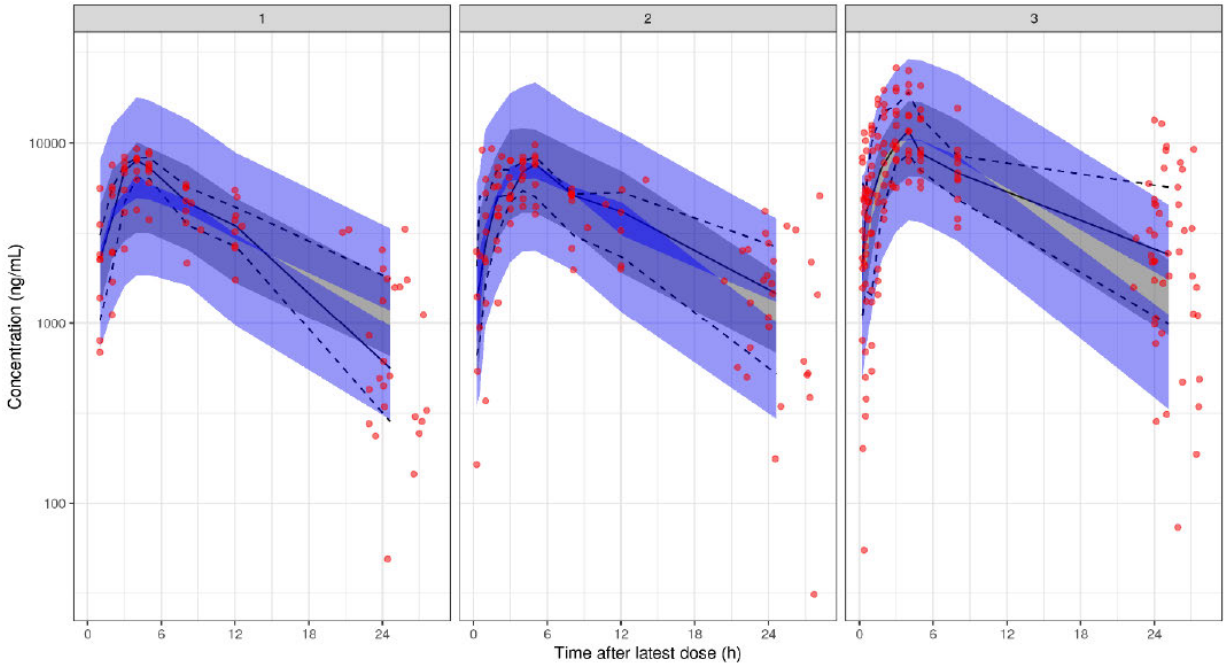
Figure 2. Goodness-of-Fit Plots for final PopPK model



Source: Attachment 6 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128) (Mar 18, 2025)

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Figure 3. pcVPC Plots for final PopPK model by cohort



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 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128) (Mar 18, 2025)

The individual DRV steady-state exposure parameters $AUC_{0\text{-}24h}$ and C_{0h} for pediatric participants in Study #216-0128 were derived from the final PopPK model using baseline covariates and starting dose in each participant and were summarized by study cohort (Table 9).

Table 99. Summary of Individual $AUC_{0\text{-}24h}$ and C_{0h} in Study #216-0128

Parameter	Cohort	DRV Dose	N	Mean (SD)	Median (Min-Max)	Geometric Mean
$AUC_{0\text{-}24h}$ (ng.h/mL)	1	Cohort 1 and 2*: [redacted (b) (4)]	8	68,971 (10,258)	70,258 (47,261-79,710)	68,208
	2		8	84,453 (13,024)	81,629 (72,310-106,617)	83,619
	3		11	146,477 (40,055)	149,358 (94,046-199,639)	141,269
	All	Cohort 3: [redacted (b) (4)] to <25 kg 600 mg QD	27	105,135 (44,138)	87,434 (47,261-199,639)	97,471
C_{0h} (ng/mL)	1		8	919 (439)	909 (421-1,559)	825
	2		8	1,237 (484)	1,157 (463-2,044)	1,143
	3		11	2,265 (1,293)	2,519 (379-4,194)	1,797
	All		27	1,562 (1,062)	1,195 (379-4,194)	1,248

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**Reviewer's note:* (b) (4) *the label proposed dose is 675 mg DRV/150 mg COBI for ≥25 to <40 kg. Additional simulation is performed under label proposed dose. See details in section below.*

Source: Table 8 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128) (Mar 18, 2025)

15.1.2.1.5 PK simulation based on PopPK model

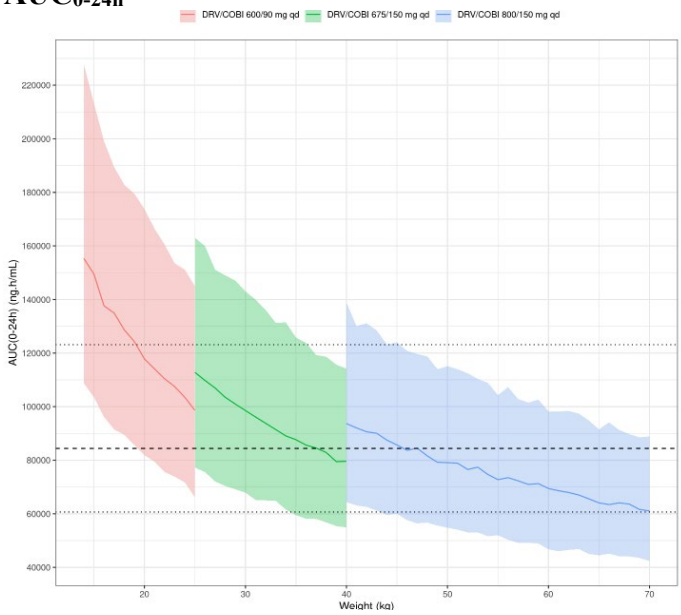
(b) (4) the actual clinical study dose/BW band, where the label proposed dose is proposed as 600/90 mg qd for ≥ (b) (4) to <25 kg and 675 mg DRV/150 mg COBI for ≥25 to <40 kg (b) (4), the applicant simulated the PK exposure parameters based on final PopPK model following the proposed DRV/COBI dosing regimen (Figure 4). The simulated DRV exposure under proposed dose (DRV/COBI 800/150 mg qd for ≥40 kg, 675/150 mg qd for ≥25 to <40 kg, and 600/90 mg qd for ≥ (b) (4) to <25 kg) is also compared with other pediatric and adult studies (Table 3). The DRV exposure in pediatric patients is higher than adult group under proposed dose based on simulation result. The mean PK ratio between pediatric patients (BW≥ (b) (4) to <25 kg) and adult is ~1.44 for $AUC_{0\text{-}24}$ and ~1.05 for C_{0h}. The DRV exposure between pediatric (BW≥ (b) (4) to <25 kg) and adult is deemed comparable when compared to pediatric studies of other DRV-containing products approved in similar pediatric age (b) (4) (e.g., NDA 21976, AUC ratio to adult = 1.49 to support approval of DRV/RTV 600 mg/100 mg Q.D. in patients' weight 15-<30 kg[1]).

[1] DARRTS, NDA 21976 (Darunavir), Clinical Pharmacology Review dated 1/10/13; Reference is also made to summary Table 6 in NDA 203094 S17 and S18 & NDA208215/S23 and S25 (emtricitabine/tenofovir alafenamide, and cobicistat), Cross-Discipline Review dated June 20, 2025

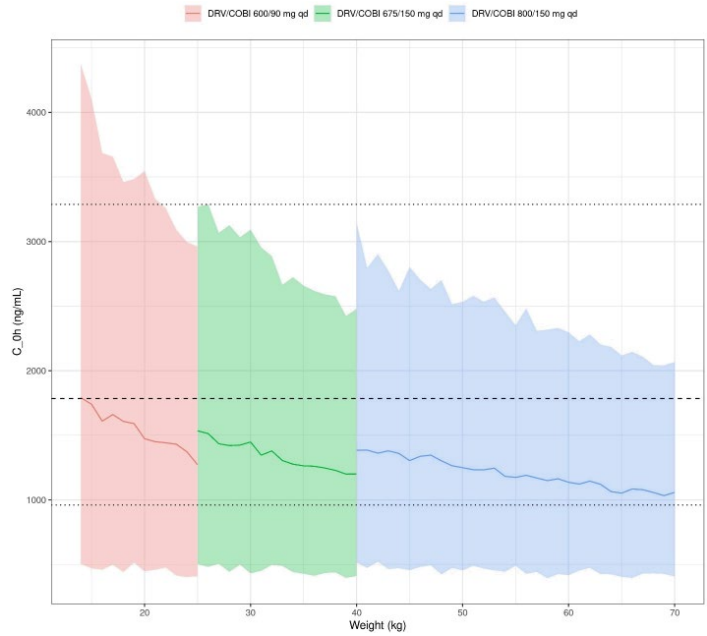
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Figure 4. Distribution of DRV exposure in Pediatric Patients (DRV/COBI: 800/150 mg QD for 40 kg, 675/150 mg qd for 25 to <40 kg, and 600/90 mg qd for (b) (4) to <25 kg) compared to Adults (Study #FD2HTX3001)

$AUC_{0\text{-}24h}$



C_{0h}



$AUC_{0\text{-}24h}$=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; PI=prediction interval; qd=once daily.
The colored lines and shaded areas represent the median and 90% PI for $AUC_{0\text{-}24h}$ or 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 $AUC_{0\text{-}24h}$ or C_{0h} in Study FD2HTX3001.
Source: Figure 2 and 3 in PopPK report, Population Pharmacokinetics of Darunavir for the Treatment of HIV-1 in Children Aged 3 to <18 Years (Phase 2/3 Study GS-US-216-0128) (Mar 18, 2025)

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/s/

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