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

Date	June 20, 2025
From	Antigone Kraft, MD, Clinical Reviewer Kimberly Struble, PharmD, Clinical Team Leader Mario Sampson, PharmD, Clinical Pharmacology Reviewer Kunyi Wu, PharmD, Clinical Pharmacology Team Leader Wendy Carter, DO, Division Director
Subject	Combined Cross-Discipline Team Leader, Clinical, Clinical Pharmacology Review and Division Director Review
Application Type	SE5 New Population
NDA/BLA # and Supplement#	NDA 203094/S-017 and S-018 & NDA 208215/S-023 and S-025
Applicant	Gilead Sciences
Date of Submission	September 27, 2024
PDUFA Goal Date	July 27, 2025
Proprietary Name	DESCOVY and TYBOST
Established or Proper Name	emtricitabine/tenofovir alafenamide and cobicistat
Dosage Form(s)	DESCOVY: 120/15 and 200/25 mg (approved) tablets TYBOST : 150 mg (approved) and 90 mg (new) tablets
Applicant Proposed Indication(s)/Population(s)	Indication: HIV-1 infection Population: Virologically suppressed pediatric patients
Applicant Proposed Dosing Regimen(s)	DESCOVY: • Patient weight ≥ 25 to < (b) (4) kg: Single 200/25-mg tablet administered orally once daily with or without food • Patient weight ≥ 14 to < 25 kg: Single 120/15-mg tablet administered orally, once daily with or without food TYBOST in combination with ATV or DRV: • Patient weight ≥ 25 to < (b) (4) kg: Single 150-mg tablet administered orally, once daily with food • Patient weight ≥ 14 to < 25 kg: Single 90-mg tablet administered orally, once daily with food
Recommendation on Regulatory Action	Approval for all DESCOVY and TYBOST sNDAs for the recommended indication/population and dosing regimen as described below
Recommended Indication(s)/Population(s)	DESCOVY is indicated for the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg to less than 35 kg in combination with other antiretroviral agents, including darunavir and cobicistat but not other protease inhibitors that require a CYP3A inhibitor TYBOST is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection in pediatric

patients weighing at least 14 kg [see Dosage and Administration (2.2), and Drug Interactions (7.3)]

Section 7.3 states TYBOST coadministered with atazanavir and TAF in pediatric patients weighing 14 to less than 35 kg is not recommended

Recommended Dosing Regimen

Body Weight (kg)	DESCOVY Dosage
25 kg to less than 35 kg	One tablet containing 200 mg of FTC and 25 mg of TAF taken orally once daily
14 kg to less than 25 kg	One tablet containing 120 mg of of FTC and 15 mg of TAF taken orally once daily

Body Weight	Atazanavir Dosage	TYBOST Dosage
Weighing at least 14 kg to less than 25 kg	200 mg orally once daily	90 mg orally once daily
Weighing at least 25 to less than 35 kg	200 mg orally once daily	150 mg orally once daily
Weighing at least 35 kg	300 mg orally once daily	

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	

APPEARS THIS WAY ON ORIGINAL

1. Executive Summary

Executive Summary/Benefit-Risk Integrated Assessment

The Applicant, Gilead Sciences, submitted supplemental New Drug Applications (sNDA) to update the prescribing information for DESCOVY (emtricitabine and tenofovir alafenamide; FTC, TAF or F/TAF) and TYBOST (cobicistat, COBI) to expand the use in pediatric patients weighing at least 14 kg and to include a new TYBOST 90 mg tablet formulation (see details below). These sNDAs (1) partially address the PREA PMRs 3531-1 and 3533-1 to evaluate the the pharmacokinetics (PK), safety and antiviral activity of DESCOVY administered in combination with atazanavir (ATV) and TYBOST, and in combination with darunavir (DRV) and TYBOST in HIV-1 infected pediatric subjects weighing less than 25 kg and (2) fulfills the PREA PMRs 3531-2 and 3533-2 to evaluate the PK, safety and antiviral activity of DESCOVY administered in combination with ATV and TYBOST, and in combination with DRV and TYBOST in HIV-1 infected pediatric subjects 6 to less than 12 years of age (weighing 25 kg to less than 35 kg).

DESCOVY is a fixed dose combination (FDC) of two nucleoside analog reverse transcriptase inhibitors (F/TAF) approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and pediatric patients weighing at least 35 kg (regardless of the third agent). F/TAF is also approved in combination with other antiretroviral agents other than protease inhibitors that require a CYP3A inhibitor for the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg and less than 35 kg.

TYBOST is a CYP3A inhibitor indicated to increase systemic exposure of ATV or DRV (both protease inhibitors) in combination with other antiretroviral agents for the treatment of HIV-1 infection. TYBOST is approved for use in pediatric patients weighing at least 35 kg (coadministered with ATV) or at least 40 kg (coadministered with DRV).

The basis of approval for these pediatric indications, as specified above, were supported by data from Trial GS-US-216-0128 (Trial 128), a Phase 2/3 multicenter, multicohort study to evaluate the PK, safety and efficacy in virologically suppressed children living with HIV-1 and receiving ATV + COBI or DRV + COBI, each in combination with two nucleotide reverse transcriptase inhibitors (NRTIs) in cohort 1 or F/TAF in cohorts 2 and 3. Virological suppression was defined as HIV-1 RNA <50 copies/mL. The study was conducted in 3 countries (6 sites in South Africa, 1 site in the US, and 1 site in Zimbabwe).

This submission contains data from Cohorts 2 and 3 of Trial 128. Within each cohort participants either received ATV + COBI + F/TAF or DRV + COBI + F/TAF. The primary endpoints were PK parameters for ATV, DRV, TAF, and tenofovir (TFV) as well as the incidence of treatment-emergent adverse events (AEs) and the incidence of treatment-emergent laboratory abnormalities through Week 24.
A total of 49 participants were enrolled in the two Cohorts. The dosing regimen per cohort was:

- Cohort 2: ≥ 6 to < 12 years of age, weighing ≥ 25 to < 40 kg
  - Treatment regimen: COBI 150 mg + F/TAF 200/25 mg + ATV (200 mg or 300 mg depending on weight) or DRV (600 or 675 mg depending on weight)
- Cohort 3: ≥ 2 years of age, weighing ≥ 14 to < 25 kg
  - Treatment regimen: COBI 90 mg + F/TAF 120/15 mg + ATV 200 mg or DRV (600 mg)

TYBOST (cobicistat, COBI) (NDA 203094-S.17 and S.18):

With ATV: Trial 128 supports the use of COBI to increase systemic exposure of ATV, in combination with other ARVs except for TAF, for the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg.

- TAF exposures in pediatric participants who received ATV+COBI in cohort 2 (25 kg to <40 kg, n=14) and cohort 3 (14 kg to <25 kg, n=15) exceeded TAF exposures in adults by 4-5-fold and 2-3-fold, respectively. Additionally, exposures in this group were also 2-3-fold higher when compared to pediatric studies of other TAF containing HIV products approved for the same age and weight range. Because the available safety data are limited the data were not considered adequate to support the increased TAF exposures, therefore, the use of TYBOST with ATV and TAF is not recommended in pediatric patients weighing at least 14 kg to less than 35 kg.
- ATV and COBI exposures in pediatric participants in cohorts 2 and 3 were similar to that observed in adults and/or in pediatric studies of other pediatric products approved for the same age and weight range, thereby, supporting the use of TYBOST with ATV in combination with other ARVs except for TAF in pediatric patients weighing at least 14 kg to less than 35 kg.

With DRV: Trial 128 supports the use of COBI to increase systemic exposure of DRV (once daily dosing regimen), in combination with other ARVs, including TAF, for the treatment of HIV-1 infection in pediatric patients weighing at least 15 kg.

- TAF exposures in pediatric participants who received DRV+COBI exceeded TAF exposures in adults by 2-3-fold but were similar to that observed in pediatric studies of other pediatric products approved for the same age and weight range.
- DRV and COBI exposures, along with supportive safety and efficacy data, in pediatric participants in cohorts 2 and 3 were similar to that observed in adults.

Ninety-eight percent of participants remained virologically suppressed through Week 48. The most commonly observed treatment emergent adverse events (AEs) were Grade 1, 2, or 3 in severity. The most common reported AEs were upper respiratory tract infections (URTIs, 18/49 participants, 36.7%), vomiting (10/49. 20.4%), and hyperbilirubinemia (5/49, 10.2%). There were no deaths or Grade 4 adverse events. Some

participants discontinued the study drug early, but all discontinuations were attributed to ATV use. One participant discontinued the study drug prior to the 48-week cutoff, the rest of the discontinuations occurred in the extension phase.

DESCOVY (emtricitabine/tenofovir alafenamide, F/TAF) (NDA 208215-S.23 and S.25):

Trial 128 supports the use of F/TAF in combination with other antiretroviral agents, including COBI and DRV, but not with other protease inhibitors that require a CYP3A inhibitor.

- TAF and FTC exposures, along with supportive safety and efficacy data, in pediatric participants who received DRV+COBI in cohorts 2 and 3 were similar to that observed in adults and/or in pediatric studies of other pediatric products approved for the same age and weight range.
- As mentioned above, the data do not support the use of F/TAF and ATV+COBI in this pediatric population. Additionally, PK, safety and efficacy of F/TAF in combination with protease inhibitors that require ritonavir (when used as a CYP3A inhibitor) in pediatric patients weighing at least 14 kg to less than 35 kg have not been established.

2. Background

There are approximately 39.9 million people living with HIV worldwide, and an estimated 1.4 million of them are children under the age of 15. Pediatric antiretroviral therapy (ART) is recommended to include a combination of 3 drugs: 2 nucleosides/nucleotides (NRTI) with a third agent. The third agent can be an integrase inhibitor (INSTI), a nonnucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI).

Tybost (cobicistat, COBI) is a CYP3A inhibitor that works to increase systemic levels (boost) of other co-administered agents that are metabolized by CYP3A enzymes. While COBI has no direct anti-HIV-1 activity, it is indicated to increase systemic exposure of atazanavir (ATV) or darunavir (DRV) in combination with other antiretroviral agents in the treatment of HIV-1 infection. In pediatric patients COBI is currently approved for those weighing at least 35 kg (for coadministration with ATV) or at least 40 kg (for coadministration with DRV).

Descovy (emtricitabine/tenofovir alafenamide, F/TAF) is a fixed-dose combination tablet that functions as a backbone for the treatment of HIV-1 infection. Descovy was approved in 2016 for the treatment of HIV-1 infection in adults and adolescents. Currently, F/TAF is indicated for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg (regardless of third agent) or 14 kg if not taken with an HIV-1 protease inhibitor.

Study GS-US-216-0128 (Trial 128) is an ongoing open-label, multicohort study evaluating the PK, safety, and efficacy of ATV + COBI or DRV+ COBI each in combination with F/TAF, in virologically suppressed pediatric participant with HIV-1 infection. Gilead initiated Trial 128 to fulfill their PREA PMRs for Tybost but enrollment was slow for various reasons. One measure taken to improve enrollment was to merge the development programs for Tybost and Descovy so that study participants would benefit from a full (and more optimal) antiretroviral drug regimen rather than using the investigational product in combination with older antiretroviral drugs. This alignment occurred in 2018, at which time the individual PREA PMRs for Tybost and Descovy were released and reissued with new language reflecting the updated development programs.

The revised PMRs were drafted for Descovy to collect safety and PK data for use with both PIs that require a CYP3A inhibitor (boosted) and ARVs that do not require a CYP3A inhibitor (unboosted). Based on adult drug-drug interaction data, the exposures of TAF in pediatric patients were expected to differ significantly when coadministered with PIs versus without PIs, and the magnitude of the changes in TAF exposures were expected to differ depending on the coadministered protease inhibitor. Drug-drug interaction magnitudes determined in adult healthy volunteers are typically extrapolated to pediatric patients. At the time the PMRs were drafted, protease inhibitors were one of the three recommended options in combination with F/TAF; therefore, we recommended the Applicant collect PK for each component of the F/TAF PI regimen for which they were seeking approval.

Despite the alignment of the Tybost and Descovy programs, enrollment in Study GS-US-216-0128 remained slow and Gilead requested a deferral extension for the Tybost and Descovy PMRs in January 2020. DAV FDA's Pediatric Review Committee (PeRC) agreed with the deferral extensions.

The pivotal data to support the evaluation of COBI with ATV or DRV and F/TAF for pediatric patients are the drug systemic exposures rather than efficacy data. Extrapolation of efficacy for antiretroviral drugs 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).

3. Product Quality

TYBOST tablets (150 mg) are already approved for use in adults and adolescents. A new lower strength tablet (90 mg) was developed for use in children. The 90 mg tablet was used in pediatric Trial 128. Approval of the 90 mg tablet was recommended by the CMC team (Product Quality review dated 3/21/2025).

4. Nonclinical Pharmacology/Toxicology

No new data were submitted with the sNDAs.

5. Study Design

Study Design

Study GS-US-216-0128 (Trial 128), sponsored by Gilead Sciences, is an ongoing, Phase 2/3, multicenter, open-label, multicohort study evaluating PK, safety, and efficacy of ATV+ COBI, DRV+ COBI, and two NRTIs in HIV-1 infected children and adolescents aged ≥4 weeks to <18 years in 5 cohorts.

These supplements contains data for participants who received ATV+COBI+F/TAF or DRV+COBI+F/TAF in Cohorts 2 or 3.

- Cohort 2: ≥ 6 to < 12 years of age, weighing ≥ 25 to < 40 kg
  - Treatment regimen: COBI 150 mg + F/TAF 200/25 mg + ATV (200 mg or 300 mg depending on weight) or DRV (600 or 675 mg depending on weight)
- Cohort 3: ≥ 2 years of age, weighing ≥ 14 to < 25 kg
  - Treatment regimen: COBI 90 mg + F/TAF 120/15 mg + ATV 200 mg or DRV (600 mg)

Enrollment Criteria

Inclusion Criteria: Subjects were required to meet all of the following inclusion criteria to be eligible for participation in this study.

- HIV-1 infected male and female subjects 3 months to < 18 years of age at the Day -10 visit (according to Cohort).
- Subjects are able to provide written assent if they have the ability to read and write.
- Parent or legal guardian able to provide written informed consent prior to any screening evaluations and willing to comply with study requirements.
- A negative serum beta-hCG pregnancy test is required for female subjects (of childbearing potential only)
- Body weight at screening as follows:
  - Cohort 2: greater than 15 kg
  - Cohort 3: greater than 10.25 kg
- Adequate renal function: Estimated Glomerular Filtration Rate (eGFR) ≥ 90 mL/min/1.73m^2 using the Schwartz Formula
- Male and female subjects of childbearing potential or who reach childbearing potential during study participation (as defined in Section 7.7 of the protocol) must agree to utilize highly effective contraception methods while on study treatment or agree to abstain from heterosexual intercourse throughout the study period and for 30 days following the last dose of study drug; highly effective methods normally utilize two separate forms of contraception, one of which must be an effective barrier contraceptive method.
  - Female subjects who utilize hormonal contraceptive as one of their birth control methods must have used the same method for at least three months prior to study dosing.

- Adequate hematologic function defined as:
    - Absolute neutrophil count > 500 cells/mm^3 (< 500/mm^3 documented at least twice within 6 months of screening, and in whom, according to the investigator, there is no evidence of active opportunistic or serious infection)
    - Hemoglobin > 8.5 g/dL
    - Platelets ≥50,000/mm3
- Hepatic transaminases (AST and ALT) ≤ 5 x upper limit of normal (ULN)
- Total bilirubin ≤ 1.5 mg/dL, and normal direct bilirubin
- Plasma HIV 1-RNA concentration (at least 2 consecutive measurements) at an undetectable level according to the assay being used, but at least < 75 copies/mL obtained at least 4 weeks apart. One sample must have been obtained at least 3 months prior to screening.
- Stable antiretroviral regimen including 2 NRTI and either ATV/ritonavir or DRV/ritonavir QD or BID as per product label for a minimum of 3 months prior to the screening visit. (Subjects undergoing dose modifications to their antiretroviral regimen for growth or switching medication formulations are considered to be on a stable antiretroviral regimen.) [see protocol amendments below for changes to ARV regimen choice]
- HIV-1 RNA < 50 copies/mL at the screening visit. Subjects with a history of virologic suppression below the level of detection but with detectable viremia at screening will be eligible if repeat HIV-1 RNA testing does not confirm HIV-1 RNA > 50 copies/mL.
- Documented negative screening for active pulmonary tuberculosis within 6 months of a screening visit.
- Must be willing and able to comply with all study requirements
- No opportunistic infection within 30 days of study entry

Exclusion Criteria:

- Screening CD4 cell count < 200 cells/mm3.
- An ongoing serious infection requiring systemic antibiotic therapy at the time of screening.
- An acquired immunodeficiency syndrome (AIDS)-defining condition with onset within 30 days prior to screening.
- Life expectancy of < 1 year.
- Known hypersensitivity to COBI or its metabolites, or formulation excipients.

Routine Clinical Tests

Appendix 2 in the Clinical Study Protocol delineates routine clinical tests that will be performed at designated timepoints throughout the study. The table below highlights the routine clinical tests (Table 1: Routine Clinical Tests).

Table 1: Routine Clinical Tests

Study Procedures	Screening[a]	Day -10	Pre-Treatment PK (Day -1)[b, c]	Day 1[d]	On Treatment PK (Day 10)[b, e]	End of Week[f]								Post Week 48 Every 12 weeks	30-Day Follow-up[g]	ESDD[h]
						4	8	12	16	24	32	40	48			
Hematology Profile[o]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry Profile[p]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count and Percentage	X	X					X	X	X	X	X	X	X	X	X	X
Cystatin C				X	X	X				X			X			X
Metabolic Assessments[q]				X						X			X	X		
Plasma HIV-1 RNA[r]	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Plasma Storage Sample[s]				X				X				X			X	
HBV and HCV Serologies[t]	X															
Urinalysis	X	X	X	X	X	X		X		X			X	X	X	X
Estimated Glomerular Filtration Rate[t]	X	X		X	X	X	X	X	X	X	X	X	X	X		X

Notable lab tests include:

- Hematology profile: CBC with differential and platelet count
- Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylast, and lipase
- Metabolic assessments: fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides

Pregnancy tests were also performed at regular intervals for those of child bearing potential:

- Serum pregnancy tests performed at the screening visit
- Urine pregnancy tests performed at Day -10, pre-treatment day (Day -1), Day 1, Day 10, Weeks 4, 8, 12, 16, 20, 24, 32, 40, 48, and every 12 weeks following Week 48

Study Endpoints

The study endpoints are as follows for both Cohorts 2 and 3:

- Primary Endpoints
  - PK parameter AUCtau for ATV, DRV, TAF, and tenofovir (TFV)
  - The incidence of treatment-emergent adverse events (AEs) and treatment-emergent laboratory abnormalities through Week 24
- Secondary Endpoints
  - PK parameters:
    - Ctau, Cmax, and CL/F for ATV and DRV
    - AUCtau, Ctau, Cmax, CL/F, and Vz/F for COBI
    - AUClast, Cmax, Clast, CL/F, and Vz/F for TAF

        - AUClast, AUCtau, Cmax, Ctau, CL/F, and Vz/F for emtricitabine (FTC)
        - AUClast, Cmax, Ctau, CL/F, and Vz/F for TFV
    - The percentage of participants with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as determined by the United States (US) Food and Drug Administration (FDA)-defined snapshot algorithm
    - The change from baseline in CD4 cell count (cells/µL) and percentage (CD4%) at Weeks 24 and 48
    - The incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities through Week 48
    - Acceptability and palatability of COBI and F/TAF through Week 48

Statistical Analysis Plan (SAP)

The statistical analysis objectives and endpoints for the study are as follows:

- The primary analysis objectives are:
    - To evaluate the steady-state PK and confirm the dose of ATV/COBI or DRV/COBI in HIV-1 infected antiretroviral treatment-experienced pediatric subjects
    - To evaluate the safety and tolerability of ATV/COBI or DRV/COBI each administered with a background regimen (BR) through 48 weeks in HIV-1 infected antiretroviral treatment-experienced pediatric subjects
- The secondary analysis objectives are:
    - To evaluate the safety, tolerability, and antiviral activity of ATV/COBI or DRV/COBI, each administered with a BR, during long-term treatment (minimum 5 years) in HIV-1 infected antiretroviral treatment-experienced pediatric subjects
    - Palatability of COBI suspension formulation will be assessed using appropriate age-validated measures.
- The primary statistical endpoints are:
    - PK parameters of AUCtau, of ATV and DRV.
    - The incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities
- The secondary statistical endpoints are:
    - PK parameters of Ctau and Cmax for ATV and DRV, and AUCtau, Cmax, Ctau CL/F, and Vz/F for COBI.
    - PK parameters of Cmax, Ctau, CL/F, and Vz/F of DRV and ATV
    - The percentage of subjects with plasma HIV-1 RNA □ 50 copies/mL at Weeks 12, 24 and Week 48
    - The time to pure virologic failure
    - The change from Day 1 in CD4+ cell count (cells/µL) and CD4 percentage at Weeks 24 and 48
    - Tanner Stages at Day 1, Weeks 24 and 48, and age of the first menses.
    - Acceptability (assessed by adherence) of COBI and palatability of oral suspension formulation of COBI in applicable age cohort

The Full Analysis Set (FAS) includes all participants who received at least 1 dose of study drug, and is the primary analysis set for efficacy analysis. The Safety Analysis Set includes all participants who received at least 1 dose of study drug. All clinical and laboratory AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1. Clinical events and clinically significant laboratory abnormalities are coded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

Protocol Amendments

The original protocol was established on 09 July 2013 and nine protocol amendments were submitted. All participants in each cohort of this study were enrolled following the implementation of protocol amendment 7, 8, or 9. The methodology of this study is based on protocol amendment 9 and the results reported are relevant specifically to participants in Cohorts 2 and 3 receiving F/TAF (Table 2).

Table 2: Protocol Amendments

Amendment Number	Date	Summary
1	25 November 2013	Multiple protocol changes, highlighted below. For a full list of changes, please refer to Amendment 1 of the protocol. • Added DRV doses for subjects >10kg and <15 kg • Added information regarding the effect of COBI on CYP3A inhibition on various concomitant medications • Revised the frequency of laboratory tests • Updated inclusion criteria for DRV pateints to not include subjects with a history of DRV resistance
2	25 March 2014	Protocol changes are highlighted below. For a full list of changes, please refer to Amendment 2 of the protocol. • Sample size increased • Part A DRV/r or ATV/r treatment data will be analyzed independently if one treatment achieves minimum enrollment before the other.
3	18 December 2014	Protocol changes are highlighted below. For a full list of changes, please refer to Amendment 3 of the protocol. • For DRV/r BID subjects, switch to DRV/co QD on Day 1 • Updates to the Rationale for the Dose Selection section language to reflect COBI developments in the adolescent population • Updates to the statistical comparisons and power computations to reflect the exposure comparison

		equivalency of COBI-boosted ATV or DRV in pediatric versus adult subjects.
4	14 November 2016	Protocol changes are highlighted below. For a full list of changes, please refer to Amendment 4 of the protocol. • Inclusion criteria for body weight at screening were changed for their respective cohort according to this plan: Cohort 1 ≥ 25 kg, Cohort 2 consists of 2 groups (Group 1≥ 25 kg, Group 2 ≥15 kg to <25 kg), Cohort 3 TBD and Cohort 4 TBD • Addition of 90 mg tablet of the test product (for Cohort 2 Group 2, ≥15 kg to <25 kg), and the option to give 1 x 150 mg tablet or 2 x 75 mg tablets (for Cohort 1 and Cohort 2 Group 1, ≥ 25 kg) • ATV powder and DRV suspension were added to the description of each treatment as alternative option for subjects who are unable to swallow capsules or tablets, respectively
5	19 January 2018	Protocol changes are highlighted below. For a full list of changes, please refer to Amendment 5 of the protocol. • Removed references to Cobicistat (COBI) 75 mg tablets due to availability of COBI 150 mg tablets
6	28 June 2018	Protocol changes are highlighted below. For a full list of changes, please refer to Amendment 6 of the protocol. • Updated concomitant medication exclusion criteria to include disallowed/discouraged use of antipsychotics based on COBI prescribing information • Updated concomitant medication language around COBI interactions with corticosteroids
7	6 May 2019	Protocol changes are highlighted below. For a full list of changes, please refer to Amendment 7 of the protocol. • The addition of emtricitabine/tenofovir alafenamide (F/TAF) was made with the goal of studying F/TAF and cobicistat (COBI) in pediatric patients in the most expedient manner. Dose, statistical methods, and study procedures have been amended as appropriate. • Removal of two-part study from Cohorts 2 and 3. Cohorts 2 and 3 will be enrolled in parallel rather than staggered.

8	24 June 2020	Protocol changes are highlighted below. For a full list of changes, please refer to Amendment 8 of the protocol. • Removed "virologically suppressed" from Objectives for Cohorts 2 and 3 • Updated inclusion/exclusion criteria to add viremic pediatric participants to enhance enrollment. The Virologic Failure section was updated to include criteria for management of virologic failure and virologic rebound for viremic participants • Updated the prior and concomitant section to include disallowed/discouraged use of antiplatelet, clopidogrel
9	7 September 2022	Final protocol submitted

Protocol deviations

Numerous protocol deviations were reported in the CSR and Appendix 16.2.2.

Reviewer's comments: The deviations mostly consisted of off-schedule procedures or incorrect consent, which are unlikely to have affected the PK results.

Concomitant medications

Numerous concomitant medications were prohibited in the protocol. Reported concomitant medications are listed in the CSR Appendix 16.2.4.1.

Reviewer's comments:
ATV and DRV are primarily metabolized by CYP3A. When coadministered with COBI, ATV or DRV exposures are not expected to be further increased by coadministration with another CYP3A inhibitor. There are no DDIs in the F/TAF label resulting in significantly increased exposure other than ATV and COBI (which are part of the dosing regimen in Trial 128).

Concomitant medications that were prohibited due to the potential to lower exposure of study drugs included CYP3A inducers, H2RAs, and PPIs. There were no reported uses of these medications.

Bioanalytical methods

Concentrations of ATV, DRV, COBI, TAF, TFV, and FTC were measured in human plasma using validated LC/MS-MS methods. Most validation and study sample analysis runs were acceptable with calibration curve, QC sample, and incurred sample reanalysis assessments meeting acceptance criteria. Study samples were analyzed within the documented duration of stability. No significant protocol deviations were reported.

Reviewer's comments: Overall, bioanalytical methods were acceptable. One review issue was that incurred sample reanalysis was performed for <10% of samples for TAF and ATV (at least 10% is recommended per FDA guidance). While our focus is review of the Cohort 2-3 data included in this supplement, the Applicant notes that Trial 128 is ongoing and they plan to meet the 10% target by the end of the study (NDA 203094 SDN 261).

6. Clinical Pharmacology

See section 7.

7. Review Issues Relevant to the Evaluation of Benefit and Risk

The review issue relevant to the evaluation of benefit and risk is focused on the exposures of ATV, DRV, COBI, FTC, TAF, and TFV, and whether or not these exposures are similar in pediatric participants in Trial 128 weighing at least 14 kg to less than 35 kg compared to adults and/or other pediatric studies where the components are approved for the same dose and age/weight range. Safety and efficacy outcomes were also evaluated.

Background

For Cohorts 2 and 3, the intensive PK visit occurred during Week 2 or 4. Sampling times were predose, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, and 24 hours postdose. ATV or DRV, COBI, FTC, TAF, and TFV were measured in plasma. Individual participant concentration-time profiles were submitted in NDA 203094 SDN 261. PK data were analyzed using noncompartmental analysis.

For each plasma analyte, we assessed whether exposures in Trial 128 participants were similar to those in adults administered the approved dosage regimen. The assessment is summarized below.

- For all analytes, AUC, Cmax, and Ctrough values were higher in Trial 128 partipants than in adults. Therefore, there are no efficacy concerns from a Clinical Pharmacology perspective. Because safety may be a concern associated with the relatively high AUC and Cmax, but not for elevated Ctrough, our analyses below focused on AUC and Cmax.
- Compared to TAF, TDF results in ~10-fold higher plasma exposures of TFV. Trial 128 TFV exposures were higher than in adult TAF studies but lower than in adult TDF studies. For our analysis of TFV exposures in Trial 128, we used two adult references, namely studies of elvitegravir/cobicistat/emtricitabine/tenfofovir alafenamide (E/C/F/TAF) and studies of elvitegravir/cobicistat/emtricitabine/tenfofovir DF (E/C/F/TDF).

- Note that the adult and pediatric PK parameters in the reference groups are present in approved labels. This included adult PK data analyzed using noncompartmental analysis (ATV, DRV [Cmax], COBI, FTC) or population PK (DRV [AUC and Ctrough], TAF, and TFV).

Assessment:

Clinical Pharmacology

The figures at the end of this section show graphical exposure comparisons between Trial 128 participants versus adults (Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6). AUC and Cmax results are discussed in text in the subsections below. AUC, Cmax, and Ctrough ratios (Trial 128/adult reference) are shown in the below tables (Table 3, Table 4, Table 5, Table 6).

Cohort 2 (≥25 kg) participants administered FTC/TAF + ATV/COBI

Among cohort 2 participants administered FTC/TAF + ATV/COBI (Table 3):

- TAF: ~4-5-fold higher Cmax and AUC compared to adults with 70-100% of participants exceeding the adult 95th percentile of Cmax or AUC. Trial 128 exposures are also ~2-4-fold higher when compared to pediatric studies of other TAF-containing pediatric HIV products approved for the same age and weight range.
- TFV (TAF adult reference): Cmax and AUC values were ~4-fold higher than adults with 100% of participants exceeding the adult 95th percentile of Cmax or AUC
- TFV (TDF adult reference): Cmax and AUC values were lower than adults in studies of TDF with no participants exceeding the adult 95th percentile of Cmax or AUC
- ATV: Cmax and AUC values were similar to adults with no participants exceeding the adult 95th percentile of Cmax or AUC
- FTC and COBI: ~2-fold higher Cmax and AUC compared to adults with ~70-90% of participants exceeding the adult 95th percentile of Cmax or AUC. However, exposures were comparable (up to 50% higher) when compared to pediatric studies of other FTC- and COBI-containing pediatric HIV products approved for the same age and weight range.

PK data support the use of ATV/COBI in combination with other antiretrovirals in patients weighing ≥25 kg, but coadministration with TAF is not recommended.

Cohort 2 (≥25 kg) participants administered FTC/TAF + DRV/COBI

Among cohort 2 participants administered FTC/TAF + DRV/COBI (Table 4):

- TAF: ~2-fold higher Cmax and AUC compared to adults with 25% of participants exceeding the adult 95th percentile of Cmax or AUC. However, exposures were comparable when compared to pediatric studies of other TAF-containing pediatric products approved for the same age and weight range.
- TFV (TAF adult reference): Cmax and AUC values were ~4-fold higher than adults, with 100% of participants exceeding the adult 95th percentile of Cmax or AUC

- TFV (TDF adult reference): Cmax and AUC values were lower than adults in studies of TDF, with no participants exceeding the adult 95th percentile of Cmax or AUC
- FTC: ~2-fold higher Cmax and AUC compared to adults with ~70-90% of participants exceeding the adult 95th percentile of Cmax or AUC. However, exposures were comparable when compared to pediatric studies of other FTC-containing pediatric products approved for the same age and weight range.
- DRV and COBI: Comparable exposures to adults; also comparable COBI exposures when compared to pediatric studies of other COBI-containing pediatric products approved for the same age and weight range.

PK data support the use of DRV/COBI in combination with other antiretrovirals, including FTC/TAF in patients weighing ≥25 kg.

Cohort 3 (14 - <25 kg) participants administered FTC/TAF + ATV/COBI

Among cohort 3 participants administered FTC/TAF + ATV/COBI (Table 5):

- TAF: Cmax and AUC were ~2- and ~3-fold higher, respectively, compared to adults, with ~70-90% of participants exceeding the adult 95th percentile of Cmax or AUC. Trial 128 exposures (AUC) are also ~2-fold higher when compared to pediatric studies of other TAF-containing pediatric products approved for the same age and weight range.
- TFV (TAF adult reference): Cmax and AUC values were ~3-fold higher than adults, with 100% of participants exceeding the adult 95th percentile of Cmax or AUC
- TFV (TDF adult reference): Cmax and AUC values were lower than adults in studies of TDF, with no participants exceeding the adult 95th percentile of Cmax or AUC
- ATV: 50-70% higher Cmax and AUC values compared to adults. However, exposures sufficiently overlap adults with 15-27% of participants exceeding the adult 95th percentile of Cmax or AUC.
- FTC and COBI: Comparable (up to 50% higher) exposures to adults; also comparable exposures when compared to pediatric studies of other FTC-containing pediatric products approved for the same age and weight range.

PK data support the use of ATV/COBI in combination with other antiretrovirals in patients weighing 14-<25 kg, but coadministration with TAF is not recommended.

Cohort 3 (14 - <25 kg) participants administered FTC/TAF + DRV/COBI

Among cohort 3 participants administered FTC/TAF + DRV/COBI (Table 6):

- TAF: AUC and Cmax were ~2- and ~3-fold higher, respectively, compared to adults, with 30-90% of participants exceeding the adult 95th percentile of AUC or Cmax. However, exposures (AUC and Cmax) were comparable when compared to pediatric studies of other TAF-containing pediatric products approved for the same age and weight range.

- TFV (TAF adult reference): Cmax and AUC values were 3-4-fold higher than adults, with 91% of participants exceeding the adult 95th percentile of Cmax or AUC
- TFV (TDF adult reference): Cmax and AUC values were lower than adults in studies of TDF, with no participants exceeding the adult 95th percentile of Cmax or AUC
- FTC: ~2-fold higher Cmax and AUC compared to adults with ~90-100% of participants exceeding the adult 95th percentile of Cmax or AUC. However, exposures were comparable when compared to pediatric studies of other FTC-containing pediatric products approved for the same age and weight range.
- DRV and COBI: Comparable (up to ~50% higher) exposures when compared to adults or to pediatric studies of other DRV-containing pediatric products approved for the same age and weight range

PK data support the use of DRV/COBI in combination with other antiretrovirals, including FTC/TAF in patients weighing 14 -<25 kg.

Table 3. Exposure Comparison for Trial 128 Cohort 2 Administered Taking FTC/TAF + ATV/COBI Versus Adults and Versus Pediatric Studies of Other Approved Pediatric Products.

Analyte	PK parameter	Adult reference	Percent of Trial 128 participants above adult 95th percentile[1]	Fold change Trial 128 vs adults	Fold change Trial 128 vs other pediatric approvals[2]	PK data supports use in ≥ 25 kg?
TAF	AUC		100	5.29	B/F/TAF: 3.69 E/C/F/TAF: 3.10	No
	Cmax		71	3.72	B/F/TAF: 2.94 E/C/F/TAF: 2.05	
	Ctrough		NC	NA[3]		
TFV	AUC	TAF studies	100	4.11		No
	Cmax		100	4.42		
	Ctrough		NC	4.02		
	AUC	TDF studies	0	0.27		Yes
	Cmax		0	0.14		
	Ctrough		NC	0.41		
FTC	AUC		71	2.15	B/F/TAF: 1.49 E/C/F/TAF: 1.23	Yes
	Cmax		79	1.84	B/F/TAF: 1.00 E/C/F/TAF: 1.12	
	Ctrough		NC	1.42		
ATV	AUC		0	1.11		Yes
	Cmax		0	1.10		
	Ctrough		NC	1.33		
COBI	AUC		77	2.29	E/C/F/TAF: 1.45	Yes
	Cmax		93	1.83	E/C/F/TAF: 1.44	
	Ctrough		NC	3.61		

Source: Prepared by reviewer from the Trial 128 CSR, NDA 208215 SDN 1466, NDA 203094 SDN 259 response to 12/3/24 request, NDA 203094 SDN 259 response to 2/4/25 request, NDA 203094 SDN 266. Fold change refers to the ratio of geometric mean in Trial 128 versus reference PK parameter values. TFV PK from adult studies of TDF from Stribild labeling.
NC = not calculated, NA = not applicable
[1]Not calculated for Ctrough
[2]Other pediatric approval of same dose and same weight range as in Trial 128
[3]As TAF is not detectable in plasma beyond ~8 hours post-dose, trough concentrations are not detectable

Table 4. Exposure Comparison for Trial 128 Cohort 2 Participants Administered FTC/TAF + DRV/COBI Versus Adults and Versus Pediatric Studies of Other Approved Pediatric Products.

Analyte	PK parameter	Adult reference	Percent of Trial 128 participants above adult 95th percentile[1]	Fold change Trial 128 vs adults	Fold change Trial 128 vs other pediatric approvals[2]	PK data supports use in ≥ 25 kg?
TAF	AUC		25	1.98	B/F/TAF: 1.38 E/C/F/TAF: 1.16	Yes
	Cmax		25	1.66	B/F/TAF: 1.31 E/C/F/TAF: 0.91	
	Ctrough		NC	NA[3]		
TFV	AUC	TAF studies	100	3.88		No
	Cmax		100	4.09		
	Ctrough		NC	3.90		
	AUC	TDF studies	0	0.25		Yes
	Cmax		0	0.13		
	Ctrough		NC	0.40		
FTC	AUC		67	2.37	B/F/TAF: 1.64 E/C/F/TAF: 1.36	Yes
	Cmax		89	2.00	B/F/TAF: 1.09 E/C/F/TAF: 1.22	
	Ctrough		NC	1.82		
DRV	AUC		0	1.09		Yes
	Cmax		22	1.19		
	Ctrough		NC	1.44		
COBI	AUC		33	1.42	E/C/F/TAF: 0.90	Yes
	Cmax		11	1.13	E/C/F/TAF: 0.89	
	Ctrough		NC	2.15		

Source: Prepared by reviewer from the Trial 128 CSR, NDA 208215 SDN 1466, NDA 203094 SDN 259 response to 12/3/24 request, NDA 203094 SDN 259 response to 2/4/25 request, NDA 203094 SDN 266. Fold change refers to the ratio of geometric mean Trial 128 versus reference PK parameter values. TFV PK from adult studies of TDF from Stribild labeling.
NC = not calculated, NA = not applicable
[1]Not calculated for Ctrough
[2]Other pediatric approval of same dose and same weight range as in Trial 128
[3]As TAF is not detectable in plasma beyond ~8 hours post-dose, trough concentrations are not detectable

Table 5. Exposure Comparison for Trial 128 Cohort 3 Participants Administered FTC/TAF + ATV/COBI Versus Adults and Versus Pediatric Studies of Other Approved Pediatric Products.

Analyte	PK parameter	Adult reference	Percent of Trial 128 participants above adult 95th percentile[1]	Fold change Trial 128 vs adults	Fold change Trial 128 vs other pediatric approvals[2]	PK data supports use in at least 14 kg to < 25 kg (15 kg to <25 kg for DRV)?
TAF	AUC		87	3.27	B/F/TAF: 2.08	No
	Cmax		67	2.46	B/F/TAF: 0.91	
	Ctrough		NC	NA[3]		
TFV	AUC	TAF studies	100	2.99		No
	Cmax		100	3.27		
	Ctrough		NC	2.81		
	AUC	TDF studies	0	0.19		Yes
	Cmax		0	0.11		
	Ctrough		NC	0.29		
FTC	AUC		33	1.47	B/F/TAF: 1.16	Yes
	Cmax		20	1.18	B/F/TAF: 0.65	
	Ctrough		NC	1.11		
ATV	AUC		15	1.46		Yes
	Cmax		27	1.72		
	Ctrough		NC	1.42		
COBI	AUC		33	1.53		Yes
	Cmax		40	1.23		
	Ctrough		NC	2.51		

Source: Prepared by reviewer from the Trial 128 CSR, NDA 208215 SDN 1466, NDA 203094 SDN 259 response to 12/3/24 request, NDA 203094 SDN 259 response to 2/4/25 request. Fold change refers to the ratio of geometric mean Trial 128 versus reference PK parameter values. TFV PK from adult studies of TDF from Stribild labeling.

NC = not calculated, NA = not applicable

[1]Not calculated for Ctrough

[2]Other pediatric approval of same dose and same weight range as in Trial 128

[3]As TAF is not detectable in plasma beyond ~8 hours post-dose, trough concentrations are not detectable

Table 6. Exposure Comparison for Trial 128 Cohort 3 Participants Administered FTC/TAF + DRV/COBI Versus Adults and Versus Pediatric Studies of Other Approved Pediatric Products.

Analyte	PK parameter	Adult reference	Percent of Trial 128 participants above adult 95th percentile[1]	Fold change Trial 128 vs adults	Fold change Trial 128 vs other pediatric approvals[2]	PK data supports use in at least 14 kg to < 25 kg (15 kg to <25 kg for DRV)?
TAF	AUC		30	2.09	B/F/TAF: 1.33	Yes
	Cmax		90	3.15	B/F/TAF: 1.16	
	Ctrough		NC	NA[3]		
TFV	AUC	TAF studies	91	3.41		No
	Cmax		91	3.81		
	Ctrough		NC	3.16		
	AUC	TDF studies	0	0.22		Yes
	Cmax		0	0.12		
	Ctrough		NC	0.325		
FTC	AUC		100	1.97	B/F/TAF: 1.55	Yes
	Cmax		91	2.16	B/F/TAF: 1.20	
	Ctrough		NC	1.11		
DRV	AUC		27	1.49	C228[4]: 1.47[5]/1.34[6]	Yes
	Cmax		73	1.88	C228[4]: 1.42[5]/1.36[6]	
	Ctrough		NC	1.66		
COBI	AUC		36	1.64		Yes
	Cmax		64	1.39		
	Ctrough		NC	1.96		

Source: Prepared by reviewer from the Trial 128 CSR, NDA 208215 SDN 1466, NDA 203094 SDN 259 response to 12/3/24 request, NDA 203094 SDN 259 response to 2/4/25 request. Fold change refers to the ratio of geometric mean Trial 128 versus reference PK parameter values. TFV PK from adult studies of TDF from Stribild labeling.

NC = not calculated, NA = not applicable

[1]Not calculated for Ctrough

[2]Other pediatric approval of same dose and same weight range as in Trial 128

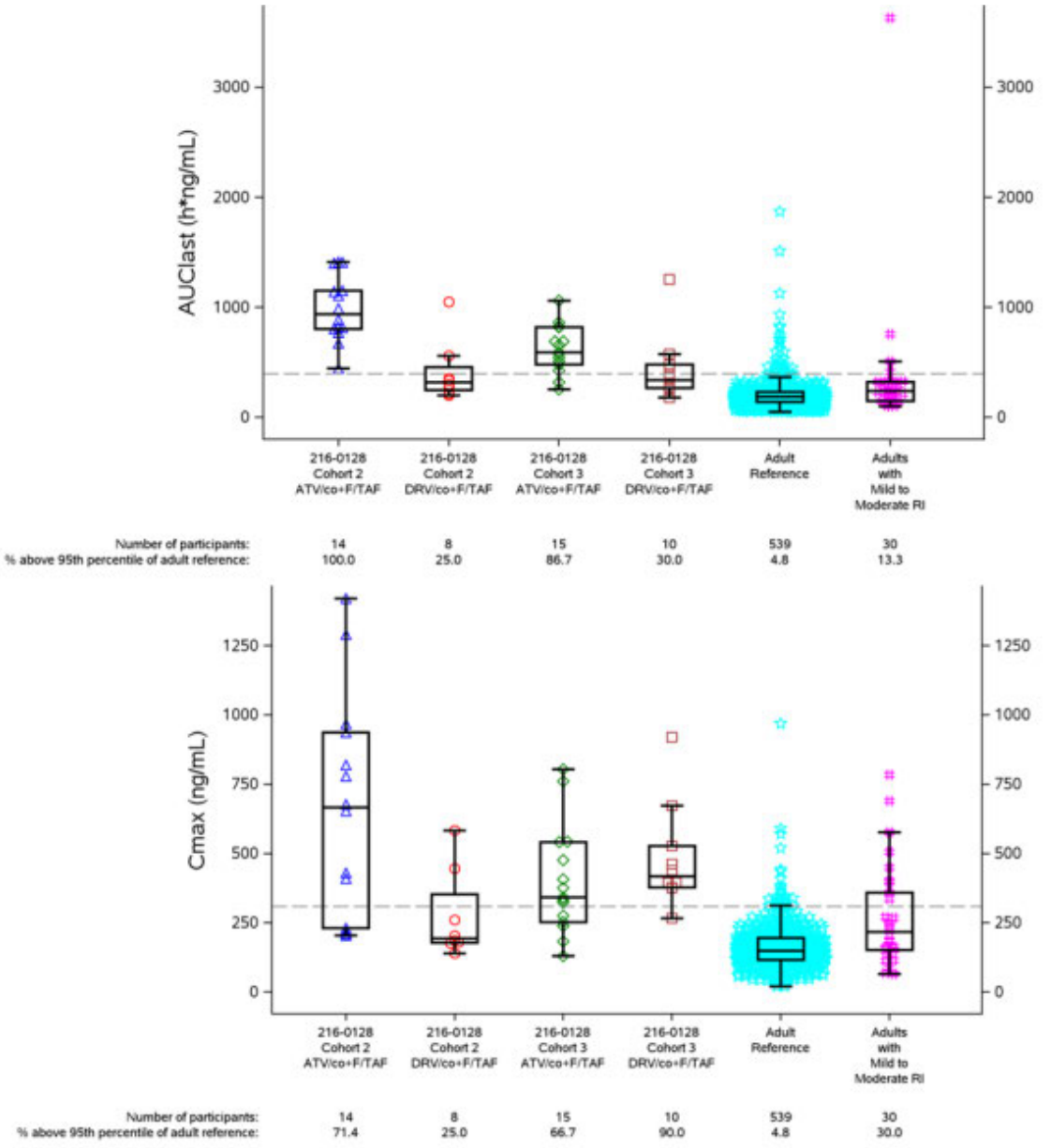
[3]As TAF is not detectable in plasma beyond ~8 hours post-dose, trough concentrations are not detectable

[4]PK data from the Trial C228 substudy (NDA 21976 SDN 722) for DRV/r 600 mg/100 mg given once daily in participants weighing 15-<30 kg were the basis of approval for this weight band (NDA 21976, Clinical Pharmacology review dated 1/10/13). However, C228 PK data for once daily dosing in 15-<30 kg are not shown in the Prezista label.

[5]Using n=6 from the C228 substudy, where baseline median (range) weight was 16.8 kg (14.9-17.5)

[6]Using n=10 from the C228 substudy, where baseline median (range) weight was 15.7 kg (13.1-17.5)

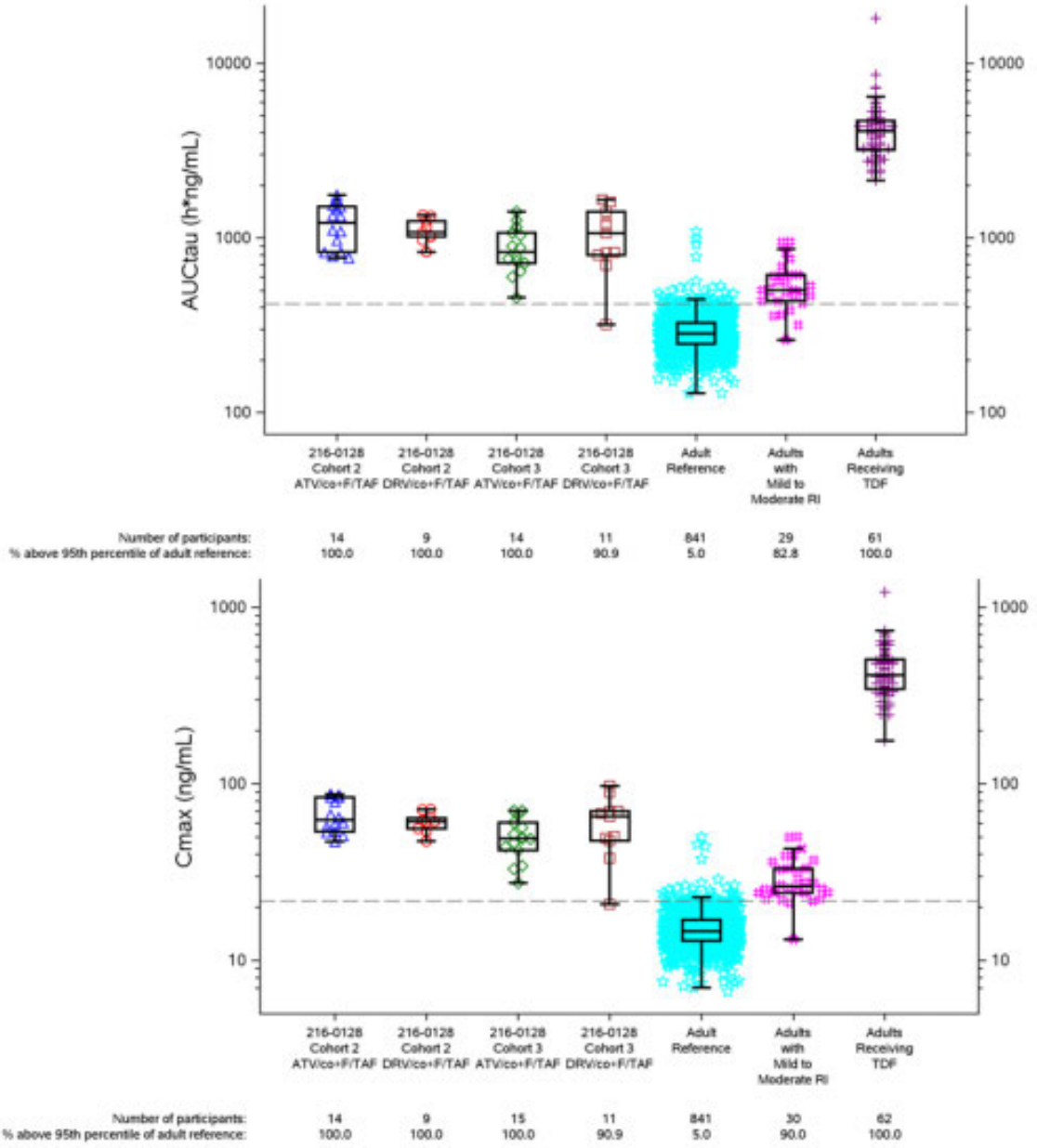
Figure 1. Box Plot of TAF Exposure Comparison (AUClast and Cmax) Between GS-US-216-0128 (Cohorts 2 and 3) and Adult Studies.



NCA = noncompartmental analysis; RI = renal impairment; IQR = interquartile range.
PK parameters for Study GS-US-216-0128 Cohorts 2 and 3 were estimated by NCA.
Adult reference was based on population PK-derived PK parameters from pooled Ph3 studies of E/C/F/TAF (GS-US-292--0104 and GS-US-292-0111).
Adults with mild to moderate RI were based on Study GS-US-292-0112 (PK parameters estimated by NCA).
Population PK-derived AUC_{tau} from the adult reference was compared with NCA-derived AUC_{last} from the other studies.
Symbols represent individual data; dashed line represents the 95th percentile of the adult reference; boxes represent IQR; horizontal lines within the boxes represent the median; whiskers represent the range of data excluding outliers beyond 1.5 x IQR above/below the upper/lower quartile.

Source: NDA 208215 SDN 1466.

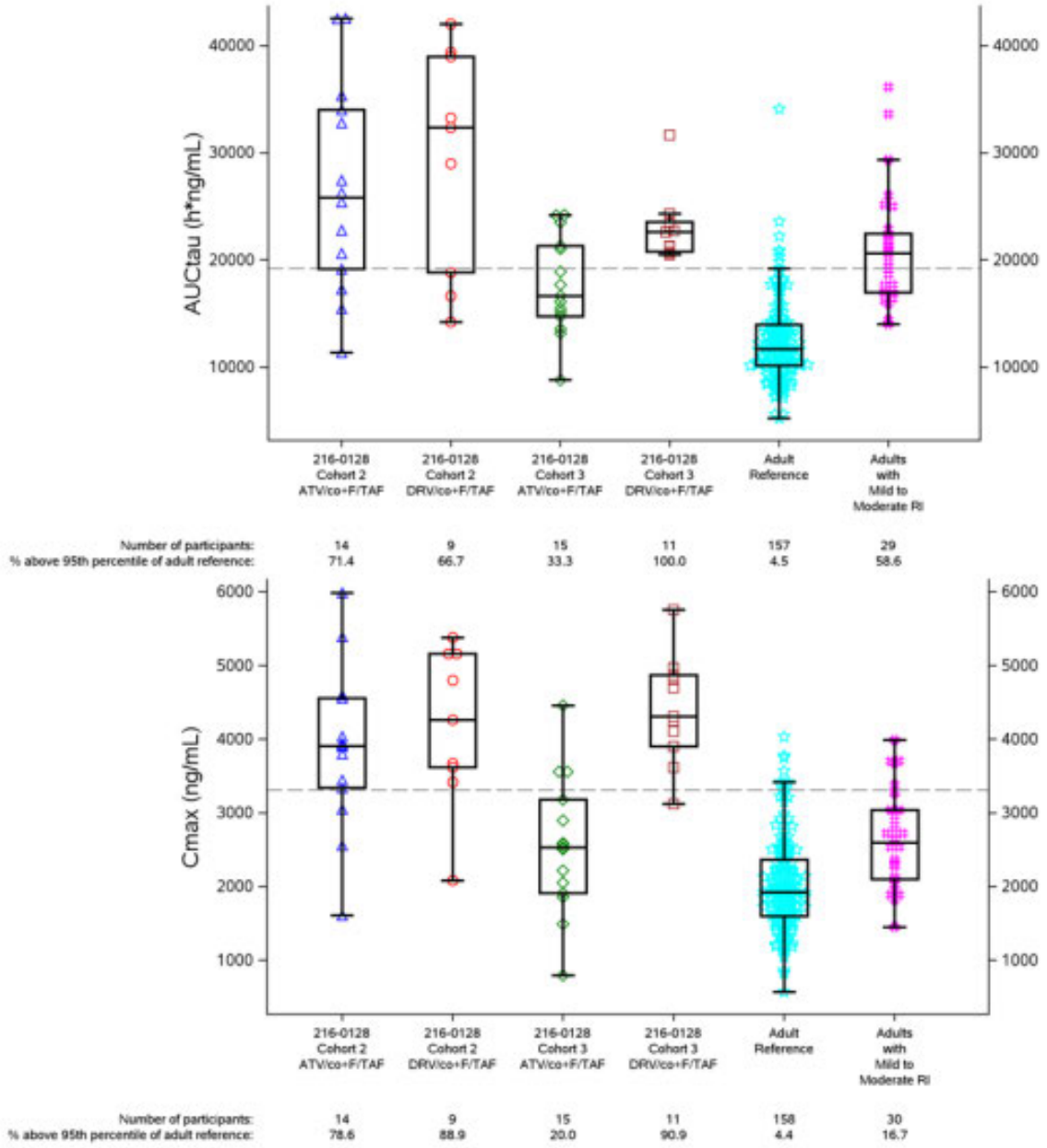
Figure 2. Box Plot of TFV Exposure Comparison (AUCtau and Cmax) Between GS-US-216-0128 (Cohorts 2 and 3) and Adult Studies.



NCA = noncompartmental analysis; RI = renal impairment; IQR = interquartile range.
PK parameters for Study GS-US-216-0128 Cohorts 2 and 3 were estimated by NCA.
Adult reference was based on population PK-derived PK parameters from pooled Ph3 studies of E/C/F/TAF (GS-US-292-0104 and GS-US-292-0111).
Adults with mild to moderate RI were based on Study GS-US-292-0112 (PK parameters estimated by NCA).
Adults receiving TDF were based on pooled E/C/F/TDF Ph 2/3 studies GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104 (PK parameters estimated by NCA).
Symbols represent individual data; dashed line represents the 95th percentile of the adult reference; boxes represent IQR; horizontal lines within the boxes represent the median; whiskers represent the range of data excluding outliers beyond 1.5 x IQR above/below the upper/lower quartile.

Source: NDA 208215 SDN 1466.

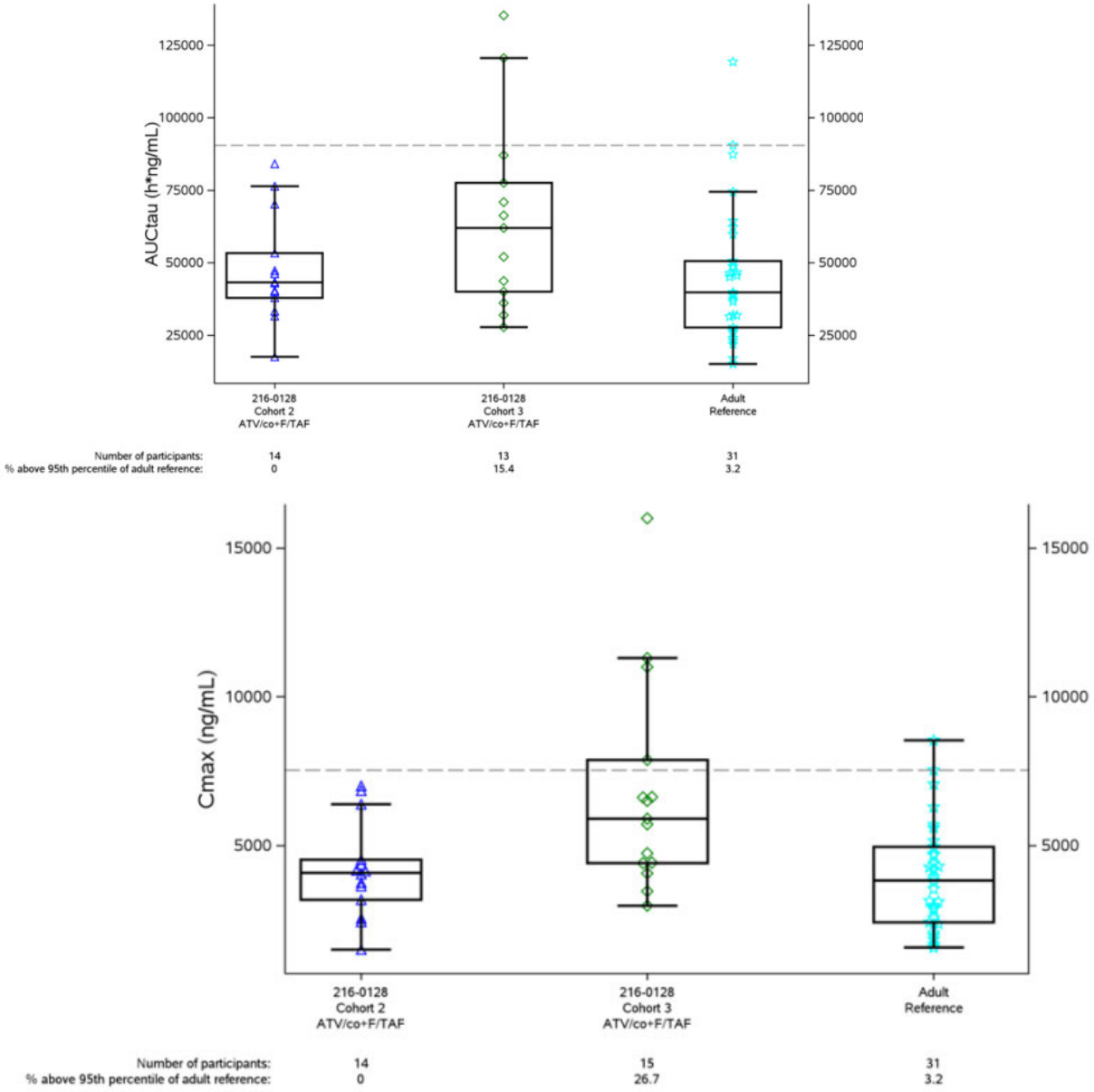
Figure 3. Box Plot of FTC Exposure Comparison (AUCtau and Cmax) Between GS-US-216-0128 (Cohorts 2 and 3) and Adult Studies.



NCA = noncompartmental analysis; RI = renal impairment; IQR = interquartile range.
PK parameters for Study GS-US-216-0128 Cohorts 2 and 3 were estimated by NCA.
Adult reference was based on NCA-derived PK parameters from pooled Ph 2/3 studies of E/C/F/TAF (GS-US-292-0102), E/C/F/TDF (GS-US-236-0102, GS-US-236-0103, GS-US-236-0104) and B/F/TAF (GS-US-380-1844, GS-US-380-1878, GS-US-380-1489, GS-US-380-1490).
Adults with mild to moderate RI were based on Study GS-US-292-0112 (PK parameters estimated by NCA).
Symbols represent individual data; dashed line represents the 95th percentile of the adult reference; boxes represent IQR; horizontal lines within the boxes represent the median; whiskers represent the range of data excluding outliers beyond 1.5 x IQR above/below the upper/lower quartile.

Source: NDA 208215 SDN 1466.

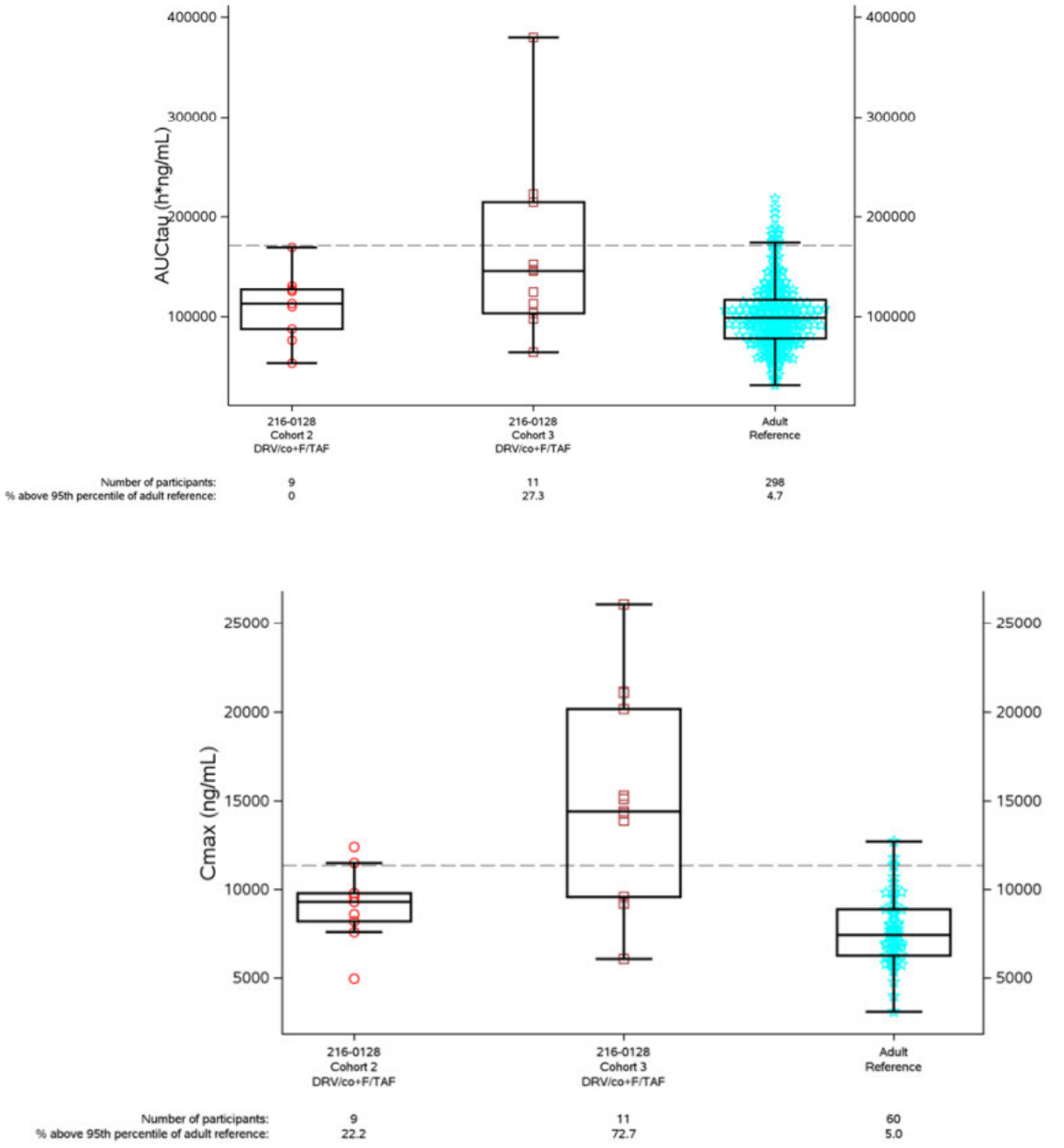
Figure 4. Box Plot of ATV Exposure Comparison (AUCtau and Cmax) Between GS-US-216-0128 (Cohorts 2 and 3) and Adult Studies.



NCA = noncompartmental analysis; RI = renal impairment; IQR = interquartile range.
PK parameters for Study GS-US-216-0128 Cohorts 2 and 3 were estimated by NCA.
Adult reference was based on NCA-derived PK parameters from pooled Ph 2/3 studies of ATV/co (GS-US-216-0105 and GS-US-216-0114).
Symbols represent individual data; dashed line represents the 95th percentile of the adult reference; boxes represent IQR; horizontal lines within the boxes represent the median; whiskers represent the range of data excluding outliers beyond 1.5 x IQR above/below the upper/lower quartile.

Source: NDA 203094 SDN 259.

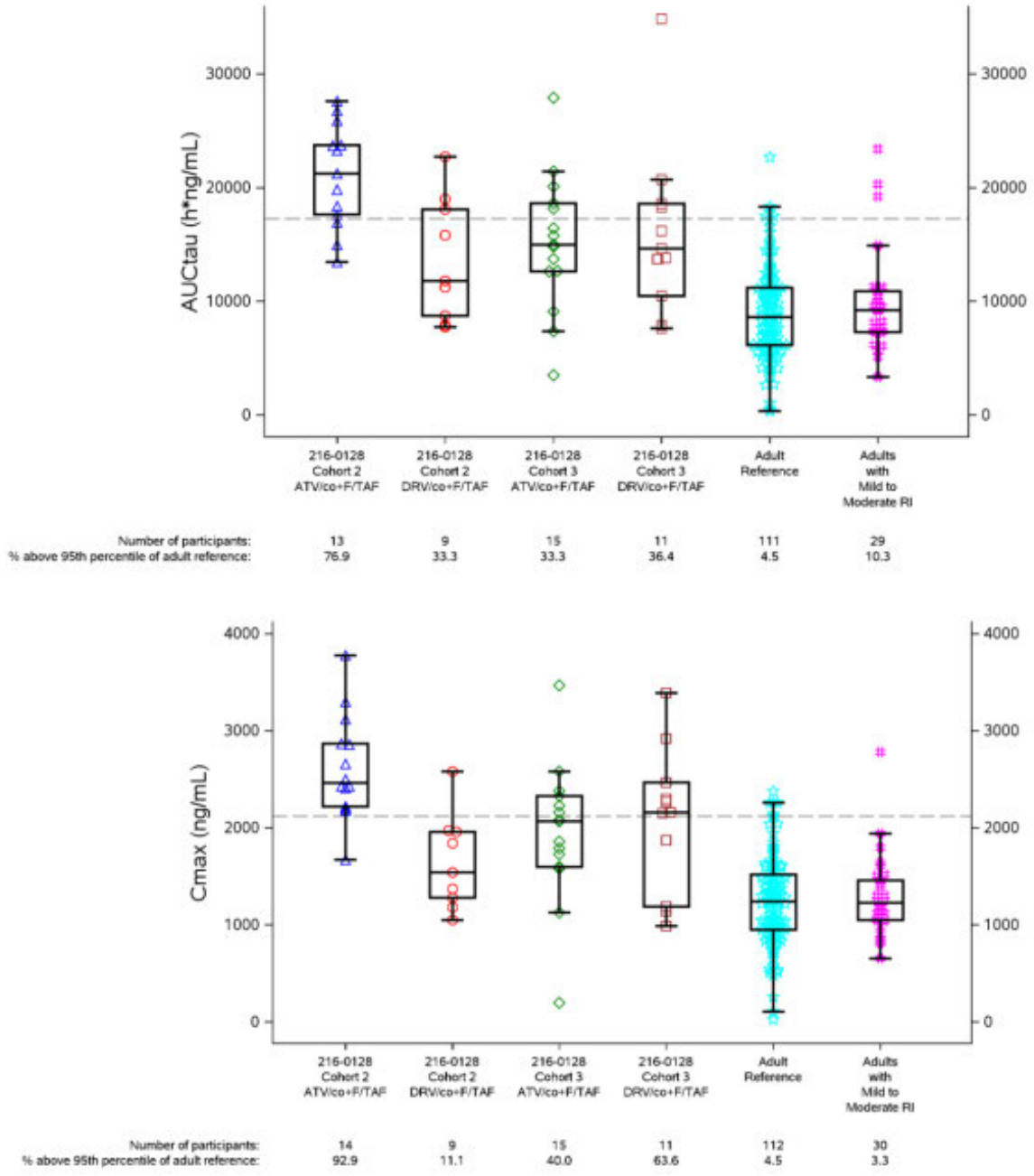
Figure 5. Box Plot of DRV Exposure Comparison (AUCtau and Cmax) Between GS-US-216-0128 (Cohorts 2 and 3) and Adult Studies.



NCA = noncompartmental analysis; RI = renal impairment; IQR = interquartile range.
PK parameters for Study GS-US-216-0128 Cohorts 2 and 3 were estimated by NCA.
Adult reference was based on population PK-derived (for AUC_{tau}) or NCA-derived (for C_{max}) PK parameters from Ph 3 study of DRV/co (GS-US-216-0130).
Symbols represent individual data; dashed line represents the 95th percentile of the adult reference; boxes represent IQR; horizontal lines within the boxes represent the median; whiskers represent the range of data excluding outliers beyond 1.5 x IQR above/below the upper/lower quartile.

Source: NDA 203094 SDN 259.

Figure 6. Box Plot of COBI Exposure Comparison (AUCtau and Cmax) Between GS-US-216-0128 (Cohorts 2 and 3) and Adult Studies.



NCA = noncompartmental analysis; RI = renal impairment; IQR = interquartile range.
PK parameters for Study GS-US-216-0128 Cohorts 2 and 3 were estimated by NCA.
Adult reference was based on NCA-derived PK parameters from pooled Ph 2/3 studies of E/C/F/TAF (GS-US-292-0102), E/C/F/TDF (GS-US-236-0102, GS-US-236-0103, GS-US-236-0104) and ATV/co (GS-US-216-0105 and GS-US-216-0114).
Adults with mild to moderate RI were based on Study GS-US-292-0112 (PK parameters estimated by NCA).
Symbols represent individual data; dashed line represents the 95th percentile of the adult reference; boxes represent IQR; horizontal lines within the boxes represent the median; whiskers represent the range of data excluding outliers beyond 1.5 x IQR above/below the upper/lower quartile.
Source: NDA 203094 SDN 259.

Clinical Safety/Efficacy

The exposures in pediatric participants were similar to or exceeded adult exposures and, as expected, the efficacy in all participants was acceptable with 98% remaining virologically suppressed through Week 48.

Limited data were available to support the increased TAF exposures; therefore the use of TYBOST with atazanavir and TAF is not recommended in pediatric patients weighing at least 14 kg to less than 35 kg. In addition to the safety data from Study 128, we reviewed two adult studies (Study GS-120-1101 and Study GS-US-311-0101) to support the higher TAF exposures observed in pediatric participants. Study GS-120-1101 evaluated TAF 50 mg (10 participants) and 150 mg (10 participants) for 14 days. Most (15/20, 75%) experienced adverse events that were deemed related to the study drug, and all AEs were grade 1 or 2 in severity. Only one Grade 3 lab abnormality occurred, and no SAEs or premature drug discontinuations due to AEs were reported. Study GS-US-311-0101 evaluated TAF 40 mg for 12 days. Out of twelve participants in this study, five (41.7%) reported adverse events but only one AE was related to the study drug and led to premature discontinuation. There were no SAEs. However, given the short duration of therapy and the limited number of participants in these studies, these data were not deemed acceptable to support an indication for TYBOST with atazanavir and TAF in pediatric patients weighing at least 14 kg to less than 35 kg.

Overall, there were no new or unexpected safety findings. See sections 9 and 10 for further details on the complete evaluation of clinical safety and efficacy.

Conclusions

TYBOST (cobicistat, COBI) (NDA 203094-S.17 and S.18):

With ATV: Trial 128 supports the use of COBI to increase systemic exposure of ATV, in combination with other ARVs except for TAF, for the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg.

- TAF exposures in pediatric participants who received ATV+COBI in cohort 2 (25 kg to <40 kg, n=14) and cohort 3 (14 kg to <25 kg, n=15) exceeded TAF exposures in adults by 4-5-fold and 2-3-fold, respectively. Additionally, exposures in this group were also 2-3-fold higher when compared to pediatric studies of other TAF containing HIV products approved for the same age and weight range. Because limited safety data are available to support the increased TAF exposures, the use of TYBOST with ATV and TAF is not recommended in pediatric patients weighing at least 14 kg to less than 35 kg.
- ATV and COBI exposures in pediatric participants in cohorts 2 and 3 were similar to that observed in adults and/or in pediatric studies of other pediatric products approved for the same age and weight range, thereby, supporting the use of TYBOST with ATV in

combination with other ARVs except for TAF in pediatric patients weighing at least 14 kg to less than 35 kg.

With DRV: Trial 128 supports the use of COBI to increase systemic exposure of DRV (once daily dosing regimen), in combination with other ARVs, including TAF, for the treatment of HIV-1 infection in pediatric patients weighing at least 15 kg.

- TAF exposures in pediatric participants who received DRV+COBI exceeded TAF exposures in adults by 2-3-fold but were similar to that observed in pediatric studies of other pediatric products approved for the same age and weight range.
- DRV and COBI exposures, along with supportive safety and efficacy data, in pediatric participants in cohorts 2 and 3 were similar to that observed in adults.

DESCOVY (emtricitabine/tenofovir alafenamide, F/TAF) (NDA 208215-S.23 and S.25):

Trial 128 supports the use of F/TAF in combination with other antiretroviral agents, including COBI and DRV, but not with other protease inhibitors that require a CYP3A inhibitor.

- TAF and FTC exposures, along with supportive safety and efficacy data, in pediatric participants who received DRV+COBI in cohorts 2 and 3 were similar to that observed in adults and/or in pediatric studies of other pediatric products approved for the same age and weight range.
- As mentioned above, the data do not support the use of F/TAF and ATV+COBI in this pediatric population. Additionally, the PK, safety and efficacy of F/TAF in combination with protease inhibitors that require ritonavir (when used as a CYP3A inhibitor) have not been established in pediatric patients weighing at least 14 kg to less than 35 kg.

8. Clinical Virology

Please refer to the reviews conducted by Drs. Lisa Naeger and Annaris Colberg-Poley for details. In cohorts 2 and 3 no resistance to study drugs were identified.

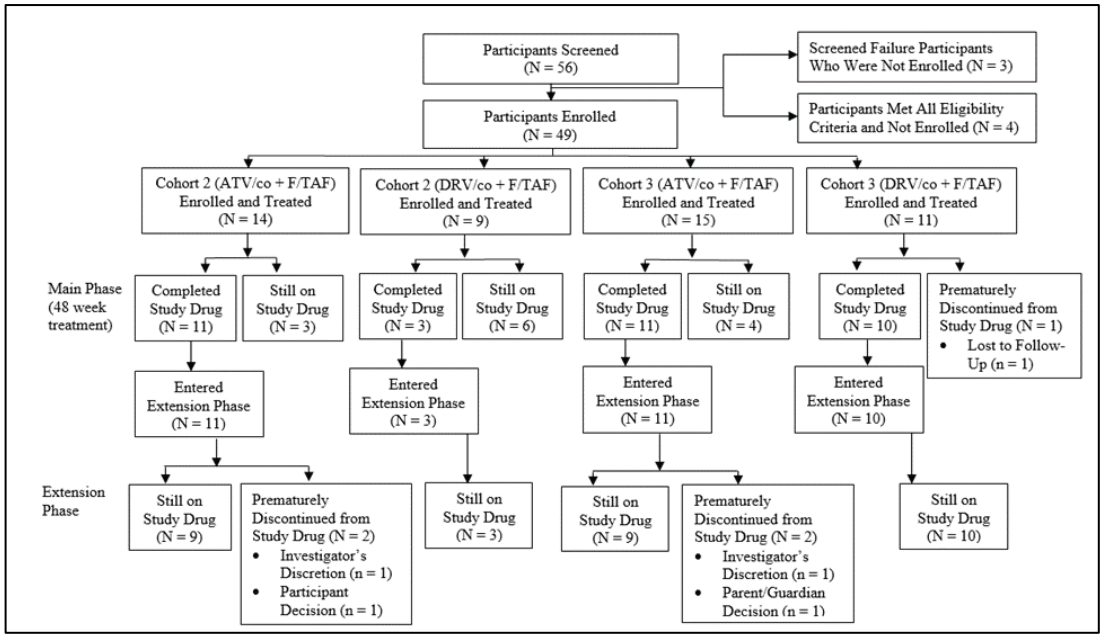
9. Clinical/Statistical – Efficacy

Disposition

A total of 49 participants were enrolled and treated in the study; 23 in Cohort 2 and 26 in Cohort 3. All participants are included in the safety analysis set.

At the data cutoff date, 98% (48 of 49) participants had completed study drug in the main, 48-week treatment phase (Figure 7). All 14 participants in the ATV+COBI+F/TAF group from Cohort 2 completed study drug in the 48-week treatment phase and entered the extension phase. In the extension phase, 11 remained on study drug while 3 had prematurely discontinued study drug. All 9 participants in the DRV+COBI+F/TAF group from Cohort 2 had completed study drug in the 48-week treatment phase and remained on study drug in the extension phase. In Cohort 3, all 15 participants in the ATV+COBI+F/TAF group had completed study drug in the 48-week treatment phase and entered the extension phase; 13 remained on study drug while 2 had prematurely discontinued study drug. One participant from Cohort 3 (DRV+COBI group) was lost to follow up between Week 24 and Week 36, but the remaining 10 participants in this group completed study drug during the 48-week treatment phase and remained on study drug in the extension phase.

Figure 7: Participant Disposition



Baseline Demographics

In the safety analysis set, the majority of participants were female (28/49, 57%). The median age of participants was 8 years old (range 3-12). Patients were predominantly Black (45/49, 91.8%). The mode of HIV infection in the majority of participants was vertical transmission (48/49, 98%) although one participant had reportedly unknown mode of transmission. All participants tested negative for both HBV surface antigen and HCV antibody. Baseline demographics are highlighted in Table 7:

Table 7: Participant Demographics

Demographic	Cohort 2 (n = 23)		Cohort 3 (n = 26)		Total (n = 49)
	ATV+COBI + F/TAF (n = 14)	DRV+COBI + F/TAF (n = 9)	ATV+COBI + F/TAF (n = 15)	DRV+COBI + F/TAF (n = 11)	
Age (years)					
Median	10	10	7	4	8
Range	8 - 12	8 - 12	5- 10	3 - 7	3 - 12
Sex, n (%)					
Male	8 (57%)	1 (11%)	7 (47%)	5 (45%)	21 (43%)
Female	6 (43%)	8 (89%)	8 (53%)	6 (55%)	28 (57%)
Race					
Black	13	8	13	11	45
Other	1	1	2	0	4
Baseline Weight (kg) **Median (range)**	28.2 (24.4 – 33.8)	29 (25.2 – 39.7)	20.5 (15.9 – 24.7)	16.8 (14.7 – 22)	24.2 (14.7 – 39.7
Baseline HIV RNA, n (%)					
< 50 copies/mL	13 (93%)	9 (100%)	13 (87%)	11 (100%)	46 (94%)
≥ 50 copies/mL	1 (7%)	0	2 (13%)	0	3 (6%)
CD4 Cell Count (cells/mm^3) **Median (range)**	808 (575 - 1456)	929 (584 – 1232)	782 (251 – 1461)	1237 (705 – 1636)	921 (251 – 1636)
HIV Disease Status, n (%)					49 (100%)
Asymptomatic	14 (100%)	8 (89%)	15 (100%)	11 (100%)	
Symptomatic		1 (11%)			

One participant in Cohort 3 received concomitant non-study antiretroviral medication during the study period. This participant received lopinavir/ritonavir when study drug was discontinued due to adverse events (days 15-28) and was then permanently placed on lopinavir/ritonavir on Day 38.

Results Primary Efficacy Analysis

The efficacy results were obtained from the updated 48-week data set submitted by the sponsor in response to an information request.

The proportion of 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:
    - Cohort 2: Overall 95% (22/23) - 9/9 (100%) DRV+COBI+F/TAF and 13/14 (93%) ATV+COBI+ F/TAF

  - Cohort 3: Overall 92.3% (24/26) – 11/11 (100%) DRV+COBI+F/TAF and 13/15 (87%) ATV+COBI+ F/TAF

- Week 48:
  - Cohort 2: Overall 100% (23/23) – 9/9 (100%) DRV+COBI+F/TAF and 14/14 (100%) ATV+COBI+F/TAF
  - Cohort 3: Overall 96% (25/26) – 10/11 (91%) DRV+COBI+F/TAF and 15/15 (100%) ATV+COBI+ F/TAF

Mean (SD) and median baseline and changes from baseline in CD4 cell count and CD4% were as follows (Table 8, Table 9).

Table 8: CD4 Change from Baseline - Cohort 2

Value	CD4 Baseline (cells/µL)	CD4 Week 24 change from baseline	CD4 Week 48 (change from baseline)	CD4% Baseline	CD4% Week 24 (change from baseline)	CD4% Week 48 (change from baseline)
ATV+COBI+F/TAF						
Mean	888	791 (-97)	845 (-43)	34.8	34.9 (+0.1)	37 (+2.2)
Median	808	741 (-67)	771 (-37)	35.9	35.8 (-0.1)	38.7 (+2.8)
DRV+COBI+F/TAF						
Mean	898	901 (+3)	907.5 (+9.5)	37	37.7 (+0.7)	38.3 (+1.3)
Median	929	843 (-86)	862 (-67)	36.2	39.8 (+3.6)	38 (+1.8)
Total Cohort						
Mean	892	835 (-57.4)	857.4 (-34.6)	35.7	36 (+0.3)	37.5 (+1.8)
Median	876	841 (-35)	771 (-105)	36.2	36.1 (-0.1)	38.4 (+2.2)

*Note patient withdrew from the study prior Week 48 and are not included in those calculations.

Table 9: CD4% Change from Baseline – Cohort 3

Value	CD4 Baseline (cells/µL)	CD4 Week 24 (change from baseline)	CD4 Week 48 (change from baseline)	CD4% Baseline	CD4% Week 24 (change from baseline)	CD4% Week 48 (change from baseline)
ATV+COBI+F/TAF						
Mean	787	840 (+56)	697 (-90)	32.6	35.9 (+3.9)	34.9 (+2.3)
Median	751	848 (+64)	661 (-90)	33.1	35.6 (+2.5)	37.4 (+3.5)
DRV+COBI+F/TAF						
Mean	1185	1044 (-146)	1111 (-122)	37.3	38 (+0.75)	38.5 (+1.45)
Median	1237	1014 (-223)	1108 (-129)	35.9	38.8 (+2.9)	37.6 (+1.7)
Total Cohort						
Mean	965	915 (-50)	917 (-48)	34.6	36.7 (+2.1)	36.4 (+1.8)
Median	959	843 (-116)	921 (-38)	34.8	37.3 (+2.5)	37.4 (+2.6)

Note: The reviewer's calculations yielded values that were slightly different than the study report but the differences were minor and not clinically significant.

Results of Secondary, Exploratory and Key Subgroup Analyses

Given the small sample size of the study, no subgroup analyses were conducted in this review.

Conclusions on Effectiveness

Overall, there were no concerning patterns noted in CD4 count during the 48-week analysis. The CD4 fluctuations are likely due to the small sample size and not deemed clinically significant. Given the small sample size, the study was not powered to determine efficacy; however, no concerns were noted in analysis of changes in CD4 count or HIV RNA through Week 48.

10. Safety

8.1 Methods

All ATV+COBI + F/TAF and DRV+COBI + F/TAF participants from Cohorts 2 and 3 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 26.1. 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.

Initially, the sNDAs included safety data through Week 24. However, prior to the filing the sNDAs, the review team noted the increased exposures of TAF and requested an updated report through Week 48 of the study. The findings below reflect our independent analysis of the submitted data. There may be slight differences in numerical values reported, but overall the findings are consistent with what the Applicant reported and is reflected in product labeling.

8.2 Major Safety Results

8.2.1 Deaths
There were no deaths reported.

8.2.2 Serious Adverse Events
Five SAEs occurred between the two cohorts. Table 10 below highlights the events.

Table 10: Serious Adverse Events

	Cohort 2		**Cohort 3**		**Total**	
	ATV+COBI +F/TAF	DRV+COBI +F/TAF	ATV+COBI +F/TAF	DRV+COBI +F/TAF	ATV+COBI +F/TAF	DRV+COBI +F/TAF
Total Number of AEs	33	18	68	43	101	61
Serious AEs						
Back pain	0	0	1	0	1	0
Hyperbilirubinemia	0	0	1	0	1	0
Jaundice	1	0	0	0	1	0
Lower Respiratory Tract Infection	0	0	1	0	1	0
Myositis	0	0	1	0	1	0

Two of the SAEs (40%) were related to elevation in bilirubin, and were the only SAEs determined to be related to the study drug. The other SAEs were determined to not be related to the study and resolved with symptomatic intervention.

Reviewer comment: I agree with the investigators assessment of causality and note all of the SAE events occurred in participants receiving ATV. While the majority of the SAEs were not related to study drug, hyperbilirubinemia is well established adverse event for ATV.

8.2.3 Discontinuations due to AEs
One participant prematurely discontinued the study drug due to an AE during the first 48 weeks of the study (Table 11). The AE leading to discontinuation of the study drug was related to abnormal bilirubin levels.

Table 11: Events Leading to Early Drug Discontinuation

Participant Age, Sex	Cohort	Arm	SAE	Description	AE Related?	Outcome
10 years Female	3	ATV+COBI +F/TAF	Hyperbilirubinemia	Grade 3 elevation in bilirubin on Day 14 (Tbili 6.6, grade 4) and elevated bilirubin again on Day 38	Yes	ATV + COBI withdrawn, then restarted on Day 38. ATV + COBI stopped again on Day 38. Bilirubin levels normal

8.2.4 Common AEs Through Week 48

Overall, most patients (N = 43, 87.8%) in both cohorts experienced AEs through Week 48 (Table 12). Twenty-four participants (82.8%) who received ATV+COBI + F/TAF experienced AEs, and 19 participants (95%) who received DRV+COBI + F/TAF experienced AEs. Collectively, the most common AEs were categorized under “infections and infestations” as well as “gastrointestinal disorders.”

Table 12: All Treatment Emergent Adverse Events Reported in >1 Participant Through Week 48

	Cohort 2		Cohort 3		Total	
	ATV+COBI + F/TAF (N=14)	**DRV+COBI + F/TAF (N=9)**	**ATV+COBI + F/TAF (N=15)**	**DRV+COBI + F/TAF (N=11)**	**ATV+COBI + F/TAF (N=29)**	**DRV+COBI + F/TAF (N=20)**
Total AEs	**12 (85.7)**	8 (88.9)	**12 (80.0)**	11 (100.0)	**24 (82.8)**	**19 (95.0)**
Upper respiratory tract infection	5 (35.7)	1 (11.1)	8 (53.3)	4 (36.4)	13 (44.8)	5 (25.0)
Vomiting	4 (28.6)	2 (22.2)	0	4 (36.4)	4 (13.8)	6 (30.0)
Hyperbilirubinaemia	2 (14.3)	0	3 (20.0)	0	5 (17.2)	0
Abdominal pain	0	1 (11.1)	2 (13.3)	1 (9.1)	2 (6.9)	2 (10.0)
Diarrhoea	0	1 (11.1)	1 (6.7)	2 (18.2)	1 (3.4)	3 (15.0)
Headache	0	2 (22.2)	1 (6.7)	1 (9.1)	1 (3.4)	3 (15.0)
Lower respiratory tract infection	0	1 (11.1)	2 (13.3)	1 (9.1)	2 (6.9)	2 (10.0)
Gastroenteritis	2 (14.3)	0	0	1 (9.1)	2 (6.9)	1 (5.0)
Nasopharyngitis	0	0	3 (20.0)	0	3 (10.3)	0
Neutropenia	1 (7.1)	1 (11.1)	1 (6.7)	0	2 (6.9)	1 (5.0)
Stomatitis	1 (7.1)	1 (11.1)	1 (6.7)	0	2 (6.9)	1 (5.0)
Tonsillitis	0	0	3 (20.0)	0	3 (10.3)	0
Abdominal pain upper	1 (7.1)	1 (11.1)	0	0	1 (3.4)	1 (5.0)
Body tinea	1 (7.1)	0	0	1 (9.1)	1 (3.4)	1 (5.0)
Dental caries	0	0	0	2 (18.2)	0	2 (10.0)
Iron deficiency anaemia	0	0	0	2 (18.2)	0	2 (10.0)

Mumps	0	0	1 (6.7)	1 (9.1)	1 (3.4)	1 (5.0)
Pharyngitis	1 (7.1)	0	1 (6.7)	0	2 (6.9)	0
Pneumonia	0	0	1 (6.7)	1 (9.1)	1 (3.4)	1 (5.0)
Pyrexia	0	0	2 (13.3)	0	2 (6.9)	0
Sinusitis	0	1 (11.1)	1 (6.7)	0	1 (3.4)	1 (5.0)
Tinea capitis	0	0	1 (6.7)	1 (9.1)	1 (3.4)	1 (5.0)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Table Section - Dataset: Adverse Events; Filter: SAFFL = 'Y', TRTEMFL = 'Y'.

Within each category and across both cohorts, the most common AEs were upper respiratory tract infections (URTIs), vomiting, and hyperbilirubinemia. Out of 49 patients, 18 (36.7%) reported URTIs, 10 (20.4%) reported vomiting, and 5 (10.2%) reported hyperbilirubinemia. Adverse events were comparable in both arms, with the exception of hyperbilirubinemia events. All of the hyperbilirubinemia events were attributed to ATV. Additionally, no Grade 4 AEs were reported (Table 13). All AEs were between Grade 1 and Grade 3, with the predominant being Grade 1.

Reviewer comment: No new safety findings or concerning patterns were noted in the adverse events reported during this review period, aside from noted AEs associated with use of ATV. Of note, there were additional AEs related to hyperbilirubinemia reported, such as "blood bilirubin abnormal" and "blood bilirubin increased" that would have increased the percentage of this AE to 14.2% (N=7).

Table 13: TEAEs by Severity-Toxicity Through Week 48

	ATV+COBI + F/TAF N = 29			DRV+COBI + F/TAF N = 20			Total N = 49		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any AE	12 (41.4)	8 (27.6)	4 (13.8)	13 (65.0)	6 (30.0)	0 (0.0)	25 (51.0)	14 (28.6)	4 (8.2)
Abdominal pain	1 (3.4)	0 (0.0)	1 (3.4)	2 (10.0)	0 (0.0)	0 (0.0)	3 (6.1)	0 (0.0)	1 (2.0)
Dental caries	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	2 (4.1)	0 (0.0)	0 (0.0)
Diarrhoea	1 (3.4)	0 (0.0)	0 (0.0)	2 (10.0)	1 (5.0)	0 (0.0)	3 (6.1)	1 (2.0)	0 (0.0)
Headache	1 (3.4)	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)	0 (0.0)	4 (8.2)	0 (0.0)	0 (0.0)
Iron deficiency anaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	2 (4.1)	0 (0.0)	0 (0.0)
Nasopharyngitis	3 (10.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.1)	0 (0.0)	0 (0.0)
Tonsillitis	3 (10.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.1)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	11 (37.9)	2 (6.9)	0 (0.0)	5 (25.0)	0 (0.0)	0 (0.0)	16 (32.7)	2 (4.1)	0 (0.0)
Vomiting	4 (13.8)	0 (0.0)	0 (0.0)	5 (25.0)	1 (5.0)	0 (0.0)	9 (18.4)	1 (2.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer. Adverse events missing severity/toxicity grades are not included in the above table.
Filters: TRT01A = "ATV/co + F/TAF" and COHORT = "Cohort 2" or "Cohort 3" and SAFFL = Y (ATV/co + F/TAF); TRT01A = "DRV/co + F/TAF" and COHORT = "Cohort 2" or "Cohort 3" and SAFFL = Y (DRV/co + F/TAF); TRT01A = "<BLANK>" or "ATV/co + F/TAF" or "DRV/co + F/TAF" and COHORT = "Cohort 2" or "Cohort 3" and SAFFL = Y (Total); TRTEMFL = "Y" and AETOXGRN = ("Grade 1", "Grade 2", or "Grade 3") (Adverse Events).
Percent threshold: Any Column ≥ 10%.

8.2.5: AEs Related To Study Drug

There were 17 participants who reported AEs that were related to study drug (**Table 14**). Eight (16.3%) of these were related to elevations in bilirubin, including hyperbilirubinemia, ocular icterus, and blood bilirubin increased or blood bilirubin abnormal.

Table 14: AEs Determined Related to Study Drug Through Week 48

	Cohort 2		Cohort 3		Total
	ATV+COBI + F/TAF (N=14)	DRV+COBI + F/TAF (N=9)	ATV+COBI + F/TAF (N=15)	DRV+COBI + F/TAF (N=11)	All Participants (N=49)
Participants Experiencing Drug-Related Adverse Event	5 (35.7)	3 (33.3)	4 (26.7)	5 (45.5)	17 (34.7)
Abdominal pain	0	0	0	1 (9.1)	1 (2)
Vomiting	1 (7.1)	2 (22.2)	0	2 (18.2)	5 (10.2)
Hyperbilirubinemia	2 (14.3)	0	3 (20.0)	0	5 (10.2)
Ocular icterus	1 (7.1)	0	0	0	1 (2)
Fungal skin infection	0	0	0	1 (9.1)	1 (2)
Upper respiratory tract infection	0	0	0	1 (9.1)	1 (2)
Blood bilirubin abnormal	0	0	1 (6.7)	0	1 (2)
Blood bilirubin increased	1 (7.1)	0	0	0	1 (2)
Headache	0	1 (11.1)	0	0	1 (2)

Reviewer comment: While the majority of reported related AEs are attributable to ATV use, the relationship of fungal skin infection and upper respiratory tract infection to DRV use is unclear.

8.2.6 AEs of Special Interest

Based on current labeling for each separate drug, the most common adverse events/adverse events of special interest would be the following:

- For DESCOVY(F/TAF), the most common adverse event reported in adult trials was nausea. This was reported in some participants in Trial 128 in both cohorts. No new AESIs were noted.

- For PREZISTA (DRV), drug-induced hepatitis has been reported with co-administration with ritonavir. The most common adverse reactions reported in adult trials with DRV were nausea, rash, diarrhea, headache, abdominal pain, and vomiting. DRV should not be given with other drugs that are highly dependent on CYP3A for clearance, and for which elevated plasma concentrations could lead to serious or life-threatening events. No events of hepatitis were reported. No new AESIs were identified and the AE profile in pediatric was consistent with adults.
- For REYATAZ (ATV), hyperbilirubinemia has been documented in most patients receiving ATV with resolution upon discontinuation. These findings were consistent in Trial 128 in participants receiving ATV.
- For TYBOST (COBI), administration is not recommended in patients who have an estimated creatinine clearance below 70 mL/min. There were no concerning renal abnormalities in Trial 128. The most common adverse drug reactions observed with TYBOST are jaundice and rash and occur when the drug is given with ATV. This is consistent with findings from the population receiving ATV in Trial 128.

Overall, the combined AE profile was consistent with known drug adverse events based on current product labeling. No new AESI's were identified through Week 48 or in the safety update.

8.3 Laboratory Findings

Clinical laboratory measurements were collected at different time points throughout the study. The sections below summarize the Week 48 (post baseline) Grade 3 and 4 laboratory abnormalities. There were no concerning graded increases in AST or ALT or in serum creatinine, or any labs related to kidney function. The most commonly reported Grade 3 and 4 laboratory abnormality was hyperbilirubinemia and associated with ATV use (Table 15). No cases of Hy's Law were observed. The hematologic laboratory abnormalities are shown below (Table 16). Most abnormalities were isolated and not clinically relevant.

Table 15: Proportion of Participants with Grade 3/4 Laboratory Abnormalities Above Baseline through week 48 – Chemistry

Parameter	Cohort 2 (n= 23)		Cohort 3 (n = 26)	
	ATV+COBI + F/TAF (n=14)	DRV+COBI + F/TAF (n=9)	ATV+COBI + F/TAF (n=15)	DRV+COBI + F/TAF (n=11)
Amylase				
Grade 4	0	0	3 (20%)	0
Grade 3	2 (14%)	2 (22%)	1 (7%)	0
Bilirubin – Hyperbilirubinemia				
Grade 4	2 (14%)	0	1 (7%)	0
Grade 3	7 (50%)	0	4 (27%)	0
Calcium Corrected for Albumin - Hypocalcemia				
Grade 3	0	1 (11%)	0	0
Magnesium - Hypomagnesemia				
Grade 4	0	1 (11%)	0	0
Grade 3	0	0	0	1 (9%)
Potassium - Hyperkalemia				
Grade 3	0	1 (11%)	0	1 (9%)

Note: Outside of the Week 48 study window, there were several Grade 3 and 4 laboratory abnormalities noted by the reviewer.

- Two participants in Cohort 3 (1 in DRV arm and 1 in ATV arm) had a Grade 4 increase in amylase after Week 48. Another participant in Cohort 2 had a Grade 3 elevation of amylase after the review cutoff date ((b) (6) , ATV). There were other participants ((b) (6)) who had the Grade 3 elevation of amylase continue past the safety cutoff date.
- Both participants in Cohort 2 (ATV arm) with Grade 4 hyperbilirubinemia continued to have elevated bilirubin past Week 48 ((b) (6) and (b) (6)), and 6 participants with Grade 3 elevation continued to have elevated bilirubin past Week 48 ((b) (6)). Additionally, 4 participants receiving ATV had Grade 3 hyperbilirubinemia after the Week 48 cutoff ((b) (6)).
- One participant had a Grade 3 elevation in AST and CK in week 132 ((b) (6)).

Reviewer comment: Several elevations in amylase (Grade 3 and 4) were noted in this analysis. All recorded elevations subsequently decreased while on study drugs. We note that while the levels did decrease, some remained elevated above normal. Some participants had elevated

amylase levels at baseline that remained elevated throughout the analysis period and are not included in this table. Elevation of amylase alone did not lead to any drug discontinuations.

Table 16: Proportion of Participants with Grade 3/4 Laboratory Abnormalities through Week 48 – Hematology

Parameter	Cohort 2 (n= 23)		Cohort 3 (n = 26)	
	ATV+COBI + F/TAF (n=14)	DRV+COBI + F/TAF (n=9)	ATV+COBI + F/TAF (n=15)	DRV+COBI + F/TAF (n=11)
Absolute Neutrophil Count Decreased				
Grade 4	1 (7%)	1 (11%)	0	0
Grade 3	2 (14%)	0	3 (20%)	0
Hematuria				
Grade 3	0	1 (11%)	0	0

Note: outside of the study window, there were 3 noted episodes of hematuria in participants. These occurred in females of menstruating age and were all attributed to menstruation.

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

8.3.3 Bone Mineral Density
Bone mineral density (BMD) was assessed by DXA scan. Overall, spine, total body and height BMD Z-score were increased relative to baseline throughout the study and through Week 48 and during the extension phase. Mean values increased overtime in each cohort. In cohort 2, at Week 48, the mean (SD) percentage increases in spine and TBLH BMD, respectively, were 6.49% (5.382%) and 6.10% (4.312%). In cohort 3, at Week 48, the mean (SD) percentage increases in spine and TBLH BMD, respectively, were 5.68% (5.345%) and 6.63% (3.905%). The label includes BMD data for those who received DRV+COBI + F/TAF.

Overall Assessment of Safety

No new or unexpected safety findings were noted and the adverse event profile and laboratory abnormalities were similar to those observed in adults and adolescents receiving similar drug regimens. The DRV and ATV exposures in pediatric participants weighing at least 14 kg to < 40 kg are similar to adults. However, the TAF exposures in participants receiving ATV in this study were significantly higher compared to adults. While there were not any new safety signals noted with the increased TAF exposures, limited safety data were available to support the increased TAF exposures in this pediatric population. Specifically, limited data from adults receiving higher TAF doses and insufficient pediatric data from other TAF products in the same age and weight range were available to support the higher exposures in this pediatric population. Therefore, use of ATV/COBI + TAF is not recommended.

11. Pediatrics

No new PMRs or PMCs are warranted. These sNDAs (1) partially address the PREA PMRs (3531-1 and 3533-1) to evaluate the the pharmacokinetics (PK), safety and antiviral activity of DESCOVY (emtricitabine and tenofovir alafenamide; FTC, TAF or F/TAF) administered in combination with atazanavir (ATV) and TYBOST (cobicistat, COBI), and in combination with darunavir (DRV) and TYBOST in HIV-1 infected pediatric subjects weighing less than 25 kg and (2) fulfil the PREA PMRs (3531-2 and 3533-2) to evaluate the PK, safety and antiviral activity of DESCOVY administered in combination with ATV and TYBOST, and in combination with DRV and TYBOST in HIV-1 infected pediatric subjects 6 to less than 12 years of age (weighing 25 kg to less than 35 kg).

12. Other Relevant Regulatory Issues

- *Financial disclosures*

Covered Clinical Study (Name and/or Number): GS-US-216-0128

Was a list of clinical investigators provided:	Yes X	No __ (Request list from Applicant)
Total number of investigators identified: 10 investigators and 38 subinvestigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/ arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No __ (Request explanation from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes	No __ (Request explanation from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes	No __ (Request explanation from Applicant)

The Applicant adequately examined financial disclosure information from all clinical investigators for the covered clinical trials, as recommended in the *Guidance for Industry: Financial Disclosure by Clinical Investigators*. The Applicant certified in Form FDA 3454 that, as the sponsor of the submitted studies, the Applicant has not entered into any financial arrangement with the listed clinical investigators (list was included in the submission) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Those investigators who are participating or have participated in the clinical trials and who have financial interest or arrangements as described in 21 CFR 54.4(a)(3) are noted in the above template. There are no investigators with a financial interest.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

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

The analytical site for measurement of PK samples ((b) (4)) was not inspected due to a recent favorable inspection of the site in (b) (4) (NDA 203094, OSIS review dated (b) (4)).

We requested inspections of the two highest enrolling sites, University of Zimbabwe Clinical Research Centre and Rahima Clinical Trials. At University of Zimbabwe Clinical Research Centre, a concern was identified regarding a protocol violation for not confirming a grade 3 laboratory abnormality within three days as required by the protocol. Grade 3 high bilirubin was observed in one participant with repeat testing done 12 days later. OSIS deferred to the review team regarding the safety of high bilirubin in this participant. At Rahima Clinical Trials, no concerns were identified (NDA 203094, OSIS review dated 5/8/2025).

Reviewer's comments: Participant GS-US-216-0128- (b) (6) *was in the ATV arm of cohort 2. As elevated bilirubin is an expected adverse event associated with ATV, we have no concerns over this event of grade 3 elevated bilirubin.*

13. Labeling

13.1 Descovy: The major labeling changes are described in this section

- Section 1 – INDICATIONS AND USAGE
  - Indication changed to reflect the lower weight band in certain patients. DESCOVY is indicated:
    - For the treatment of HIV-infection in pediatric patients weighing at least 14 kg to less than 35 kg in combination with other antiretroviral agents, including darunavir and cobicistat but not other protease inhibitors that require a CYP3A inhibitor
- Section 2 – DOSAGE AND ADMINISTRATION
  - A new table is included for the recommended dosage of DESCOVY based on weight for the new pediatric population as follows:

Body Weight (kg)	**DESCOVY Dosage**
25 kg to less than 35 kg	One tablet containing 200 mg of FTC and 25 mg of TAF taken orally once daily
14 kg to less than 25 kg	One tablet containing 120 mg of of FTC and 15 mg of TAF taken orally once daily

- Section 6 – ADVERSE REACTIONS
  - Section 6.1, Clinical Trials Experience
    - Addition of reference to the adverse reactions in Study 128 (DRV+COBI groups) regarding the safety profile of virologically suppressed pediatric patients between the ages of 6 to less than 12 years of age and weighing at least 25 kg (Cohort 2 - N=9) and virologically suppressed pediatric patients at least 2 years of age and weighing at least 14 kg to less than 25 kg (Cohort 3 - N=11). The safety profile of DESCOVY was similar to that in adults. The bone mineral density results are also included included.
    - (b) (4)
- Section 7– DRUG INTERACTIONS
  - Section 7.3: Established and Other Potentially Significant Interactions
    - Addition of a row in Table 6 for coadministration with ATV+COBI, stating coadministered use with DESCOVY in pediatric patients weighing 14 to <35 kg is not recommended.

    - Section 7.4: Drugs without Clinically Significant Interactions with DESCOVY
        - Previous language stated there is no clinically significant interaction between DESCOVY and ATV+COBI, which was revised to DESCOVY and ATV+COBI in those weighing ≥35 kg.
- Section 8 – USE IN SPECIFIC POPULATIONS
    - Section 8.2: Lactation
        - This section was updated to align with other approved HIV product USPIs, including, BIKTARVY and CABENUVA, regarding breastfeeding in women with HIV-1 infection. Animal lactation data was replaced with a statement regarding published data in humans, in alignment with PLLR and the approved BIKTARVY USPI (bictegravir, emtricitabine, and tenofovir alafenamide).
    - Section 8.4: Pediatric Use
        - This section was reorganized and updated to reflect the inclusion of pediatric patients weighing at least 14 kg to less than 35 kg and the data to support the use of DESCOVY in combination with other ARVs, including DRV+COBI, but no other protease inhibitors that require a CYP3A inhibitor. The rationale was included for not recommending use of DESCOVY with ATV+COBI in pediatric patients weighing at least 14 kg to less than 35 kg.
- Section 12 – CLINICAL PHARMACOLOGY
    - Section 12.3: Pharmacokinetics
        - Updated PK parameters of TAF following oral administration of DESCOVY with DRV+COBI in pediatric participants with HIV-1 and weighing 25 to less than 40 kg
        - Updated PK parameters of TAF following oral administration of DESCOVY with DRV+COBI in pediatric participants with HIV-1 and weighing 14 to less than 25 kg
- Section 14 – CLINICAL STUDIES
    - Section 14.1: Overview of Clinical Trials
        - Updated clinical trials table to reflect Trial 128 data through Week 48
    - Section 14.2: Clinical Trial Results in Pediatric Subjects with HIV-1 Infection
        - Cohort 2 and 3 from Study 128 are included to support the updated labeling. Similar to section 6, reference to those receiving ATV+COBI+F/TAF were not included because the use of this regimen is not recommended in pediatric patients at least 14 kg to less than 35 kg Labeling highlights that:
            - In Cohort 2 (ages 6 to < 12 years and weighing at least 25 to less than 40 kg), 100% (9/9) participants remained virologically suppressed at Week 48. Mean CD4+ cell count was 898 at baseline, with a change if 199 cells per mm3 and the mean (SD) change in CD4% was 1.26% at Week 48.
            - In Cohort 3 (minimum age 2 years and weighing at least 14 kg to <25 kg), 91% (10/11) remained virologically suppressed at Week

48. Mean CD4+ cell count was 1185 at baseline, with a change of 122 cells per mm3 and the mean (SD) change in CD4% was 1.45% at Week 48.

13.2 Tybost: the major labeling changes are described in this section

- Section 1 – INDICATIONS AND USAGE
  - Indication changed to reflect the lower weight band
    - TYBOST is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection in pediatric patients weighing at least 14 kg.
- Section 2 – DOSAGE AND ADMINISTRATION
  - A new table is included showing the recommended dosage of TYBOST based on weight for the new pediatric population as follows:

Body Weight	Atazanavir Dosage	TYBOST Dosage
Weighing at least 14 kg to less than 25 kg	200 mg orally once daily	90 mg orally once daily
Weighing at least 25 to less than 35 kg	200 mg orally once daily	150 mg orally once daily
Weighing at least 35 kg	300 mg orally once daily	

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	

    - A new section is included which highlights the differences in the 150 mg and 90 mg tablets
- Section 6 – ADVERSE REACTIONS
    - Section 6.1, Clinical Trials Experience
        - Addition of reference to pediatric patients 2 to less than 12 years of age (Cohort 2, virologically suppressed, N=9 with weight ≥25 but less than 40 kg and Cohort 3, virologically suppressed, N=11, virologically suppressed with weight ≥14 but less than 25 kg) who received DRV + COBI through Week 48.
- Section 7– DRUG INTERACTIONS
    - Section 7.3: Established and Other Potentially Significant Interactions
        - Addition of a row in Table 7 for coadministration with tenofovir alafenamide. For pediatric patients weighing ≥15 kg, there is no dose adjustment for use of DRV+COBI with TAF. For pediatric patients weighing 14 to <35 kg, use of ATV+COBI with TAF is not recommended.
        - Table 7 contains several recommendations in the clinical comment column for dose adjustments of TYBOST or coadministered drugs. Where specific dose recommendations were stated, the population (in all cases adults) was inconsistently specified. The language was revised to clarify that the dose recommendations refers to the adult dose.
- Section 8 – USE IN SPECIFIC POPULATIONS
    - Section 8.4: Pediatric Use
        - This section was reorganized and updated to reflect the inclusion of pediatric patients weighing at least 14 kg and the data to support the use of TYBOST and ATV or DRV. The rationale for not recommending use of TYBOST with TAF in pediatric patients weighing at least 14 kg to less than 35 kg was included.
- Section 12 – CLINICAL PHARMACOLOGY
    - Section 12.3: Pharmacokinetics
        - Updated PK parameters of Cobicistat, ATV, and DRV following oral administration of TYBOST with ATV or DRV in HIV-1 infected pediatric subjects weighing at least 14 kg.
    - Section 12.4: Microbiology
- Moving the clinical resistance text in pediatric patients to Section 14.2. Specifically one evaluable participant in Cohort 1 experienced virologic failure at Week 24 without significant emergent resistance associated substitutions in reverse transcriptase or protease.Section 14 – CLINICAL STUDIES
    - Section 14.2: Clinical Trial Results in HIV-1 Infected Virologically Suppressed Pediatric Subjects – Trial 128
        - Participants who received DRV in cohort 2 and 3 of Study GS-US-216-0128 are included to support the updated labeling. Labeling highlights that:

- In Cohort 2 (ages 6 to < 12 years and weighing at least 25 to less than 40 kg), 100% (9/9) participants remained virologically suppressed at Week 48. Mean CD4+ cell count was 898 at baseline, with a change if 199 cells per mm3 and the mean (SD) change in CD4% was 1.26% at Week 48.
- In Cohort 3 (minimum age 2 years and weighing at least 14 kg to <25 kg), 91% (10/11) remained virologically suppressed at Week 48. Mean CD4+ cell count was 1185 at baseline, with a change of 122 cells per mm3 and the mean (SD) change in CD4% was 1.45% at Week 48.

14. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

REMS for use in pediatric patients are not warranted.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The outstanding PMRs for DESCOVY and TYBOST will be replaced with new PMCs because both products have orphan designation for the treatment of HIV-1 infection in pediatric patients.

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

/s/

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