CLINICAL AND CROSS DISCIPLINE TEAM LEADER REVIEW

Date	August 13, 2019
From	Sarita Boyd, PharmD (Clinical Reviewer) Adam Sherwat, MD (Medical Team Leader)
Subject	Clinical and Cross Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 203094 S-13 (b) (4)
Applicant	Gilead Sciences, Inc.
Date of Submission	February 27, 2019
PDUFA Goal Date	August 27, 2019
Proprietary Name / Established (USAN) names	Tybost / cobicistat
Dosage forms / Strength	Film-coated tablet / 150 mg
Proposed Indication	Expansion of current indication to pediatric patients weighing at least 35 kg: TYBOST is a CYP3A inhibitor indicated (b) (4) in combination with other antiretroviral agents in the treatment of HIV-1 infection in adults **and pediatric patients weighing at least 35 kg.**
Proposed Dosing Regimen	Recommended Dosing Regimens in (b) (4) Pediatric Patients Weighing at Least 35 kg

Body Weight (kg)	**TYBOST Dosage**	**Coadministered Agent Dosage**
(b) (4)		
35 (b) (4) (b) (4)	150 mg once daily	Atazanavir 300 mg once daily (b) (4) (b) (4)

Recommended:	We recommend approval of cobicistat with atazanavir (S-13). (b) (4)

1. Introduction

This review summarizes the main issues for NDA 203094, [redacted] which the Applicant submitted to seek approval of cobicistat coadministered with atazanavir (ATV/c) [redacted] This review highlights the pharmacokinetic (PK), safety, and efficacy (antiviral activity) data in this age group from GS-US-216-0128 (Trial 128): *A Phase 2/3, Multicenter, Open-label, Multicohort, Two-Part Study Evaluating Pharmacokinetics (PK), Safety, and Efficacy of Cobicistat-boosted Atazanavir (ATV/co) or Cobicistat-boosted Darunavir (DRV/co), Administered with a Background Regimen (BR) in HIV-1 Infected, Treatment-Experienced, Virologically Suppressed Pediatric Subjects.*

2. Background

Tybost (cobicistat) 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 adults. Cobicistat 150 mg film-coated tablets dosed once daily with either ATV 300 once daily (in treatment-naïve or treatment-experience adults) or with DRV 800 mg once daily (in treatment-naïve or treatment-experienced adults with no DRV resistance-associated substitutions) was originally approved in September 2014. The approval of cobicistat allowed for an alternative to ritonavir for CYP3A inhibition of ATV or DRV.

Atazanavir coadministered with ritonavir (ATV/r) is approved in pediatric patients at least 3 months of age and weighing at least 5 kg. Darunavir coadministered with ritonavir (DRV/r) once daily is approved in pediatric patients at least 3 years of age and weighing at least 10 kg. At the time of Tybost approval, PREA PMRs were issued to develop cobicistat to match the respective age cutoffs for ATV/r and DRV/r, and a Written Request was issued to match the PREA PMRs. Trial 128 is an ongoing trial to satisfy the requirements outlined in the PREA PMRs and Written Request. This sNDA submission contains data from Trial 128 in adolescent patients 12 years of age and older along with the Applicant's proposed labeling update.

The pivotal data to support approval of ATV/c [redacted] for adolescent patients are the PK data rather than efficacy data. Extrapolation of efficacy for antiretroviral drugs such as ATV/c [redacted] 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). Additionally, cobicistat (with elvitegravir), ATV (with ritonavir), [redacted] have independently met the criteria for approval in adolescent patients. Therefore, the main issue is whether cobicistat adequately and safely increases [redacted] ATV exposures in the adolescent population consistent with that previously established in adults.

3. CMC/Device

The drug product used in the clinical trials submitted in the sNDA is identical to the product approved. The sNDA submission contains no new CMC information.

4. Nonclinical Pharmacology/Toxicology

The sNDA submission contains no new pharmacology/toxicology information.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Dr. Mario Sampson's clinical pharmacology review for full details. As previously mentioned, PK data provide the pivotal data to support approval of ATV/c (b) (4) for adolescent patients.

Mean cobicistat exposures, whether coadministered with ATV (b) (4), were similar or higher in adolescents (Trial 128) compared to historical adult data from the Tybost (cobicistat) program.

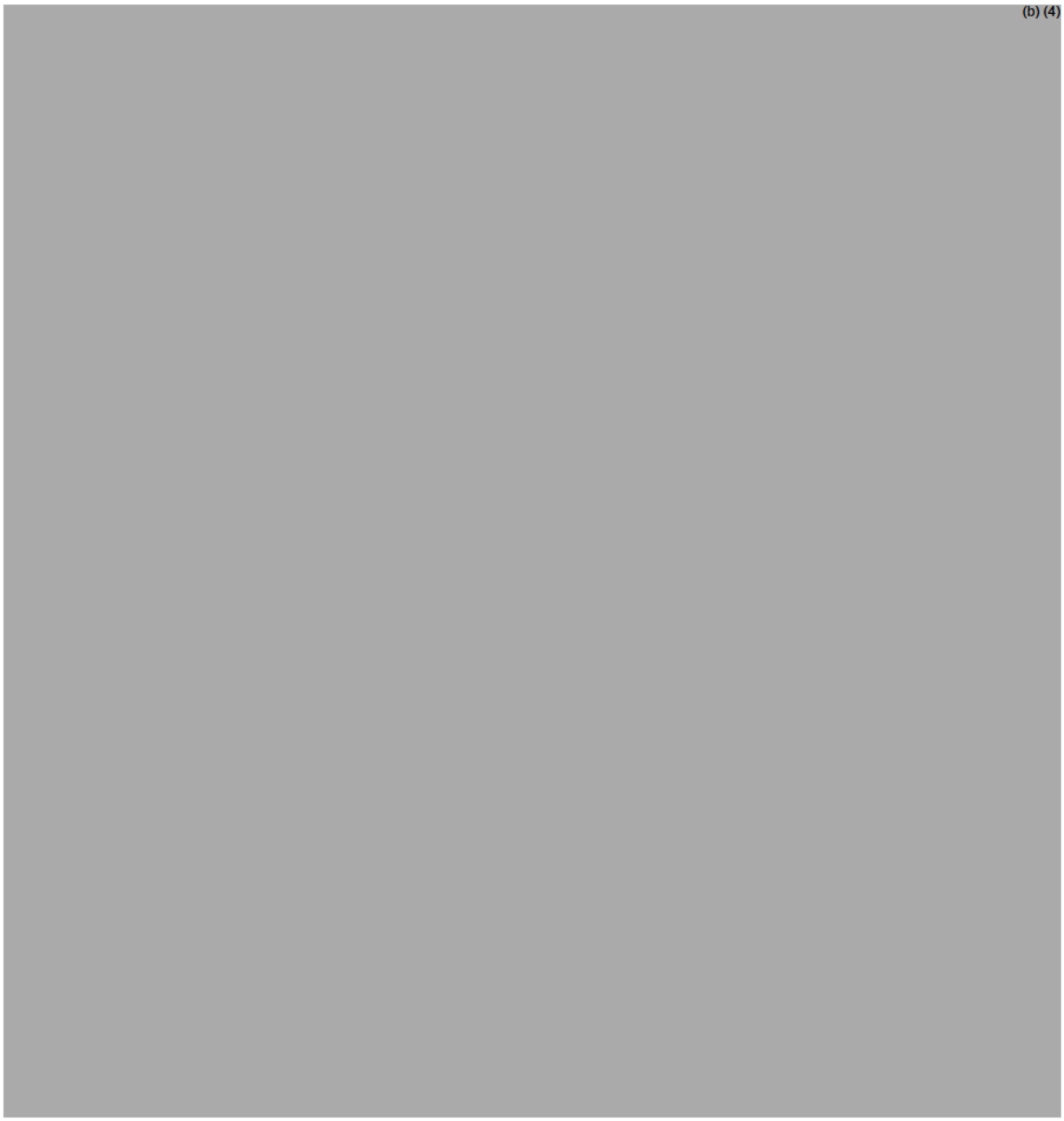
For ATV coadministered with cobicistat, the Applicant reported ATV maximum plasma concentrations (C_{max}), area under the concentration-time curve (AUC), and minimum plasma concentrations (C_{tau}) were approximately 24%, 29%, and 71% higher in adolescents (Trial 128) compared to adults (Trials GS-US-216-0105, GS-US-216-0114). This comparison included both participants in Trial 128 who weighed < 40 kg at baseline and received ATV 200 mg through Day 10. Excluding those two participants did not substantially alter the comparison; C_{max} and AUC were 22% and 21% higher, respectively, and C_{tau} was 92% higher in adolescents (n=12) compared to adults. The main exposure-safety concern is increased hyperbilirubinemia with increasing ATV exposures. The Applicant states the increase in ATV exposures with cobicistat in adolescents compared to adults is not clinically relevant because the exposures are similar to those observed when ATV is coadministered with ritonavir as referenced in the Reyataz (atazanavir) label. In addition, intra-individual ATV exposures in Trial 128 when coadministered with ritonavir (Day -1) or cobicistat (Day 10) were comparable (Table 1).

Table 1. Pharmacokinetic Parameter Estimates for ATV when Coadministered with Cobicistat Compared to Ritonavir in Adolescents: Trial 128

ATV PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	ATV/co Day 10 (Test, N = 14)	ATV/r Day -1 (Reference, N = 14)	
AUC_{tau} (h•ng/mL)	51654.40	52344.42	98.68 (83.31, 116.90)
C_{max} (ng/mL)	4375.00	4811.54	90.93 (75.01, 110.23)
C_{tau} (ng/mL)	986.68	1177.30	83.81 (53.01, 132.51)

GLSM = geometric least-squares mean
PK parameters for the test group were from Day 10 intensive PK assessment when ATV was boosted by COBI.
PK parameters for the reference group were from Day -1 intensive PK assessment when ATV was boosted by RTV.
Source: Table 15.10.1.5.1
Sponsor's Analysis; Source: Interim Clinical Study Report for GS-US-216-0128 (Trial 128)

Reviewer Comment: As stated in Dr. Sampson's review, AUC and C_{max} are of greatest concern regarding safety. We agree that the increases in ATV C_{max} and AUC, when coadministered with cobicistat, observed in adolescents compared to adults do not pose a significant safety risk. In the Reyataz label, ATV exposures when coadministered with ritonavir in multiple populations are variable and, in some cases, similar to those observed in adolescents. In addition, comparable ATV exposures with ritonavir or cobicistat in adolescents in Trial 128 is reassuring, and ATV coadministered with ritonavir is indicated in adolescents. Lastly, no new safety concerns were identified in adolescents in Trial 128 through Week 48 and, for some participants, beyond Week 48 (see Section 8 below). The high rate of indirect hyperbilirubinemia observed in adolescents was not unexpected, and these laboratory abnormalities were not associated with clinical events.



(b) (4)

6. Clinical/Statistical- Efficacy

Using the Applicant's SDTM and ADaM datasets, the primary clinical reviewer conducted all analyses presented in this section using JMP 14.0 and/or JReview 13.1.

6.1 Study Design

Trial 128 was a Phase 2/3 open-label, multicenter, multicohort, "switch" study to evaluate the PK, safety, and efficacy of ATV/c or DRV/c in HIV-infected virologically suppressed adolescent patients ages 12 years and older. Participants were on a stable antiretroviral regimen consisting of ATV or DRV, administered with ritonavir, and a background regimen. On Day 1, they were switched from ritonavir to cobicistat and continued ATV or DRV and the background regimen. Intensive PK sampling was collected on Day -1 (while taking ATV/r or DRV/r) and on Day 10 (after switching to ATV/c or DRV/c), and safety and antiviral activity were followed through Week 48. After Week 48, participants were eligible to enroll in a 5-year extension phase.

The primary objectives were as follows:

- To evaluate steady-state PK and confirm the dose of ATV/c or DRV/c
- To evaluate safety, tolerability, and efficacy of ATV/c or DRV/c, each coadministered with a background regimen, through Week 48

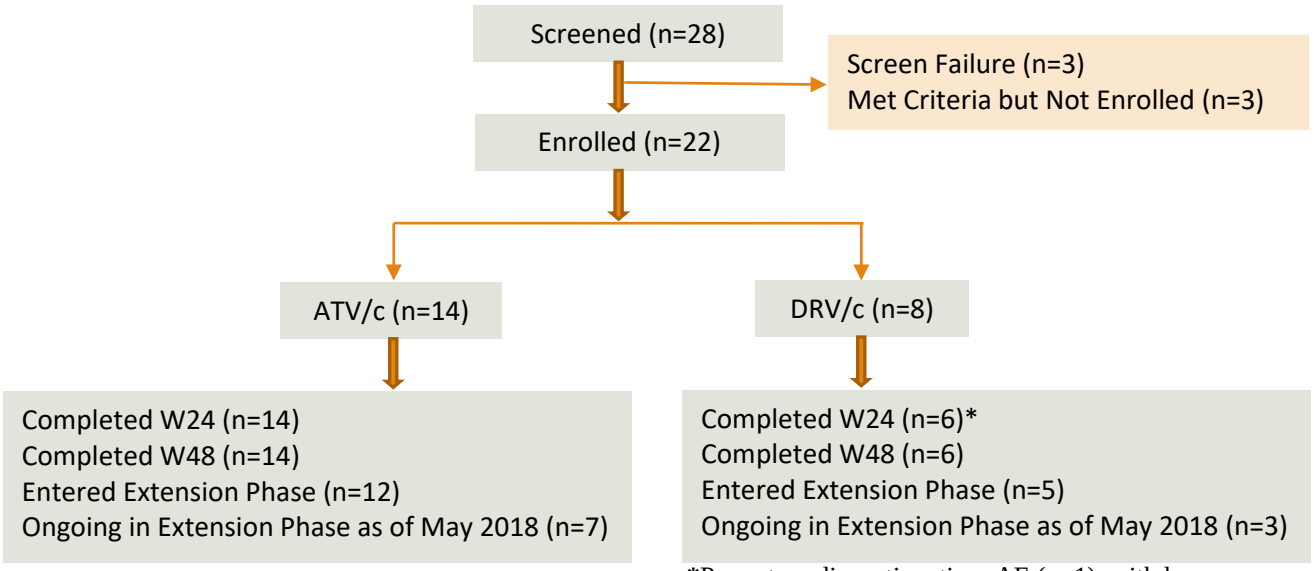
Key eligibility criteria were as follows:

- HIV-1 infected, treatment-experienced, virologically suppressed
- Cohort 1: Age 12 years to <18 years
- Cohort 1: Weight ≥ 25 kg
- eGFR (Schwartz formula) ≥ 90 mL/min/1.73m^2
- Prior to screening: HIV RNA undetectable per assay but not more than 75 copies/mL, ≥ 2 consecutive measurements obtained at least 4 weeks apart and one sample ≥ 3 months prior to screening
- At screening: HIV RNA <50 copies/mL and CD4 cell count ≥ 200 cells/mm^3
- Stable ARV regimen with 2 NRTIs + either ATV/r, DRV/r once daily, or DRV/r BID for ≥ 3 months
- For DRV participants, no history of DRV resistance-associated substitutions

6.2 Disposition

Figure 1 depicts the disposition of study participants.

Figure 1. Disposition: Trial 128



FDA Reviewer Analysis, ADSL, JReview 13.1

In the ATV/c group, two participants weighing <40 kg were enrolled, one weighing 30 to <35 kg and one weighing 35 to <40 kg. Both participants received ATV 200 mg, consistent with the Reyataz (atazanavir) label at the time of dosing. In May 2017, the dosing for ATV with ritonavir was updated from 200 mg to 300 mg for pediatric patients weighing at least 35 to <40 kg, and the Applicant is proposing (b) (4) dose for ATV with cobicistat in this submission. Because the Applicant adequately justified labeling of ATV 300 mg with cobicistat in patients

weighing at least 35 kg, we retained both participants in the efficacy analysis. The rationale for retaining both participants is that efficacy with a lower dose (200 mg) supports efficacy at a higher dose (300 mg). Additionally, the participant weighing <35 kg at baseline weighed 35 kg by Week 24, and the weight in both participants increased to 40 kg during the trial, at which time the ATV dose was increased to 300 mg.

6.3 Baseline Demographics and Disease Characteristics

Table 3 displays the baseline demographics and disease characteristics of participants in both treatment groups. Study sites were in the US and Thailand. The mode of infection in all participants was vertical transmission, and all participants tested negative for HBV surface antibody and HCV antibody. One participant in the ATV/c group had a baseline HIV RNA = 50 copies/mL. All participants across groups, except one in ATV/c group, had a baseline CD4 cell count >500 cells/mm^3.

Table 3. Baseline Demographics and Disease Characteristics: Trial 128

	ATV/c (n=14)	**DRV/c (n=7)**
Age, years		
Median (range)	14.3 (12-17)	14.4 (12-16)
Sex, n (%)		
Male	10 (71)	4 (57)
Female	4 (29)	3 (43)
Race, n (%)		
Asian	8 (57)	0
White	4 (29)	3 (43)
Black	2 (14)	2 (29)
Multi-Race	0	2 (29)
Weight, kg		
Median (range)	53 (32-81)	57 (45-78)
Baseline HIV RNA (copies/mL), n (%)		
< 50	13	7
≥ 50	1	0
CD4 cell count (cells/mm^3)		
Median (range)	770 (486-1765)	1117 (658-2416)
HIV Disease Status		
Asymptomatic	11 (79)	7 (100)
Symptomatic	1 (7)	0

	ATV/c (n=14)	DRV/c (n=7)
AIDS (historic diagnosis)	2 (14)	0

FDA Reviewer Analysis, ADSL, ASLB, ADEFFOUT, JMP 14.0 and JReview 13.1

6.4 Efficacy Results

This section focuses on the Week 48 virologic and immunologic results for Trial 128, which provide supportive evidence of efficacy. Additional supportive efficacy data from the extension phase are discussed, as applicable.

Virologic Outcomes

Table 4 displays the efficacy results for the ATV/c group using the FDA snapshot method. In this trial, virologic success represents maintenance of virologic suppression. Three of the four participants in the ATV/c group who met the criteria for virologic failure at Week 24 again achieved HIV RNA <50 copies/mL at Week 48. At Week 48 HIV RNA in one participant was 200 to <400 copies/mL, which met criteria for virologic failure. Overall, these results provide supportive evidence of efficacy for ATV/c with a background regimen in adolescent patients.

Table 4. Efficacy Analysis by FDA Snapshot Method: Trial 128, ATV/c

ATV/c (n=14)	Week 24 N (%)	Week 48 N (%)
Virologic Success: HIV-1 RNA <50 c/mL	9 (64)	13 (93)
Virologic Failure: HIV-1 RNA ≥50 c/mL	4 (29)	1 (7)
No Virologic Data	1 (7)	0

FDA Reviewer Analysis, ADLB, ADEFFOUT, JMP 14.0 and JReview 13.1

(b) (4)

Immunologic Outcomes

Table 7 and Table 8 show CD4 cell counts and change from baseline, respectively, through Week 48. In addition to the analyses shown in the tables, each participant was individually analyzed because of the large declines in some participants. CD4 percentage (not shown) at baseline, Week 24, and Week 48, as well as change from baseline at Week 24 and Week 48 were consistent with absolute CD4 cell count analyses in both groups.

Table 7. Median CD4 Cell Count: Trial 128

	ATV/c	
	N	**CD4 Cell Count (cells/mm^3), Median (Range)**
Screening	14	714 (495-1765)
Baseline	14	770 (486-1765)
Week 24	14	721 (384-1234)
Week 48	14	605 (473-1490)

(b) (4)

FDA Reviewer Analysis, ADLB, JMP 14.0 and JReview 13.1

Table 8. CD4 Cell Count, Median Change from Baseline: Trial 128

	ATV/c (n=14)
	CD4 Cell Count, Change from Baseline (cells/mm^3), Median (Range)
Week 24	-28 (-550, 449)
Week 48	-60 (-500, 705)

(b) (4)

(b) (4)

FDA Reviewer Analysis, ADLB, JMP 14.0 and JReview 13.1

In the ATV/c group, the change in CD4 cell counts in most participants either was relatively minimal (+/- 100 cells/mm^3; n=7) or substantially increased (+>500 cells/mm^3; n=2). Five of the 14 participants experienced a CD4 cell count decline of >200 to 500 cells/mm^3 at Week 48, but all remained >400 cells/mm^3 (three of whom remained >500 cells/mm^3).

(b) (4) the small sample size likely contributed to the wide variability. Overall, the changes in CD4 cell counts were not clinically meaningful in these participants, and ultimately, the totality of data do not support any trends.

7. Clinical Microbiology

Please refer to Dr. Anamaris Colberg Poley's virology review for full details. Virologic failure per protocol was defined as a confirmed rebound in HIV RNA to ≥ 400 copies/mL. However, the review team defines virologic failure as a rebound in HIV RNA to ≥ 50 copies/mL, consistent with the Division's approach for HIV treatment trials. Of the five virologic failures (HIV RNA ≥ 50 copies/mL) through Week 48, all in the ATV/c group, four were evaluable for resistance analysis (HIV RNA ≥ 400 copies/mL). However, genotypic and phenotypic test results were available for only one participant (USUBJID (b) (6)), who was taking ATV/c with lamivudine (3TC) and tenofovir disoproxil fumarate (TDF). No resistance-associated substitutions associated with reduced susceptibility to ATV, 3TC, or TDF emerged.

8. Safety

8.1 Overview and Methods

All participants in the full analysis set (n=22) of Trial 128 are included in the safety review. USUBJID (b) (6), who was excluded from the PK and efficacy analyses, was retained in the safety review because we deemed it important to discuss the AE leading to discontinuation. Using the Applicant's SDTM and ADaM datasets, the primary clinical reviewer conducted all safety analyses presented in this section using JReview 13.1, unless otherwise specified. Safety analyses were generally conducted separately for ATV/c and DRV/c, although the combined data were considered to elucidate any major trends. Presentation of ATV/c and DRV/c in separate columns in any table is not intended to be a comparison but rather for ease of display.

The term adverse event (AE) indicates the event occurred irrespective of causality. The term adverse drug reaction (ADR) indicates the AE was deemed at least possibly related to study drug by the investigator. The Applicant used MedDRA version 21.0 for coding. The primary

clinical reviewer verified that each verbatim AE term was appropriately coded to the respective preferred term (PT) using JMP 14.0.

Overall, the safety findings are consistent with those of the Applicant and generally consistent with adult safety findings from prior trials incorporated in existing labeling. Limitations of the safety review include low number of participants and lack of a comparator group for ATV/c or DRV/c.

Table 9 summarizes the major safety results from Trial 128 through Week 48 irrespective of causality.

Table 9. Safety Overview: Trial 128 through Week 48

	ATV/c (n=14)	DRV/c (n=8)
	N (%)	N (%)
Deaths	0	0
Discontinuation due to AE	0	1 (12.5)
Serious AE	3 (21)	2 (25)
Grade 3 or 4 AE	2 (14)	1 (12.5)

FDA Reviewer Analysis, ADAE, JReview 13 1

8.2 Deaths

No deaths were reported through Week 48 or in the extension phase.

8.3 Serious Adverse Events (SAEs) and Severe Adverse Events

Table 10 summarizes the five SAEs and three Grade 3-4 AEs (not mutually exclusive) that occurred in Trial 128 through Week 48. USUBJID (b) (6) experienced another SAE (foot fracture) in the extension phase; both fractures in this participant were a result of a motorcycle accident. The narrative for each SAE was reviewed, and no event appeared related to study treatment.

Table 10. Serious Adverse Events (SAEs) and/or Grade 3-4 AEs: Trial 128 through Week 48

USUBJID	Preferred Term	Related to Study Drug	Severity	Serious Event	Action Taken with Study Drug	Outcome of AE
ATV/c (n=14)						
(b) (6)	Appendicitis	Not related	Grade 2	Hospitalization	None	Resolved
	Clavicle fracture	Not related	Grade 2	Hospitalization	None	Resolved
	Substance abuse	Not related	Grade 3	Hospitalization	None	Resolved
	Wrist fracture	Not related	Grade 3	Not serious	None	Resolved

USUBJID	Preferred Term	Related to Study Drug	Severity	Serious Event	Action Taken with Study Drug	Outcome of AE
DRV/c (n=8)						
(b) (6)	Bipolar disorder	Not related	Grade 4	Life-threatening	None	Resolved
	Chest pain	Not related	Grade 2	Other serious	Discontinued	Resolved

FDA Reviewer Analysis, ADAE, JReview 13 1

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

One participant (USUBJID (b) (6) discontinued treatment due to an AE (chest pain) prior to Week 48 as shown in Table 8. A summary of the narrative is as follows:

The participant was a 12-year-old black male with a baseline weight of 37 kg and BMI of 16.7 kg/m^2 and history of hyperlipidemia and sleep apnea. On-study treatment consisted of DRV/c (600 mg/100 mg once daily) and abacavir/lamivudine, prior to which he received DRV/r and abacavir/lamivudine. At a study visit on Day 56, the participant reported chest pain for the prior two weeks. He was stable with a normal ECG, chest x-ray, and laboratory results. Cobicistat was discontinued, and the investigator originally deemed the event possibly related to cobicistat; the investigator later changed causality to not related. The participant was evaluated by a cardiologist, who reported normal ECG and echocardiogram results. Subsequently, it was reported that chest pain during exercise, lasting 2-3 minutes, associated with dizziness and occasional loss of consciousness ("blackout") had been ongoing for the past year. The event reportedly resolved approximately 17 days later, on Day 73, after albuterol was prescribed, and was subsequently referred to as non-cardiac chest pain. Several months after the initial report, based on additional cardiology follow-up visits and multiple ECGs, first-degree AV block was diagnosed and deemed unrelated to study drug (originally entered as "related" in error). Cardiology records three years later show the participant remained stable.

Reviewer Comment: The final investigator assessment that chest pain and first-degree AV block were unrelated to study drug are reasonable. The original onset of chest pain episodes preceded initiation of cobicistat, and the onset of first-degree AV block occurred several months after discontinuation of cobicistat. In addition, the biologic plausibility of cobicistat as a causal factor in this event is unclear given cobicistat's mechanism of action.

In the extension phase, one participant discontinued study treatment due to an AE of hyperlipidemia (Grade 2).

8.5 Treatment Emergent Adverse Events and Adverse Drug Reactions

No new safety concerns were identified based on a review of all AEs by system organ class (SOC) and/or PT. Because of the low number of participants in the trial, the relatively low frequency and severity of most AEs, and the specific AEs reported, this analysis focuses on

AEs deemed related by the investigator, or ADRs. Table 11 displays ADRs reported through Week 48. One additional ADR, hyperbilirubinemia, was reported in the extension phase. Most ADRs are currently labeled, or the general concept is labeled.

Table 11. Adverse Drug Reactions: Trial 128 through Week 48

Preferred Term	N (%)	Current Label
ATV/c (n=14)		
Vomiting	1 (7)	Yes
Proteinuria	1 (7)	Yes
Jaundice	1 (7)	Yes
Dyspepsia	1 (7)	Yes
DRV/c (n=8)		
Hyperlipidemia	2 (25)	Yes
Nausea	2 (25)	Yes
Decreased appetite	1 (12.5)	No

FDA Reviewer Analysis, ADAE, JReview 13 1

8.6 Laboratory Findings

No new safety concerns were identified based on a review of laboratory abnormalities through Week 48 or in the extension phase. Grade 3 total bilirubin elevation occurring in 8 of the 14 participants in the ATV/c group was the only cluster of major abnormalities identified in either treatment group. This abnormality reflects indirect hyperbilirubinemia, which is expected and adequately labeled.

Additional Grade 3 abnormalities included ALT increase, bicarbonate decrease, amylase increase, and fasting LDL increase, occurring in one participant each. None of these abnormalities were associated with a reported AE or led to discontinuation, and all abnormalities appeared transient. One Grade 4 abnormality (creatine kinase increase) occurred and was associated with myalgia. Creatine kinase (CK) temporarily normalized but then remained slightly above normal range from Weeks 32 to 108, after which the participant was discontinued at the investigator's discretion.

The changes in serum creatinine and estimated glomerular filtration rate (eGFR) were similar to changes observed in adult cobicistat trials. Notably, no participant experienced a graded increase in serum creatinine through Week 48.

8.7 Special Populations

8.7.1 Demographic Factors

The seven ADRs across both treatment groups occurred in either Asian, Black, or multi-racial participants, with none occurring in White participants. Differences by sex were not apparent.

However, interpretation of any differences or lack thereof is difficult due to the small sample size.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application.

10. Pediatrics

This application is in response to PREA PMR 3533-3, which had a final report submission deadline of January 2019.

3533-3
Conduct a study to evaluate the pharmacokinetics (PK), safety and antiviral activity of once daily atazanavir and cobicistat (ATV/COBI), and of once daily darunavir and cobicistat (DRV/COBI) combined with a background regimen in HIV-1 infected pediatric subjects weighing at least 35 kg. The safety and activity of ATV/COBI and of DRV/COBI must be assessed for a minimum of 24 weeks.

Reviewer Comment: (b) (4) *Otherwise, this PMR is fulfilled. The review team's assessment was presented to FDA's Pediatric Review Committee (PeRC) on July 24, 2019. The consensus was to issue a fulfilled letter for PMR 3533-3 for the following reasons: (1)* (b) (4) *(2) approval of this supplement will result in labeling for use in pediatric patients weighing at least 35 kg,* (b) (4) *for ATV/c; and (3) Trial 128 is ongoing to satisfy PMRs in lower weight bands, as specified below,* (b) (4) .

The following PREA PMRs for the remaining pediatric population remain outstanding with a final report submission deadline of April 2020.

3533-1
Conduct a study to evaluate the pharmacokinetics (PK), safety and antiviral activity of DESCOVY (emtricitabine and tenofovir alafenamide) administered in combination with atazanavir and TYBOST (cobicistat), and in combination with darunavir and TYBOST in HIV-1 infected pediatric subjects weighing less than 25 kg. The safety and activity of the treatment regimen must be assessed for a minimum of 24 weeks. The minimum age criteria for the treatment regimen being evaluated are specified below.

- DESCOVY administered in combination with atazanavir co-administered with TYBOST must be evaluated in pediatric patients 3 months of age and older

- DESCOVY administered in combination with darunavir co-administered with TYBOST must be evaluated in pediatric patients 3 years of age and older

3533-2
Conduct a study to evaluate the PK, safety and antiviral activity of DESCOVY administered in combination with atazanavir and TYBOST, and in combination with darunavir and TYBOST in HIV-1 infected pediatric subjects 6 to less than 12 years of age (weighing 25 kg to less than 35 kg). The safety and activity of the treatment regimen must be assessed for a minimum of 24 weeks.

- **Labeling**

INDICATIONS AND USAGE (1), DOSAGE AND ADMINISTRATION (2)

These sections were updated with the pediatric indication and dosing recommendations. Specifically, cobicistat may be coadministered with ATV in pediatric patients weighing at least 35 kg.

ADVERSE REACTIONS (6)

A general statement was added to reflect that safety findings from Trial 128 in adolescents were similar to that in adults.

USE IN SPECIAL POPULATIONS, Pediatric Use (8.4)

This section was updated to include the rationale for the pediatric indication and dosing recommendations for cobicistat with ATV.

CLINICAL PHARMACOLOGY, Pharmacokinetics (12.3)

ATV and cobicistat PK data from Trial 128 were added and compared to PK data from historical adult trials.

CLINICAL STUDIES (14)

Trial 128 study design, baseline demographics and characteristics, and efficacy results for the cobicistat with ATV group were added.

- **Recommendations/Risk Benefit Assessment**

  - Recommended Regulatory Action

Trial 128 PK, safety, and efficacy results through Week 48, along with adult data from prior trials support approval of cobicistat coadministered with ATV in pediatric patients weighing at least 35 kg. We recommend approval of Supplement 13 with the agreed upon labeling changes.

(b) (4)

- Benefit Risk Assessment

HIV pediatric trials are predominately single-arm, uncontrolled trials with the primary aim of showing PK parameters comparable to adults, providing at least 24 weeks of safety data, and demonstrating the activity of the drug is generally within the range observed for adults. The required data to support an indication in pediatric patients infected with HIV-1 are the PK and safety data. Efficacy data are considered supportive. The effectiveness in pediatrics is extrapolated based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adult and pediatric patients. Thus, the PK data are sufficient to extrapolate efficacy; that is, if the exposures achieved in pediatric trials are comparable to the effective exposures (AUC_{0-24}, C_{min}) from adult trials, the new drug may be presumed to be effective in the pediatric population.

The submission includes complete PK data demonstrating that cobicistat 150 mg with ATV 300 mg achieved exposures in adolescents within the targeted exposure range. The initial basis for dose selection for the weight band of ≥ 35 kg for ATV/c was the existing labeling for ATV/r, and dosing for this weight band was ultimately confirmed with available pediatric data from Trial 128. Thus, the Applicant has shown that the selected dose meets the trial's primary PK endpoint, and we conclude that efficacy for ATV/c can be extrapolated to the adolescent population with HIV-1 infection. The proportion of participants who maintained HIV-1 RNA <50 copies/mL at Week 48 was 93% (13/14) with ATV/c. Virologic failure (HIV RNA ≥ 50 copies/mL) at Week 48 occurred in only one participant. These results further support the effectiveness of ATV/c in pediatric patients weighing at least 35 kg.

The submission also includes complete safety data through Week 48 that suggests that ATV/c is generally safe and well-tolerated in adolescent participants. There were no deaths, related SAEs, related Grade 3 or higher clinical events, or discontinuations due to a related clinical event. No new or unique safety findings compared to adults were observed.

Overall, cobicistat coadministered with ATV has a favorable benefit-risk profile for the intended adolescent population.

- Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are required for this application.

- Recommendation for other Postmarketing Study Requirements

None

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