20 May 2021
EMA/CHMP/294308/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

EVOTAZ

International non-proprietary name: atazanavir / cobicistat

Procedure No. EMEA/H/C/003904/II/0038

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

%CV	percentage coefficient of variation
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ATV	atazanavir
ATV/co	atazanavir coadministered with cobicistat as individual components
ATV/COBI	atazanavir and cobicistat administered together as the fixed-dose tablet (Evotaz®)
ATV + COBI	atazanavir coadministered with cobicistat as individual components
ATV + RTV	atazanavir coadministered with ritonavir as individual components
AUCtau	area under the plasma/serum concentration versus time curve over the dosing interval
BMS	Bristol-Myers Squibb
BR	background regimen
CD4	cluster determinant 4
CFR	Code of Federal Regulations
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum observed plasma/serum concentration of drug
Cmin	minimum observed plasma/serum concentration of drug
COBI	cobicistat (Tybost®)
CSR	clinical study report
Ctau	observed drug concentration at the end of the dosing interval
CYP3A	cytochrome P450 3A
DRV	darunavir
DRV/COBI	darunavir and cobicistat administered together as the fixed-dose tablet (Rezolsta® in EU)
DRV + COBI	coadministration of darunavir and cobicistat as individual components
EC	European Commission
EC50	half maximal effective concentration
EU	European Union
GCP	Good Clinical Practice
Gilead	Gilead Sciences
GLSM	geometric least square mean
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
ICH	International Council for Harmonisation
IND	Investigational New Drug
INSTI	integrase strand transfer inhibitor
LPV	lopinavir
M = E Missing = Excluded	
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of subjects
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
PI	protease inhibitor
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
Q1	first quartile
Q3	third quartile
QD	once daily
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SUID	subject identification
TVD	Truvada® (emtricitabine/tenofovir)
US	United States
USFDA	United States Food and Drug Administration

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 26 August 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the use of EVOTAZ in combination with other antiretroviral agents in the treatment of HIV-1 infection in adolescent patients aged ≥ 12 to < 18 years, weighing ≥ 35 kg without known mutations associated with resistance to atazanavir; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Summary of Product Characteristics (SmPC) are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial corrections.

The variation requested amendments to the SmPC, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0009/2018 on the agreement of paediatric investigation plan (PIP).
At the time of submission of the application, the PIP P/0009/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Timetable	Actual dates
Submission date	26 August 2020
Start of procedure:	12 September 2020
CHMP Rapporteur Assessment Report	10 November 2020
PRAC Rapporteur Assessment Report	18 November 2020
PRAC members comments	18 November 2020
Updated PRAC Rapporteur Assessment Report	23 November 2020
PRAC Outcome	26 November 2020
CHMP members comments	30 November 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	4 December 2020
Request for supplementary information (RSI)	10 December 2020
CHMP Rapporteur Assessment Report	27 April 2021
Updated PRAC Rapporteur Assessment Report	28 April 2021
PRAC Outcome	6 May 2021
CHMP members comments	10 May 2021
Updated CHMP Rapporteur Assessment Report	14 May 2021
Opinion	20 May 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The MAH submitted a Type II variation to support the extension of indication to include the use of Evotaz (atazanavir (sulphate)/cobicistat) in combination with other antiretroviral agents in the treatment of HIV-1 infection in paediatric patients aged ≥ 12 to < 18 years, weighing ≥ 35 kg.

2.1.2. About the product

Atazanavir (ATV) is an azapeptide protease inhibitor (PI) of human immunodeficiency virus type-1 (HIV-1). The compound selectively inhibits processing of viral proteins in HIV-infected cells, thereby preventing the formation of mature virions and infection of other cells. ATV capsules (100, 150, 200 and 300 mg) and oral powder (50 mg), co-administered with low-dose ritonavir (RTV) are indicated in the European Union (EU), United States (US), and many countries worldwide for the treatment HIV-1 infection in adults and paediatric patients weighing at least 5 kg. In the US, ATV (400 mg QD) may also be administered without RTV in adults and paediatric patients who cannot tolerate RTV.

Cobicistat (COBI) is an inhibitor of cytochrome P-450 (CYP)3A enzymes and was developed for use as a

pharmacokinetic (PK) enhancer of PIs. COBI is a structural analogue of RTV and has no antiretroviral activity. In vitro, it has been shown to be a more specific mechanism based CYP3A inhibitor than RTV. The COBI 150 mg film-coated tablet (TYBOST) is available as a single agent in the US, EU, Canada, and Australia.

Evotaz [atazanavir/cobicistat (ATV/COBI)] is a fixed-dose combination (FDC) oral immediate-release film-coated tablet. The tablet contains 300 mg ATV and 150 mg COBI. It is indicated in the US, EU, and other countries for the treatment of HIV-1 infection in adults.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

A discussion on Environmental Risk Assessment (ERA) is however provided.

2.2.1. Environmental Risk Assessment

The present variation (type II) aims to modify the approved therapeutic indication for this medicinal product to include new target population: adolescents aged ≥ 12 to < 18 years, weighing at least 35 kg, for treatment of HIV-1. Consequently, the risk assessment to environmental compartments should be performed: the PEC value for both active substances atazanavir and cobicistat (based on prevalence data) should be calculated for the new population group and then summed to the previous PEC to reach the total PEC. This paediatric patient population (adolescents aged ≥ 12 to < 18 years, weighing at least 35 kg) was already considered in a previous EVOTAZ procedure (EMEA/H/C/003904/IB/002), where both atazanavir and cobicistat were shown not to present a risk to environment compartments.
Furthermore, the HIV cases are found overwhelmingly among adults. For example, in 2019, the adult (ages 15–49 years) HIV prevalence in Estonia was 0.9%. When adding in the paediatric population (ages 0–14 years), however, the HIV prevalence of the total population was 0.55% indicating that the prevalence actually decreases when the paediatric population is added. Additionally, there is limited availability of age-specific breakdowns in HIV prevalence.

Overall, considerations above were considered acceptable and satisfactory by the CHMP, thus no need to update the ERA.

2.2.2. Conclusion on the non-clinical aspects

In conclusion, this application of extension of indication to adolescents aged ≥ 12 to < 18 years, weighing at least 35 kg for this medicinal product in the treatment of HIV-1, does not lead to a significant increase in environmental exposure. Therefore, Evotaz (atazanavir/cobicistat) is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects by Treatment	Study Population/ Entry Criteria	Study Status; Type of Report
PK Efficacy and Safety	GS-US-216-0128	Primary objectives: • Evaluate the PK and confirm the dose of ATV + COBI or DRV + COBI administered with a BR through 48 weeks. • Evaluate the safety, tolerability, and efficacy of ATV + COBI or DRV + COBI administered with a BR through 48 weeks. Secondary objective: • Evaluate the safety, tolerability, and antiviral activity of long-term treatment of ATV + COBI or DRV + COBI administered with a background regimen	Phase 2/3, open-label, multicenter, multicohort, two-part study	Cohort 1: COBI 150 mg + ATV based on bodyweight **OR** COBI 150 mg + DRV based on bodyweight	48 weeks plus an additional 5 year, long-term extension	Planned: 100 Part A: 79 Part B: 21 subjects Analyzed (Cohort 1 Part A): 22 Intensive PK Analysis Set for COBI: 22 Intensive PK Analysis Set for ATV: 14 Intensive PK Analysis Set for DRV: 8 Subjects Still on Study Treatment: 10	HIV-1 infected, treatment-experienced (2 NTRIs and either ATV + RTV or DRV + RTV), virologically suppressed (HIV-1 RNA < 50 copies/mL) pediatric subjects aged 3 months to < 18 years Subjects divided into the following age cohorts: Cohort 1: 12 to < 18 years Cohort 2: 6 to < 12 years Cohort 3: 3 to < 6 years Cohort 4: 3 months to < 3 years	Study ongoing; Week 48 Interim CSR[10]; Cohort 1 Part A

ATV + COBI = atazanavir coadministered with cobicistat; ATV + RTV = ritonavir-boosted atazanavir; BR = background regimen; COBI = cobicistat; CSR = clinical study report; DRV + COBI = darunavir coadministered with cobicistat; DRV + RTV = ritonavir-boosted darunavir; HIV-1 = human immunodeficiency virus type 1; NRTIs = nucleoside reverse transcriptase inhibitors; PK = pharmacokinetic(s); RNA = ribonucleic acid

2.3.2. Pharmacokinetics

Study GS-US-216-0128

Title of Study: 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 Paediatric Subjects.

Study code: GS-US-216-0128

Study Sponsor: Gilead Sciences, Inc. (USA)

Study Period:

16 January 2014 (First Subject Screened)

30 May 2018 (Last Subject Observation for this Report)

Methodology:

A total of approximately 100 paediatric subjects, ages 3 months to < 18 years, of either sex are being enrolled sequentially in age-descending cohorts, divided into the age and weight cohorts as follows:

Part A:

A minimum of 79 subjects are planned to be enrolled to evaluate the steady state PK and confirm the dose of ATV/co and DRV/co.

Cohort #	Age	ATV/co	DRV/co
1	12 years to < 18 years old	n ≥ 14	n ≥ 7
2	6 years to <12 years old	n ≥ 14	n ≥ 8
3	3 years to < 6 years old	n ≥ 14	n ≥ 8
4	3 months to < 3 years	n ≥ 14	not applicable

Part B:

A minimum of 21 additional subjects are planned to be enrolled in Part B to evaluate the safety, tolerability, and efficacy of the ATV/co or DRV/co regimen.

Test Product, Dose, Mode of Administration:

Cohort 1 Part A: COBI 150 mg (administered as 75 mg x 2 tablets or 150 mg x 1 tablet) administered orally once-daily with food, in combination with DRV or ATV and a BR

Number of Subjects (Planned and Analysed):

Planned: 100 subjects

Analysed (by analysis set): For Interim Analysis 1, 22 subjects in Cohort 1 Part A received study drug. Numbers of subjects in the Safety, Full, PK, and Intensive PK Analysis Sets are shown for Cohort 1 Part A.

- All Enrolled Analysis Set: 22
- Safety Analysis Set: 22
- Full Analysis Set (FAS): 22
- PK Analysis Set: 22
- Intensive PK Analysis Set for COBI: 22
- Intensive PK Analysis Set for ATV: 14
- Intensive PK Analysis Set for DRV: 8

Pharmacokinetics:

An intensive PK evaluation was performed at Day -1 (for ATV or DRV), and Day 10 (for ATV or DRV and COBI) for subjects enrolled in Cohort 1 Part A. Intensive PK blood samples were collected at pre-dose and at 1, 2, 3, 4, 5, 8, and 12 hours post-dose on Day -1 (for ATV or DRV) and on Day 10 (for ATV or DRV and COBI).

The primary PK endpoint was the PK parameter of AUC_{tau} for ATV and DRV at Day 10. The secondary PK endpoints were the PK parameters of C_{tau}, C_{max}, and CL/F for ATV and DRV, and AUC_{tau}, C_{tau}, C_{max}, CL/F, and V_z/F for COBI at Day 10.

Sparse trough PK samples were collected at baseline (pre-dose) and 20 to 28 hours post-dose at Weeks 12, 24, and 48 for Cohort 1 Part A subjects.

Bioanalytical Methods:

Azatanavir

Determination of Azatanavir in Human Plasma was made by a validated LC-MS/MS method. This method was linear between 10 ng/mL and 5000 ng/mL. Dilution Integrity was determined with a concentration of 20000 ng/mL diluted 10-fold. Analysis of samples began on 13 Apr 2015 (date of first extraction) and concluded on 30 Jan 2017 (date of last injection). A total of 965 days transpired between the first sample collection date and the last extraction date; however, no more than 721 days transpired between any individual sample collection date and its corresponding extraction date. All study samples were analysed within the established long-term stability of 721 days at -70°C. The %CV of the QCs for atazanavir at 30, 800, and 4000 ng/mL ranged from 4.5% to 19.0% while %RE ranged from -2.8% to 6.5%. A total of 18 samples were re-assayed due to concentrations above the quantifiable limit.

Cobicistat

Determination of Cobicistat in Human Plasma was made by a validated LC-MS/MS method. This method was linear between 5 ng/mL and 2500 ng/mL. Dilution Integrity was determined with a concentration of 4000 ng/mL diluted 20-fold. Analysis of samples began on 29 Apr 2015 (date of first extraction) and concluded on 22 Feb 2017 (date of last injection). A total of 974 days transpired between the first sample collection date and the last extraction date. All study samples were analysed within the established long-term stability of 1297 days at -60°C to -80°C. The %CV of the QCs for GS-9350 at 15, 100, 1000, and 2000 ng/mL ranged from 5.2% to 113.0% while %RE ranged from -5.8% to 74.0%. The large %CV and %RE values are attributed to outliers for QC 15 and QC 100 in Run 11 that appear to have been inadvertently switched. Three samples were re-assayed because they were impacted by carryover and one sample was re-assayed due to a concentration above the quantifiable limit.

Statistical Methods:

Pharmacokinetic parameters for ATV boosted by ritonavir (RTV, r) on Day -1 and by COBI on Day 10, respectively, were summarized for all subjects in the Intensive PK Analysis Set by application of a nonlinear model using standard noncompartmental methods (WinNonlin software). Pharmacokinetic parameters for COBI were summarized similarly. Plasma concentrations for each analyte (Day -1 for ATV and Day 10 for ATV and COBI) were listed for all subjects and summarized by nominal time point for subjects in the Intensive PK Analysis Set.

To determine whether the respective exposure of ATV boosted by the adult dose of COBI (150 mg) in adolescents were similar to those in adults, statistical comparisons were performed to compare PK data from the current study with historical data in HIV-1 infected adults.

The precision around estimation of CL/F of ATV, which was examined to confirm appropriateness of the dose per protocol, was assessed by comparing the 95% CIs of the geometric mean estimates of each to the FDA-specified boundary of 60% to 140%. The precision around estimation of CL/F and V_z/F for COBI was also assessed.

A one-way analysis of variance (ANOVA) model was fitted to the natural logarithmic transformed values of AUC_{tau} (as the primary parameter) and C_{max} and C_{tau} (as the secondary parameters, if available) for ATV with treatment group as a fixed effect. The treatment groups were defined as the test treatment (adolescents in this study) and reference treatment (adults from the historical studies).

Exposure equivalency of COBI-boosted ATV versus RTV-boosted ATV was also evaluated. An ANOVA model was fitted to the natural logarithmic transformed values of AUC_{tau}, C_{max}, and C_{tau} for ATV with treatment group as a fixed effect. The treatment groups were defined as the test treatment (PI boosted by COBI) and reference treatment (PI boosted by RTV). The geometric least-squares mean (GLSM) of each treatment group, and the mean ratio (test/reference) and corresponding 90% CI for each PK parameter of the analytes was reported. For each analyte, 90% CIs for the ratio of the GLSMs of test (adolescents in this study) and reference (adults from historical studies) treatments were calculated for AUC_{tau}, C_{tau}, and C_{max}, consistent with the 2 one-sided tests each performed at an alpha level of 0.05.

Equivalency in PK would be concluded if the 90% CI were within the equivalence boundaries 70% to 143%.

Subject Disposition and Demographics:

Of the 28 screened subjects for Cohort 1 Part A, 22 were enrolled into the study and received at least 1 dose of study drug. Most subjects (63.6%) were male. Median age (range) was 14 (12 to 17) years. Overall, 36.4% of subjects were Asian and 31.8% of subjects were white, and 68.2% were not Hispanic or Latino. Median (Q1, Q3) baseline body weight and body weight Z-score were 52.7 (46.5, 63.3) kg and -0.10 (-0.58, 0.95), respectively; median (Q1, Q3) baseline height and height Z-score were 159.0 (152.0, 162.5) cm and -0.67 (-1.34, -0.38), respectively. Median (Q1, Q3) baseline body mass index (BMI) was 21.2 (18.8, 25.7) kg/m2, and median (Q1, Q3) body surface area (BSA) was 1.53 (1.41, 1.71) m2.

Pharmacokinetics Results:

In the intensive PK analysis, the steady-state PK of ATV, DRV, and COBI were evaluated in adolescents 12 to < 18 years of age (N = 14 for ATV, N = 8 for DRV) administered adult-strength COBI 150 mg with approved doses of ATV or DRV. While the protocol allowed enrolment of adolescents 12 to < 18 years, weighing ≥ 25 kg, only 1 subject in the COBI-boosted ATV group was < 35 kg. As such, the data presented support the use of COBI 150 mg with ATV or DRV in adolescents weighing ≥ 35 kg. The following figures reflect the mean plasma profiles following the coadministration of ATV + COBI and support the use of COBI 150 mg with ATV in adolescents weighing ≥ 35 kg.

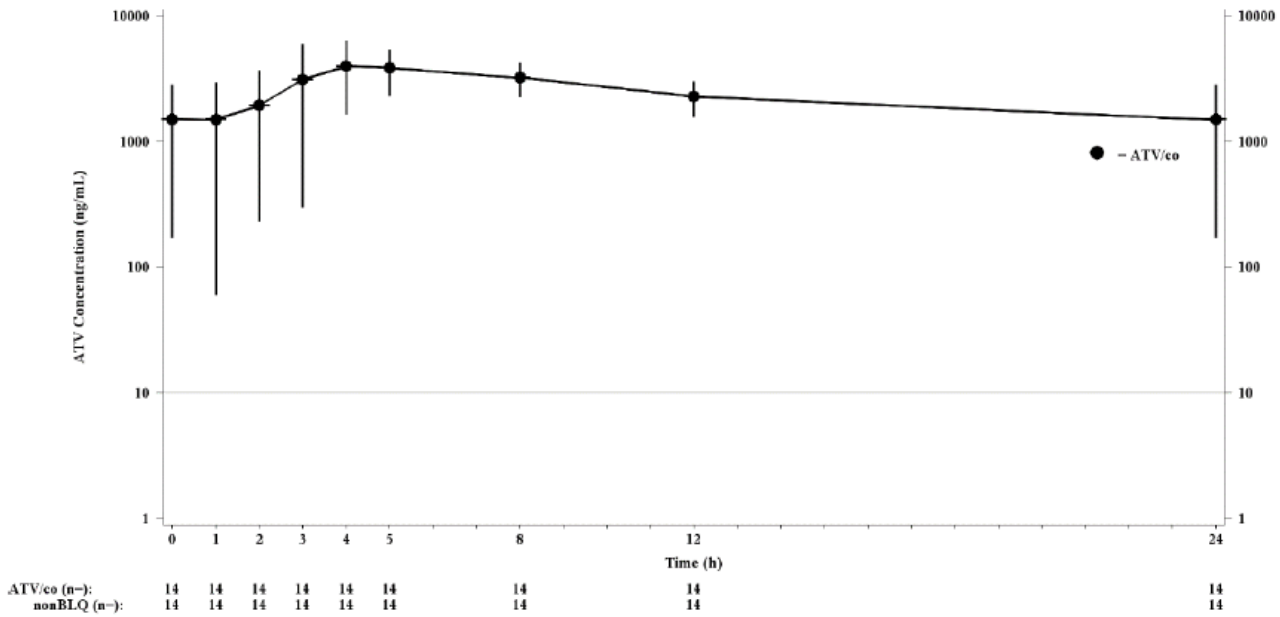
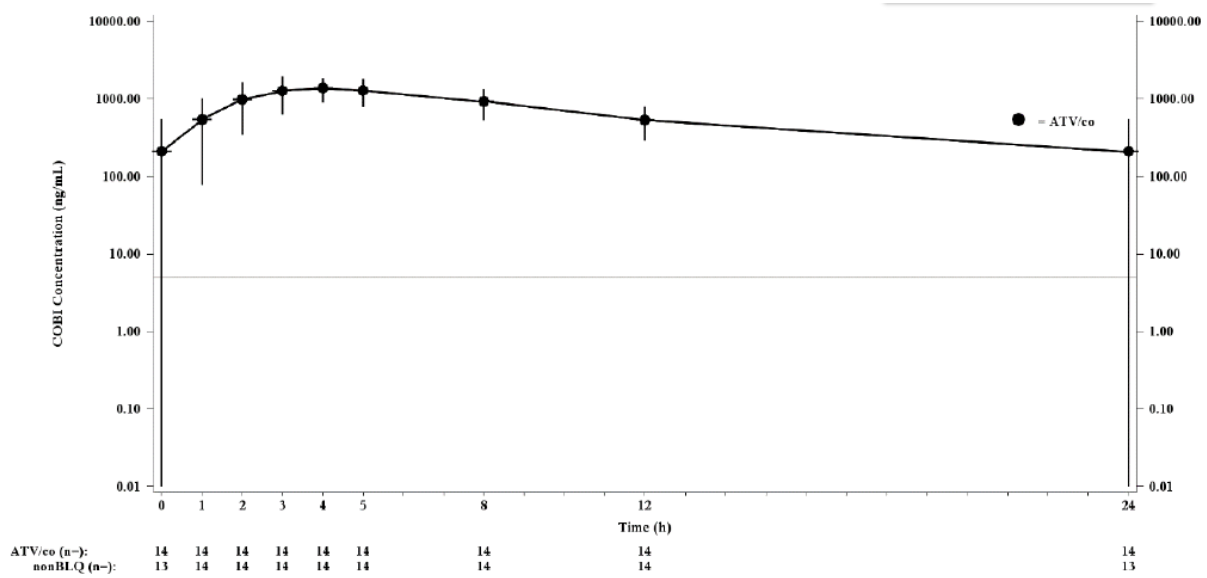


Figure . GS-US-216-0128: Mean (SD) Plasma Atazanavir Concentrations vs. Time (Semilogarithmic Scale), Cohort 1 Part A (Intensive PK Analysis Set for ATV [ATV Boosted by COBI])



Lower limit of quantitation (LLOQ) was defined as 5.0 ng/mL for analyte COBI.
Values below the lower limit of quantitation (BLQ) were treated as 0 for predose and 1/2 LLOQ for postdose summaries.
Solid reference line indicates LLOQ. Mean concentration values that were less than or equal to LLOQ are not displayed on the figure.

Figure . GS-US-216-0128: Mean (SD) Plasma Cobicistat Concentrations vs. Time (Semilogarithmic Scale) Following Administration of ATV/co, Cohort 1 Part A (Intensive PK Analysis Set for COBI)

Pharmacokinetics of Atazanavir in HIV-1 infected adolescents

Steady-state PK parameters for ATV following the administration of RTV-boosted ATV (ATV/r; Day -1) or ATV/co (Day 10) to virologically suppressed HIV-1 infected adolescents ≥35 kg are presented in the Table below.

ATV PK Parameter	Mean (%CV)[a]	
	ATV/co (Day 10) (N = 14)	ATV/r (Day -1) (N = 14)
AUC_{tau} (h•ng/mL)[b]	56523.2 (45.8)	57746.3 (51.2)
C_{max} (ng/mL)	4765.7 (46.0)	5295.7 (47.6)
C_{tau} (ng/mL)[b]	1512.5 (88.6)	1565.6 (94.5)
T_{max} (h)	4.50 (4.00, 5.00)	4.50 (3.00, 5.00)
$t_{1/2}$ (h)	8.29 (6.33, 28.85)[c]	12.87 (10.06, 17.55)[d]

a Median (Q1, Q3) for T_{max} and $t_{1/2}$
b Concentration at predose (0 hour) was used as surrogate for concentration at 24 hour for the purposes of estimating AUC_{tau} and C_{tau}.
c N=12
d N=11

ATV PK Parameter	CL/F (L/h) (N = 14)
Mean (%CV)	6.1 (49.3)
Geomean	5.5
95% CI/Geomean	0.751, 1.332

Geomean = geometric mean
PK parameters were from Day 10 intensive PK assessment when ATV was boosted by COBI.

Statistical Comparisons of Atazanavir Plasma PK Parameter Estimates Between Adolescents and Adults, Cohort 1 Part A (Intensive PK Analysis Set for ATV) are presented in the table below.

ATV PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	Adolescents in Study GS-US-216-0128 (Test, N = 14)	Adults in Studies GS-US- 216-0105, GS-US-216-0114 (Reference, N = 30)	
AUC_{tau} (h•ng/mL)	51654.40	39960.83	129.26 (100.99, 165.45)
C_{max} (ng/mL)	4375.00	3537.60	123.67 (97.93, 156.17)
C_{tau} (ng/mL)	986.68	576.46	171.16 (100.21, 292.34)

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 estimated from historical studies in HIV-infected adult subjects (ie, ATV/co + TVD-treated subjects) who participated in the intensive PK substudies in Studies GS-US-216-0105 and GS-US-216-0114.

Statistical Comparisons of Pharmacokinetic Parameter Estimates Between COBI-boosted ATV and RTV-boosted ATV in Adolescents, Cohort 1 Part A (Intensive PK Analysis Set for ATV) are presented in the table below.

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.

For ATV, AUC_{tau}, C_{max} and C_{tau} were 29%, 24% and 71% higher, respectively, in adolescents receiving COBI-boosted ATV compared to those observed in adults. With respect to exposures of ATV boosted by COBI compared to those boosted by RTV in these same adolescents, AUC_{tau}, and C_{max} were similar and C_{tau} was 16% lower with COBI relative to RTV. These differences were considered as without clinical concern, as they were similar to those observed following treatment with RTV-boosted ATV, which is approved for use in this population.

Pharmacokinetics of Cobicistat in HIV-1 infected adolescents

Steady-state PK parameters for COBI following the administration of ATV/co to virologically suppressed HIV-1 infected adolescents are presented in the table below.

COBI PK Parameter	Mean (%CV)[a]	
	ATV/co (Day 10) (N = 14)	DRV/co (Day 10) (N = 8)
AUC_{tau} (h•ng/mL)[b]	14851.9 (49.0)	9248.4 (34.3)
C_{max} (ng/mL)	1459.4 (35.7)	1121.4 (18.5)
C_{tau} (ng/mL)[b]	225.1 (145.4)	82.7 (85.6)
T_{max} (h)	4.00 (3.00, 4.00)	4.00 (4.00, 5.00)
$t_{1/2}$ (h)	4.40 (3.75, 5.45)	2.93 (2.45, 4.71)

a Median (Q1, Q3) for T_{max} and $t_{1/2}$

COBI PK Parameter	ATV/co	
	CL/F (L/h) (N = 14)	V_z/F (L) (N = 14)
Mean (%CV)	12.9 (60.6)	107.4 (70.2)
Geomean	11.3	90.9
95% CI/Geomean	0.742, 1.347	0.725, 1.380

From the interim analysis of Study GS-US-216-0128, it is concluded that no clinically relevant differences in ATV exposures with COBI 150 mg were observed in adolescents compared with adults from the Phase 3 populations, and exposures of COBI were within the safe and efficacious ranges associated with robust pharmacokinetic boosting in other products programs.

Absorption

No new information is submitted.

Distribution

No new information is submitted.

Elimination

No new information is submitted.

Dose proportionality and time dependencies

No new information is submitted.

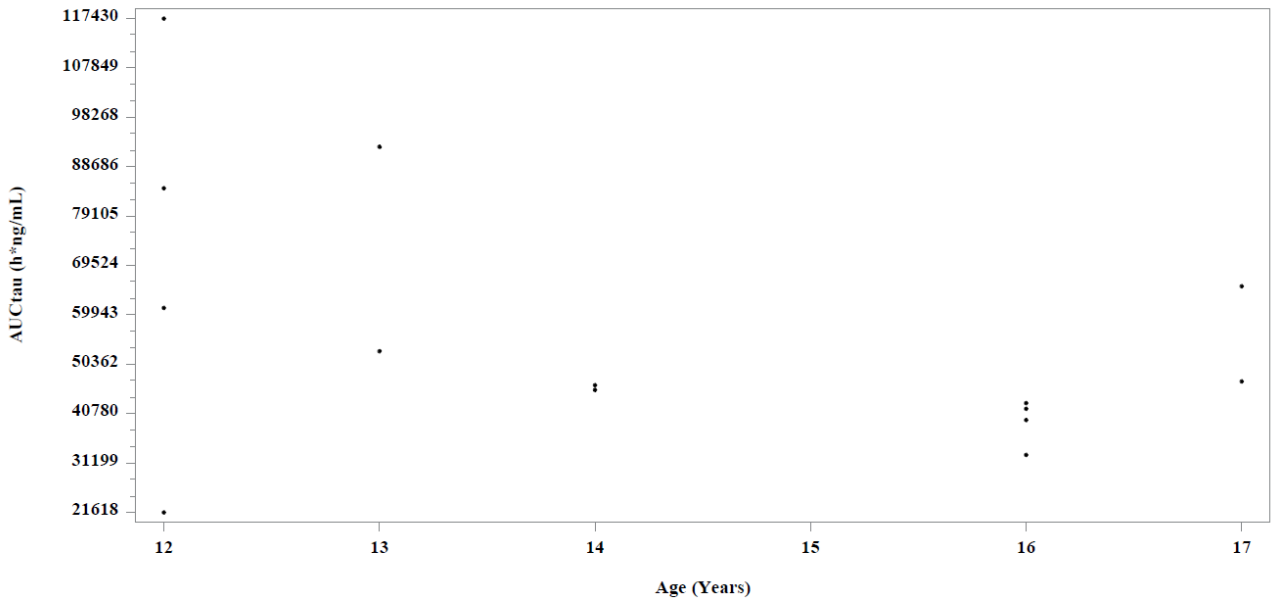
Special populations

Age

The impact of age on ATV and COBI PK was evaluated in adolescents 12 to < 18 years of age in Study GS-US-216-0128 through an Ad Hoc analysis, submitted after request on the first round of questions. Exposures of ATV and COBI versus baseline age in Cohort 1 Part A are shown in the following figures for AUC_{tau}.

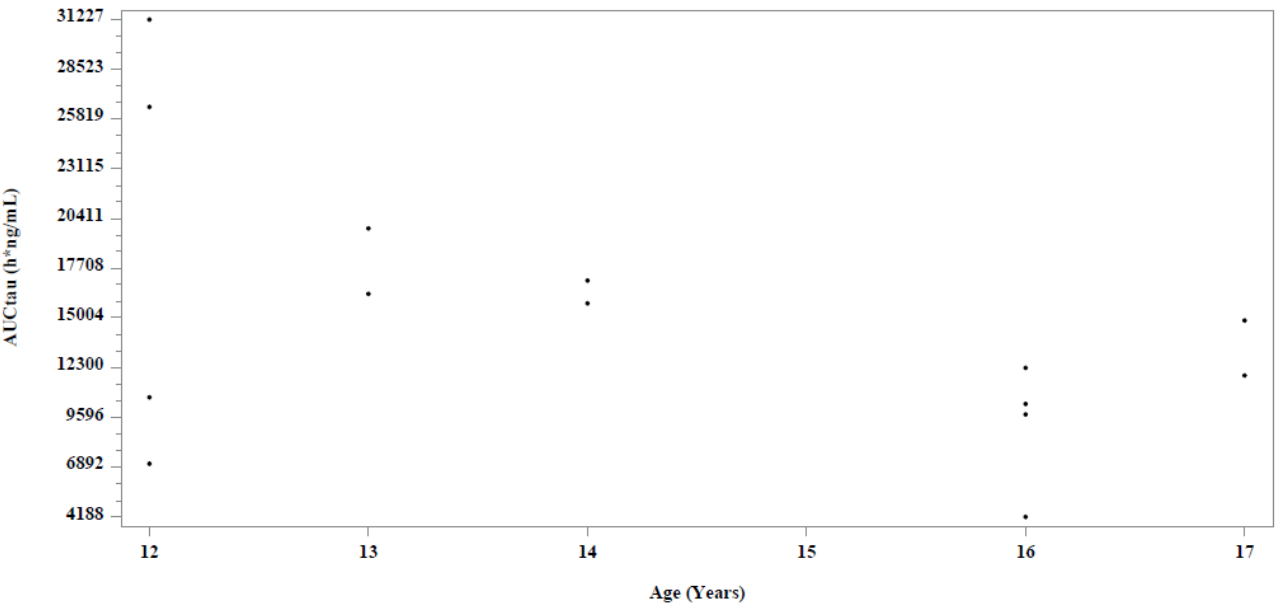
ATV - AUC_{tau}

Figure req10043.13: Scatter Plot of ATV AUCtau (Booosted by COBI) vs Baseline Age
Intensive PK Analysis Set for ATV
Study GS-US-216-0128 Cohort 1, Part A: Age 12 to < 18 Years



COBI - AUC_{tau}

Figure req10043.19: Scatter Plot of COBI AUCtau (Used with ATV) vs Baseline Age
Intensive PK Analysis Set for COBI
Study GS-US-216-0128 Cohort 1, Part A: Age 12 to < 18 Years

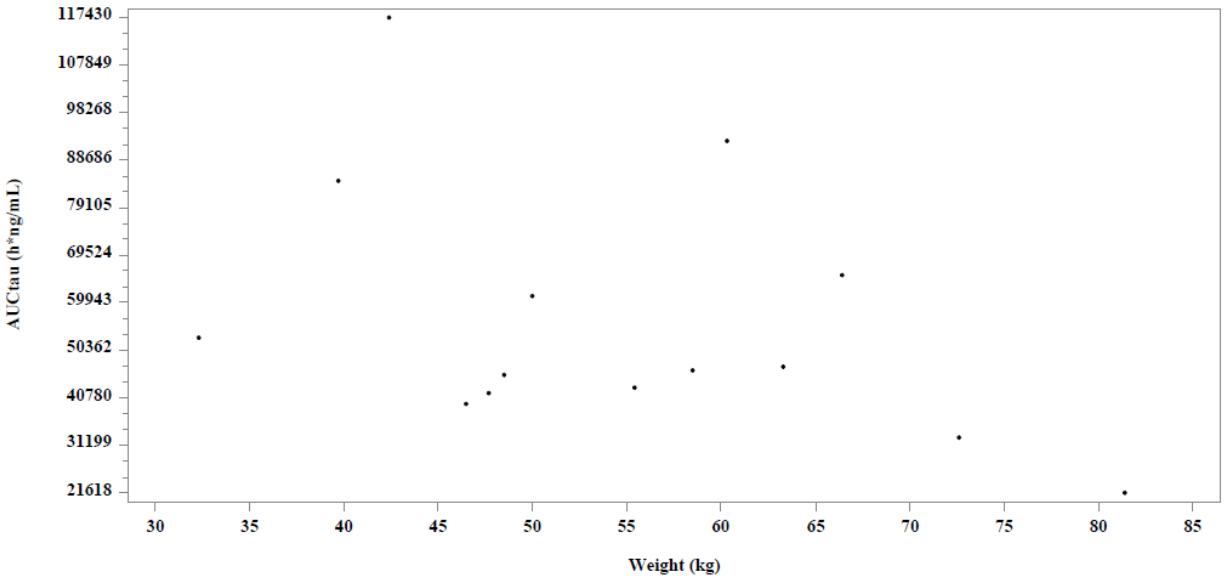


Body Weight

The impact of body weight on ATV and COBI PK was evaluated in paediatric subjects in Study GS-US-216-0128 with weight 32.3 to 81.4 kg through an Ad Hoc analysis, submitted after request on the first round of questions. Exposures of ATV and COBI versus baseline body weight in Cohort 1 Part A are shown in the following figures for AUC_{tau}..

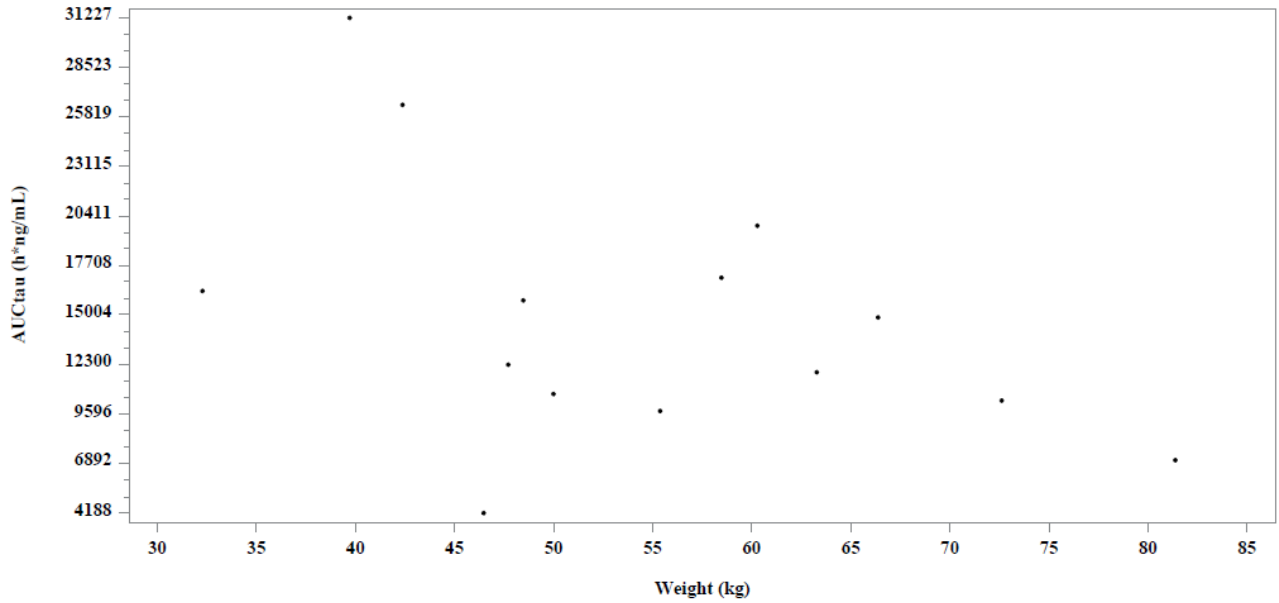
ATV - AUC_{tau}

Figure req10043.1: Scatter Plot of ATV AUCtau (Booosted by COBI) vs Baseline Weight
Intensive PK Analysis Set for ATV
Study GS-US-216-0128 Cohort 1, Part A: Age 12 to < 18 Years



COBI - AUC_{tau}

Figure req10043.7: Scatter Plot of COBI AUCtau (Used with ATV) vs Baseline Weight
Intensive PK Analysis Set for COBI
Study GS-US-216-0128 Cohort 1, Part A: Age 12 to < 18 Years



Pharmacokinetic interaction studies

Pharmacokinetics of Atazanavir in HIV-1 infected adolescents

Plasma exposures of ATV in adolescents weighing ≥ 35 kg receiving ATV/co were compared to intensive PK data from adult subjects receiving ATV/co in the Phase 2 and 3 Studies GS-US-216-0105 and GS-US-216-0114 (N = 30). All subjects received COBI 150 mg. The geometric least square mean (GLSM) ratio and associated 90% confidence intervals (CIs) for ATV AUC_{tau}, C_{max}, and C_{tau} were outside the 70% to 143% boundary and were 29%, 24%, and 71% higher, respectively, in adolescents receiving ATV/co compared to those observed in adults. With respect to exposures of ATV boosted by COBI compared to those boosted by RTV in these same adolescents, AUC_{tau}, and C_{max} were similar and C_{tau} was 16% lower with COBI relative to RTV.

Statistical Comparisons of Atazanavir Plasma PK Parameter Estimates Between Adolescents and Adults, Cohort 1 Part A (Intensive PK Analysis Set for ATV) are presented in the table below.

ATV PK Parameter	GLSM		%GLSM Ratio (90% CI) Test/Reference
	Adolescents in Study GS-US-216-0128 (Test, N = 14)	Adults in Studies GS-US- 216-0105, GS-US-216-0114 (Reference, N = 30)	
AUC_{tau} (h•ng/mL)	51654.40	39960.83	129.26 (100.99, 165.45)
C_{max} (ng/mL)	4375.00	3537.60	123.67 (97.93, 156.17)
C_{tau} (ng/mL)	986.68	576.46	171.16 (100.21, 292.34)

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 estimated from historical studies in HIV-infected adult subjects (ie, ATV/co + TVD-treated subjects) who participated in the intensive PK substudies in Studies GS-US-216-0105 and GS-US-216-0114.

Statistical Comparisons of Pharmacokinetic Parameter Estimates Between COBI-boosted ATV and RTV-boosted ATV in Adolescents, Cohort 1 Part A (Intensive PK Analysis Set for ATV) are presented in the table below.

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.

The differences between ATV/co treated adolescents and adults were not considered clinically relevant as ATV exposures in adolescents were within the safe and efficacious range of exposures observed historically in adults and paediatric patients treated with ATV/r, which is approved for use in this population (steady-state geometric mean of ATV AUC_{tau} in paediatric subgroups 5 to < 10 kg to ≥ 35 kg ranged from 32503 to 55687 ng*h/mL.

The lower ATV C_{tau} in adolescents with COBI relative to with RTV was not considered clinically important as mean ATV C_{tau} was higher compared to the ATV/co-treated adult historical control group and was > 100-fold above the protein-adjusted EC50 (ie, half maximal effective concentration) against wild-type HIV-1 virus (15 ng/mL) (Boffito 2011). Atazanavir AUC and C_{tau} boosted with COBI or RTV in adolescents in this study were higher than reported previously with ATV/r in paediatric patients ≥ 35 kg (steady-state geometric mean of AUC and C_{min} were 37643 h•ng/mL and 653 ng/mL, respectively. This was not considered clinically concern as these ATV exposures in adolescents with COBI or with RTV were within the safe and efficacious range of exposures observed historically in adults and paediatric patients, as noted above.

Pharmacokinetics of Cobicistat in HIV-1 infected adolescents

Plasma exposures of COBI in adolescents receiving ATV/co were compared to intensive PK data from subjects receiving ATV/co in the Phase 2 and 3 Studies GS-US-216-0105 and GS-US-216-0114 (N = 30).

In adolescents receiving ATV/co, COBI AUC_{tau} and C_{tau} were 37% and 181% higher, respectively, relative to adults (next Table). The C_{max} of COBI was similar in adolescents and adults; the %GLSM ratios and associated 90% CI were within 70% to 143%.

Statistical Comparisons of Cobicistat Plasma PK Parameter Estimates Between Paediatric Subjects (12 to < 18 years) and Adults Following Administration of COBI-boosted ATV, Cohort 1 Part A (Intensive PK Analysis Set for COBI) are presented in the table below.

COBI PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	Pediatric Subjects in Study GS-US-216-0128 (Test, N = 14)	Adults in Studies GS-US-216-0105, GS-US-216-0114 (Reference, N = 30)	
AUC_{tau} (h•ng/mL)[a]	14851.9 (49.0)	10558.8 (41.8)	137.17 (104.70, 179.71)
C_{max} (ng/mL)	1459.4 (35.7)	1368.4 (35.6)	107.14 (86.85, 132.17)
C_{tau} (ng/mL)[a]	225.1 (145.4)	52.5 (112.7)	281.21 (145.48, 543.57)

The higher COBI exposures (AUC_{tau} and C_{tau}) in adolescents relative to adults were not considered clinically relevant as they were within the range of exposures associated with robust pharmacokinetic boosting and safety established in the Tybost, Genvoya, and Stribild programs in adult and paediatric HIV patients.

Pharmacokinetics using human biomaterials

No new information was submitted.

2.3.3. Pharmacodynamics

The following topic describes the mechanism of action and primary pharmacology characteristics of atazanavir and cobicistat, as stated in the EPAR of the isolated active substances.

Mechanism of action

Atazanavir

Atazanavir (ATV) is a human immunodeficiency virus (HIV) protease inhibitor. It is an azapeptide that blocks the processing of viral gag-pol proteins in HIV-1 infected cells, thus preventing formation of mature virions.

Cobicistat

Tybost, cobicistat, COBI has been shown to inhibit the activity of human CYP3A enzymes (IC50 values 0.03 to 0.15 μM) and enzyme kinetic studies have demonstrated that it is an efficient inactivator of human CYP3A activity. The potency of the observed inhibition and inactivation was comparable to that observed with RTV and hence, the applicant has identified COBI as a mechanism-based inhibitor. The Applicant has provided evidence that the inhibition of CYP3A is time, NADPH and concentration dependent, which suggests that cobicistat is capable of mechanism-based inhibition. However, the Applicant states that the precise molecular mechanism of inhibition is not completely understood and that overall, the mechanism may be mixed.

Primary and secondary pharmacology

Atazanavir

Inhibition of HIV protease by ATV

Atazanavir inhibited the cleavage activity of HIV-RF protease with a Ki of 0.75 nM, which is comparable to the inhibitory activity of other protease inhibitors. Indinavir, nelfinavir, saquinavir, and ritonavir gave Ki values of 0.73 nM, 1.05 nM, 0.39 nM, and 1.01 nM, respectively, in this assay.

Atazanavir inhibited the cleavage of gag (p55) by HIV protease with an IC50 of 47 nM.

The cytotoxic concentration of ATV is 6500-23000 fold higher than IC and revealed a selective index comparable to other approved HIV protease inhibitor.

Antiviral activity of ATV in vitro

Experiments with wild type HIV laboratory strains have been performed in the absence and in the presence of 40 % of human serum to assess the antiviral activity of atazanavir.

In the absence of serum, comparative studies revealed that atazanavir (with an EC50 value of 2 – 5 nM) is 2- to 20-fold more active than other protease inhibitors including indinavir (IDV), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), and amprenavir (APV). The activity of atazanavir (EC50 values) against seven subtypes of group M and against a group O isolate varied by more than 10-fold. Activity against other subtypes of HIV-1 or against HIV-2 has not been explored.

In 40% human serum the atazanavir EC50 value increased from 1.5 nM to 7.8 nM (5-fold), similar to the other protease inhibitors but significantly less than nelfinavir (≥ 17-fold). The resulting atazanavir EC50 value is 3-to 19-fold lower than the EC50 of each of the approved protease inhibitors. Lopinavir/ritonavir was not tested. In 50% human serum the antiviral activity of lopinavir against HIV IIB in MT4 cells was 102+44 nM.

The two metabolites of ATV identified in the systemic circulation following administration of atazanavir to humans have no antiviral activity.

Cobicistat

CYP3A inhibition studies vs. RTV in human hepatic microsomes included established markers for activities of CYP3A enzymes as well as ATV, EVG and telaprevir. COBI was shown to be a strong inhibitor of all tested human hepatic microsomal CYP3A activities. The IC50 values for COBI and RTV were closely comparable. Kinetic parameters for COBI (kinact = 0.47 min-1, KI = 1.1 μM) were comparable to those of RTV (kinact = 0.23 min−1, KI = 0.26 μM).

The COBI IC50 for CYP2B6 was comparable with that for RTV while that for CYP2D6 was higher than for RTV.

Study in support of proposed variation

In support of the proposed variation, the MAH has provided with results from study GS-US-216-0128, a Phase 2/3, open label, multicenter, multicohort, two-part study composed of several cohorts with the primary objective of evaluation of PK and confirmation of the dose of ATV + COBI or DRV + COBI administered with a BR through 48 weeks, plus the evaluation of the safety, tolerability, and efficacy of ATV + COBI or DRV + COBI administered with a BR through 48 weeks.

The study population was HIV-1 infected, treatment-experienced (2 NTRIs and either ATV + RTV or DRV + RTV), virologically suppressed (HIV-1 RNA < 50 copies/mL) paediatric subjects aged 3 months to < 18 years and subjects were divided into the following age cohorts:

Cohort 1 - 12 to < 18 years

Cohort 2 - 6 to < 12 years

Cohort 3 - 3 to < 6 years

Cohort 4 - 3 months to < 3 years

Tabular Summary of Clinical Pharmacology Studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects by Treatment	Study Population/ Entry Criteria	Study Status; Type of Report
PK Efficacy and Safety	GS-US-216-0128	Primary objectives: • Evaluate the PK and confirm the dose of ATV + COBI or DRV + COBI administered with a BR through 48 weeks. • Evaluate the safety, tolerability, and efficacy of ATV + COBI or DRV + COBI administered with a BR through 48 weeks. Secondary objective: • Evaluate the safety, tolerability, and antiviral activity of long-term treatment of ATV + COBI or DRV + COBI administered with a background regimen	Phase 2/3, open-label, multicenter, multicohort, two-part study	Cohort 1: COBI 150 mg + ATV based on bodyweight **OR** COBI 150 mg + DRV based on bodyweight	48 weeks plus an additional 5 year, long-term extension	Planned: 100 Part A: 79 Part B: 21 subjects Analyzed (Cohort 1 Part A): 22 Intensive PK Analysis Set for COBI: 22 Intensive PK Analysis Set for ATV: 14 Intensive PK Analysis Set for DRV: 8 Subjects Still on Study Treatment: 10	HIV-1 infected, treatment-experienced (2 NTRIs and either ATV + RTV or DRV + RTV), virologically suppressed (HIV-1 RNA < 50 copies/mL) pediatric subjects aged 3 months to < 18 years Subjects divided into the following age cohorts: Cohort 1: 12 to < 18 years Cohort 2: 6 to < 12 years Cohort 3: 3 to < 6 years Cohort 4: 3 months to < 3 years	Study ongoing; Week 48 Interim 1 CSRCohort 1 Part A

ATV + COBI = atazanavir coadministered with cobicistat; ATV + RTV = ritonavir-boosted atazanavir; BR = background regimen; COBI = cobicistat; CSR = clinical study report; DRV + COBI = darunavir coadministered with cobicistat; DRV + RTV = ritonavir-boosted darunavir; HIV-1 = human immunodeficiency virus type 1; NRTIs = nucleoside reverse transcriptase inhibitors; PK = pharmacokinetic(s); RNA = ribonucleic acid

Clinical Virology data for Study GS-US-216-0128; ATV + COBI

Regarding clinical virology data for Study GS-US-216-0128, an interim analysis was performed, with resistance analyses being conducted on all subjects according to the Resistance Analysis Population (RAP), which was comprised of subjects who met prespecified virologic failure (VF) criteria and had HIV-1 RNA ≥ 400 copies/mL at the confirmation visit.

Pretreatment Virology Data was supported on HIV-1 historical genotypes with protease and reverse transcriptase data that were available for 13 of 14 subjects (92.9%) in Cohort 1 Part A. Pretreatment primary NNRTI associated resistance was observed in 2 of the 13 subjects, consisting of the K103N substitution in both subjects. Pretreatment primary NRTI-associated resistance substitutions were observed in 6 of the 13 subjects, consisting of M41L (3 subjects), D67N (2 subjects), K70R (2 subjects), L74I (1 subject), M184V (4 subjects), L210W (1 subject), T215F/Y (4 subjects), and K219E/Q (2 subjects). The HIV-1 subtype was determined for 9 of 13 subjects (69.0%) with pretreatment genotypic data. Among these 9 subjects, 7 had subtype B and 2 had subtype AE.

Virology Analyses in Subjects Experiencing Virologic Failure through Week 48 and Included in the Resistance Analysis Population are described as followed.

Of the 14 subjects in Cohort 1 Part A, 3 subjects (21.4%) receiving ATV + COBI met the VF and RAP inclusion criteria. Postbaseline genotypic and phenotypic data were obtained for 1 subject who had confirmed VF at the Week 24 retest visit with no relevant new resistance substitutions identified in PR or RT, and the subject subsequently re-suppressed to HIV-1 RNA < 50 copies/mL at Week 48 while continuing study drugs.

Postbaseline data were not available for the 2 remaining subjects in the RAP, who both experienced confirmed VF at Week 48, but had assay failures due to low viral load (HIV-1 RNA was 771 copies/mL) or insufficient sample volume for testing. The subject with 771 copies/mL of HIV-1 RNA at confirmed VF subsequently re-suppressed at the Week 48 retest visit and had HIV-1 RNA < 50 copies/mL by the US FDA-defined snapshot algorithm. The other subject remained viremic at their Week 48 retest visit (HIV-1 RNA ≥ 50 copies/mL by snapshot analysis). Transient viremia and the absence of treatment-emergent resistance after virologic failure suggest nonadherence to study drugs.

Pharmacodynamic/Efficacy Endpoints

Based on efficacy analyses at Week 24 and Week 48 using the USFDA defined snapshot algorithm, the rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were 64.3% at Week 24 and 92.9% at Week 48 for ATV + COBI, and high rates of virologic suppression were maintained beyond Week 48. There were no clinically relevant changes in CD4 cell counts and CD4%. No subjects developed treatment-emergent drug resistance substitutions in protease or reverse transcriptase.

2.3.4. PK/PD modelling

In this study, no PK/PD modelling was performed. A detailed PK analysis was performed in this study and is discussed in more detailed in the Pharmacokinetics section.

2.3.5. Discussion on clinical pharmacology

Pharmacodynamics

Based on efficacy analyses at Week 24 and Week 48 using the USFDA defined snapshot algorithm, the rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were 64.3% at Week 24 and 92.9% at Week 48 for ATV + COBI, and high rates of virologic suppression were maintained beyond Week 48. There were no clinically relevant changes in CD4 cell counts and CD4%. No subjects developed treatment-emergent drug resistance substitutions in protease or reverse transcriptase.

For those who received ATV + COBI the Resistance Analysis Population contained 3 subjects in Cohort 1 Part A who experienced protocol-defined virologic failure during the first 48 weeks of the study. Post-baseline genotypic and phenotypic data were available for 1 subject and showed no resistance in protease or reverse transcriptase. The other 2 subjects had no postbaseline data due to assay failure. Transient viremia in the absence of treatment-emergent resistance after virologic failure suggests intermittent nonadherence to daily study drug dosing or administration.

No clinically relevant differences in ATV exposures with COBI 150 mg were observed in HIV-1-infected, virologically suppressed paediatric subjects weighing ≥ 35 kg compared with either treatment-naïve or treatment-experienced adults from the Phase 3 study populations. Likewise, the exposures of COBI were within the safe and efficacious ranges and were associated with robust pharmacokinetic boosting, as observed in other cobicistat-containing programs. In addition, results from PK studies have shown that the exposure of ATV 300 mg with COBI 150 mg is consistent with exposure of ATV 300 mg when

coadministered with RTV 100 mg. As such, the PK, efficacy, safety, and acceptability/palatability data support the use of COBI 150 mg-boosted ATV 300 mg, including the bioequivalent fixed-dose product Evotaz, in HIV-1 infected paediatric patients weighing ≥ 35 kg.

Pharmacokinetics

Clinical Study GS-US-216-0128 is an ongoing study wherethe PK of the combination of Cobicistat-boosted Atazanavir (ATV/co) or Cobicistat-boosted Darunavir were studied. In this study, the overall age range includes subjects from 3 months to < 18 years of age, who are enrolled sequentially in age-descending cohorts, divided into the age and weight cohorts. The current cohort considers only HIV-1 infected adolescent subjects aged 12 years and older. Although no weight limitations were considered, only one subject had less than 35kg and, so, this application is concerning only subjects weighing at least 35 kg.

Therefore, the CHMP considers this application applicable only to subjects weighing at least 35 kg.

This study allowed to directly compare DRV and ATV boosted by Ritonavir (day -1) and by Cobicistat (Day 10) and indirectly with historical data on the adult population. A rich sampling was collected on days -1 and 10 of the trial. Sparse sampling was also performed on latter days. For the above sample size computations, inter-subject standard deviations of 0.38 h•ng/mL for ATV AUC_{tau} (based on 64 adult subjects in Studies GS-US-216-0110, GS-US-216-0114, and GS-US-216-0105 combined) and of 0.3 h•ng/mL for DRV AUC_{tau} (based on population PK data from 298 adult subjects in Study GS-US-216-0130), respectively, were used in the computation. It was assumed that equivalent assessments were to be conducted using two 1-sided t-tests each at 0.05 alpha levels, and equivalence boundaries of 70% to 143% were applied. Bioanalysis on DRV, ATV and COBI was made by HPLC-MSMS validated methods. The PK analysis was made by standard non-compartmental methods using WinNonlin. Statistical analysis is also based on standard comparisons by ways of ANOVA.

Considering the several plots of PK exposure parameters vs age for ATV and COBI, CHMP agreed that age between 12 and 18 years did not have a clinically meaningful impact on the exposure of both drugs. This is consistent with historical paediatric data of ATV with RTV, and of COBI within the fixed-dosed combination Genvoya and Stribild.

Based on the several plots of the PK exposure parameters vs weight for ATV and COBI, a trend with exposure and body weight was observed for all analytes. This trend follows historical paediatric data of ATV with RTV, and of COBI within Genvoya and Stribild. Therefore, the CHMP agreed that no dose adjustment is considered needed as the exposures of ATV and COBI in adolescents are within the range of adult exposures associated with safety and efficacy.

The CHMP committee observed a higher ATV exposure of the paediatric population when compared with the adult historical data. However, in the day -1 to Day 10 comparison (ATV/r vs ATC/co), similarity was observed in AUC_{tau} and C_{max}. A slightly 16% lower C_{tau} was observed in adolescents with COBI relative to with RTV. This is, however, above the historical data on adults.

In adolescents receiving ATV/co or DRV/co, COBI exposure (AUC_{tau} and C_{tau}) were higher relative to adults. The Cmax of COBI was similar in adolescents and adults in both treatment arms. This is similar to what was observed in children taking GENVOYA® (with even higher GLSM AUC_{tau}, but slightly lower GLSM C_{tau}). The range of observed values is within the range of safety exposures associated with other robust pharmacokinetic COBI containing medicines programs in adult and paediatric HIV patient. Therefore, the CHMP committee agreed that this does not raise a clinical concern.

Adolescents aged 12 to <18 and weighing ≥ 25 kg enrolled in Cohort 1 Part A of this study had intensive PK samples collected over 12 hours post-dose on Day 10. Plasma concentrations of COBI at pre-dose (0 hours) on day 10 were used as a surrogate for the concentrations at 24 hours (end of the dosing interval) for the purposes of estimating AUC_{tau} and C_{tau}. On further review of COBI PK in presence of ATV (ATV/co) in 14 adolescent subjects, two subjects were identified as having a substantially prolonged COBI $T_{1/2}$ of 27.37 and 30.29 hours with acceptable safety profile, respectively, as compared to the established COBI $T_{1/2}$ of 4-5 hours

Additionally, in these two subjects, COBI concentrations at 24-hours post-dose were approximately 1.8-fold higher than the 12-hour concentrations

These results suggest that these pre-dose samples were likely collected in error, and do not represent actual trough concentrations in these two subjects. Based on these data, these two subjects were excluded from the analysis presented in this document. For consistency, geometric least-squares mean (GLSM) values for the PK parameters were calculated for each study and the ratio of GLSM means and their 90% confidence intervals for Study GS-US-216-0128 ("test") relative to the values in each of the studies (reference) were determined.

Comparison of COBI PK parameters in the adolescents in Study GS-US-216-0128 with the other studies revealed, generally it was shown comparable C_{max} across studies while COBI AUC_{tau} was either comparable or modestly (<1.7-fold) higher AUC_{tau}.

Nevertheless, the higher estimates for cobicistat C_{tau} found in Study GS-US-216-0128 have been justified due to a plausible CYP3A4 inhibition by Atazanavir during co-administration with different agents which might be altering COBI clearance. Regardless, the higher COBI C_{tau} when coadministered with ATV is not considered clinically relevant given the favourable safety profiles in studies where similar or higher C_{tau} values were observed.

Overall, the CHMP considered cobicistat co-administered with atazanavir was well tolerated in both adults and paediatric subjects and C_{tau} high estimates were therefore considered as not clinical concern.

2.3.6. Conclusions on clinical pharmacology

Pharmacodynamics

The results from the submitted study do not raise any pharmacodynamic issue that prevents the use of this combination in the population tested.

Pharmacokinetics

No clinically relevant differences in ATV exposures with COBI 150 mg were observed in HIV-1 infected, virologically suppressed adolescents weighing ≥ 35 kg, compared with adults from the Phase 3 study populations. Exposures of COBI were also within the safe and efficacious ranges associated with robust pharmacokinetic boosting in the Tybost, Genvoya, and Stribild programs. The PK data support the use of COBI 150 mg-boosted ATV in paediatric patients weighing ≥ 35 kg.

2.4. Clinical efficacy

To support the current variation, the applicant has submitted, as interim report, one ongoing study (GS-US-216-0128) that evaluated PK, safety, and efficacy data of atazanavir coadministered with cobicistat in paediatric patients aged ≥ 12 to < 18 years weighing at least 35 kg. Data from this study supported as well as the extension of indication for Tybost to cover the use of COBI (150 mg) as a pharmacokinetic

(PK) enhancer for the HIV-1 protease inhibitors (PIs) ATV (300 mg) or darunavir (DRV) (800 mg) in combination with other antiretroviral agents in the treatment of HIV-1 infection in paediatric patients aged ≥ 12 to < 18 years weighing at least 35 kg coadministered with ATV or at least 40 kg coadministered with DRV (EMEA/H/C/002572/II-0051; EC Decision 09-Mar-2020). Although, Study GS-US-216-0128 is evaluating paediatric subjects who are receiving ATV + COBI or DRV + COBI, the data submitted focuses on the ATV + COBI data from the Interim Analysis 1 of Cohort 1 Part A, consisting of paediatric subjects 12 to < 18 years of age weighing ≥ 25 kg; it includes all data from Cohort 1 Part A collected up to 01-Jun-2018.

2.4.1. Main study

Title of Study

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 Paediatric Subjects (GS-US-216-0128).

Methods

Study Design

Study GS-US-216-0128 is an ongoing, open-label, multicenter, multicohort, two-part study evaluating the PK, safety, efficacy, and antiviral activity of ATV/co or DRV/co administered with a BR in HIV-infected, antiretroviral treatment-experienced, virologically suppressed paediatric subjects.

A total of 100 paediatric subjects, ages 3 months to < 18 years and of either sex are being enrolled, sequentially, using a staggered and staged (Part A and Part B) approach. The study proceeds in 2 parts (Part A and Part B), as follows:

Part A: A minimum of 79 subjects are planned to be enrolled to evaluate the steady state PK and confirm the dose of ATV/co and DRV/co. Subjects are enrolled sequentially by cohort as follows:

Cohort #	Age	ATV/co	DRV/co
1	12 years to < 18 years old	n ≥ 14	n ≥ 7
2	6 years to < 12 years old	n ≥ 14	n ≥ 8
3	3 years to < 6 years old	n ≥ 14	n ≥ 8
4	3 months to < 3 years	n ≥ 14	not applicable

Part B: A minimum of 21 additional subjects are planned to be enrolled in Part B to evaluate the safety, tolerability and efficacy of the ATV/co or DRV/co regimen. For all cohorts in Part B, additional subjects will be screened and initiated sequentially by each age cohort and PI (ATV or DRV) following confirmation of appropriate COBI exposure and PI exposures from the corresponding age cohort in Part A.

Study participants

Main inclusion criteria

Eligible subjects were antiretroviral treatment-experienced, virologically suppressed HIV-1 subjects aged 3 months to < 18 years on a stable antiretroviral regimen comprising 2 nucleoside reverse transcriptase

inhibitors (NRTIs) and either ATV/r once daily (QD) or DRV/r QD or twice daily (BID) for ≥ 3 months prior to screening; plasma HIV-1 RNA concentrations (at least 2 consecutive measurements obtained at least 4 weeks apart) at an undetectable level according to the assay being used, but not more than 75 copies/mL; HIV-1 RNA < 50 copies/mL at screening; estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2 (as calculated using the Schwartz formula; $eGFR_{Schwartz}$); and adequate hematologic and hepatic function.

For the CHMP committee, the inclusion and exclusion criteria have been considered acceptable.

Treatments

For Cohort 1, COBI 150 mg (administered as 75 mg x 2 tablets or 150 mg x 1 tablet) is administered orally once-daily with food, in combination with DRV or ATV and a BR. For all subjects, the BR must include 2 NRTIs. The BR may contain additional antiretroviral agents except for the following disallowed agents: saquinavir, indinavir, nelfinavir, double PI regimens, raltegravir, elvitegravir, efavirenz, nevirapine, delavirdine, maraviroc, etravirine, rilpivirine, dolutegravir, and investigational antiretroviral agents.

ATV is administered as either capsules or powder depending upon the subject's body weight and ability to swallow capsules. ATV powder was not administered to any subjects in Cohort 1.

Objectives

The primary objectives of this ongoing study are as follows:

- To evaluate the steady-state PK and confirm the dose of ATV/co or DRV/co in HIV-1 infected, antiretroviral treatment-experienced, virologically suppressed paediatric subjects 3 months to < 18 years of age
- To evaluate the safety, tolerability, and efficacy of ATV/co or DRV/co, each co-administered with a BR through 48 weeks in HIV-1 infected antiretroviral treatment-experienced virologically suppressed paediatric subjects 3 months to < 18 years of age

The secondary objective of this ongoing study is as follows:

- To evaluate the safety, tolerability, and antiviral activity of long-term treatment of ATV/co or DRV/co, each co-administered with a BR, in HIV-1 infected antiretroviral treatment-experienced virologically suppressed paediatric subjects 3 months to < 18 years of age

Outcomes/endpoints

The primary endpoints of this study are:

- PK parameters of AUC_{tau}, of ATV and DRV at Day 10.
- The incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities

The secondary endpoints of this study are:

- PK parameters of C_{tau}, C_{max}, and CL/F for ATV and DRV; and AUC_{tau}, C_{tau}, C_{max} CL/F, and Vz/F for COBI.
- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 12, 24 and Week 48, and every 12 weeks after Week 48

- The time to pure virologic failure
- The change from Day 1 in log_{10} HIV-1 RNA (copies/mL), CD4 cell count (cells/μL), and CD4 percentage at Weeks 24 and 48, and every 12 weeks after Week 48
- Acceptability and palatability of COBI in each cohort

The choice of endpoints has been agreed by the CHMP committee.

Sample size

ATV + COBI-treated subjects in Cohort 1 were enrolled and treated at a total of 7 study centers in 2 countries (4 in the US and 3 in Thailand). Of the 28 subjects screened, 22 were enrolled and 14 received at least 1 dose of ATV + COBI (eight other subjects were enrolled to receive DRV + COBI).

Randomisation

Study GS-US-216-0128 was not a randomized study.

Blinding (masking)

As this was an open-label study, blinding procedures were not applicable.

Statistical methods

The following populations were defined:
The full analysis set (FAS) will include all subjects who received at least one dose of study drug. This is the primary analysis set for efficacy analyses.

The safety analysis set will include all subjects who received at least one dose of study drug. All the data collected up to 30 days after subjects permanently discontinue their study regimen will be included in the safety summaries.

The intensive PK analysis sets for ATV, DRV, and COBI, respectively, will include all Part A subjects who received at least one dose of study drug and for whom steady-state PK profiles at Day 10 intensive PK visits are evaluable. The intensive PK analysis set will be used for detailed PK analysis of ATV, DRV, and COBI.

The PK analysis set will include all subjects who received at least one dose of study drug and for whom at least one observed concentration data of any analyte of interest (ie, ATV, DRV, and COBI) is available. The PK analysis set will be used for analysis of general PK and trough blood concentrations.

Results

At the time of the Interim Analysis 1, 50.0% (7 of 14) of ATV + COBI-treated subjects remained on study drug regimen, while the other 50.0% (7 of 14) of subjects receiving ATV + COBI were prematurely discontinued from the study. The reasons for discontinuation were withdrawal of consent (n = 3), noncompliance with study drug (n = 2), and investigator's discretion (n = 1) and pregnancy (n = 1).

Recruitment

Patients were recruited at 7 study centers in 2 countries (4 in the US and 3 in Thailand).

Conduct of the study

Protocol Amendments

The original protocol was issued on 09 July 2013. There were six amendments to the protocol prior to the interim analysis; important changes are described below:

Protocol Amendment 1 (25 November 2013)

- Removed term "optimized" from study protocol title and in protocol where used in association with term BR.
- Corrected text that noted Part B subjects would switch from twice daily (BID) to once daily (QD) dosing on Day 1. All subjects who were taking DRV BID at study entry were switched to DRV QD dosing at Day -1.
- Added that both acceptability and palatability will be assessed for the tablet and/or dispersible tablet formulations in all cohorts and deleted reference to "suspension" formulation.
- Dosing table updated to provide DRV doses down to 10 kg. Added that if children under 6 years of age can swallow tablets, that this formulation may be used
- Amended text to note issue of immunosuppression related to low neutrophil count and deleted reference to acute infection for the absolute neutrophil count > 500 cells/mm^3 inclusion criterion
- In the inclusion and exclusion criteria, pre-screening timeframes noted as 21 or 30 days prior study entry were changed to prior to Day -10, rather than prior to Day 1.
- Added new text noting hepatitis C virus (HCV) polymerase chain reaction would be done at screening if subject was HCV antibody positive at screening to confirm if subject had na active infection.
- New safety section added on management of hyperbilirubinemia
- Update locations of study centers
- Removed references to extension phase of the study and noted study duration would end in Year 5 and added statement that at the end of the subject's participation in the study, management of the subject's antiretroviral treatment would return to the subject's treating physician (study medications would not continue to be provided after study ends).
- Updated time of pre-dose draw for intensive PK days
- Updated list of disallowed antiretroviral medications
- Added text to clarify that ATV and DRV would be provided to subjects as required outside of the US
- Updated inclusion criteria for DRV patients to not include subjects with history of DRV resistance mutations
- Revised frequency of laboratory tests to accommodate maximum daily or monthly blood volume restrictions in Cohorts 2-4.
- Added cystatin C assessment for every 12 week visits in long-term follow-up phase

- Revised urine storage sample collection to add periodic scheduled testing for urine calcium, phosphorus, and creatinine
- Added Day 7 safety assessment phone call visit for Part B
- Revised trough PK sample collection timeframe
- Revised information for PK and pharmacodynamic analyses
- Added DRV doses for subjects >10 and < 15 kg
- Updated estimated glomerular filtration rate (calculated using the Schwartz method; $eGFR_{Schwarz}$) formula
- Revised inclusion criteria for total bilirubin for ATV patients
- Added information regarding COBI's effect on CYP3A inhibition on various concomitant medications.
- Updated information on recommendations for concomitant use of acid reducing medications to note that these guidelines are applicable only for subjects receiving ATV/co.
- Updated prior and concomitant medications list of disallowed and discouraged medications
- Revised requirements and documentation for informed consents and assents
- Updated information regarding follow-up for positive pregnancy testing
- Updated fasting timeframe for intensive PK days for Cohort 4
- Updated order and timing of activities related to pre-dose meal and blood draws for intensive PK days (Day -1 and Day 10).
- Added PK trough samples collected for Part B subjects
- Added PK sample collection at the time of confirmed virologic failure
- Revised information regarding use of Gilead electronic serious adverse event (SAE) reporting system
- Added new section to section on procedures for Day 7/Week 1 safety phone call for Part B subjects.
- Added new Appendix 3 (Study Procedures Table for Cohort 3).

Protocol Amendment 2 (25 March 2014)

- Sample size increased per FDA's recommendations in Part A that the equivalence boundaries for the 90% confidence interval should be set at 80%-125% per age group and per drug (DRV and ATV)
- Number of Part A subjects was increased per FDA's recommendations resulting in a minimum number of Part B subjects per cohort no longer required. Updated text for Part B to reflect sequential enrolment by cohort for each PI (ritonavir-boosted darunavir [DRV/r] or ritonavir-boosted atazanavir [ATV/r])
- Minimums removed for Cohort B enrolment as increased number of subjects required for steady state PK assessment in Part A exceeded minimum numbers of subjects needed for each age cohort for the purpose of safety
- Part A DRV/r or ATV/r treatment data would be analysed independently if one treatment achieves minimum enrolment before the other
- Tanner Stage assessments were deleted as part of safety analysis
- Efficacy endpoints updated per FDA's recommendations

- Statistical updates made per FDA's recommendations
- Updates were made to concomitant medications for proton pump inhibitors and H_2 antagonists for patients on ATV
- Clarification was made on definition of childbearing potential
- Clarification was made on palatability assessment for the trial

Protocol Amendment 3 (18 December 2014)

- Removed Day -10 and Day -1 visits
- Added trough PK on Day 1 pre-dose for Part A subjects
- For DRV/r BID subjects, switched to DRV/co QD on Day 1
- Changed Study Medical Monitor per Administrative Letter # 1
- Updated the Rationale for the Dose Selection language to reflect COBI developments in the adolescent population
- Updated the Management of Virologic Rebound and Adverse Event section to match Gilead standard language
- Clarified definition of childbearing potential
- Revised pharmacokinetic analysis to align with other paediatric studies/guidance
- Updated the statistical comparisons and power computations to reflect the exposure comparison equivalency of COBI-boosted ATV or DRV in paediatric versus adult subjects

Protocol Amendment 4 (14 November 2016)

- Updated introduction section with results from other paediatric studies in COBI
- Updated rationale for dose selection with results from other COBI studies
- Changed inclusion criteria for body weight at screening for the respective cohorts according to this plan: Cohort 1 ≥ 25 kg, Cohort 2 to consist of 2 groups (Group 1 ≥ 25 kg, Group 2 ≥ 15 kg to < 25 kg), Cohort 3 TBD, and Cohort 4 TBD
- Added 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)
- Added ATV powder and DRV suspension to the description of each treatment as alternative options for subjects who were unable to swallow capsules or tablets, respectively
- Added language around potential for use of dispersible tablets as oral suspension for those who could not swallow tablets

Protocol Administrative Amendment (17 February 2017)

- Notification to sites that Gilead would no longer manufacture 75 mg strength COBI tablets. Until the remaining supply of 75 mg tablets was depleted, subjects ≥ 25 kg receiving a 150 mg dose of COBI were to receive 2 x 75 mg tablets or 1 x 150 mg tablet.

Protocol Amendment 5 (19 January 2018)

- Included disallowed/discouraged use of direct oral anticoagulants based on the Tybost Investigator's Brochure (IB) Edition 10

- Included recommendations on atorvastatin and drospirenone usage based on the Tybost IB Edition 10
- Removed references to COBI 75 mg tablets due to availability of COBI 150 mg tablets

Protocol Amendment 6 (28 June 2018)

- Included disallowed/discouraged use of antipsychotics based on approved US prescribing information for Tybost
- Updated language around drug interaction with corticosteroids to be broadened to include all routes of administration, excluding cutaneous, based on the Tybost IB Edition 11
- Added language regarding lower exposures of COBI reported during pregnancy compared to postpartum based on the Tybost IB Edition 11

Protocol Deviations

A total of 17 important protocol deviations occurred in 10 subjects during the study. Of the 10 subjects with important protocol deviations, 6 subjects had a single important deviation and 4 subjects had 2 or more important deviations. The majority of important protocol deviations (15 of 17) were for study drug compliance < 70% or missed study protocol assessments.

According to the MAH, none of these important protocol deviations affected the overall quality or interpretation of the study data.

Table 7. GS-US-216-0128: Important Protocol Deviations, Cohort 1 Part A (All Enrolled Analysis Set)

Protocol Deviation, n (%)	Cohort 1 Part A: Age 12 to < 18 Years (N = 22)
Number of Subjects with at Least 1 Important Protocol Deviation	10 (45.5%)
Number of Subjects with Study Drug Compliance < 70%	7 (31.8%)
Number of Subjects with Off Schedule Procedure	4 (18.2%)
Number of Subjects with Missing Data	1 (4.5%)
Number of Subjects who Received Prohibited Concomitant Medication	1 (4.5%)

For this study, a study drug compliance rate of < 70% between 2 study visits was defined as an Important Protocol Deviation.

Baseline data

Overall, the majority of subjects receiving ATV + COBI were male (71.4%) with a median age of 14 (range: 12 to 17) years. The median (first quartile [Q1], third quartile [Q3]) baseline estimated glomerular filtration rate by Schwartz formula ($eGFR_{Schwartz}$) was 166.8 mL/min/1.73 m^2 (148.4 mL/min/1.73m^2, 198.8 mL/min/1.73m^2). Body weight for all subjects varied from 32.3 to 81.4 kg. The median (first quartile [Q1], third quartile [Q3]) baseline body weight for all subjects was 52.7 (interquartile range 46.5 to 63.3) kg, with a range of 32.3 to 81.4 kg. One patient in Cohort 1 was less than the proposed indication weight cut-off of ≥ 35 kg, but was above the study entry criteria weight cut-off of Cohort 1 (≥ 25 kg).

The study enrolled a virologically suppressed, HIV-1 infected population; thus, all subjects in the Safety Analysis Set for Cohort 1 Part A had baseline plasma HIV-1 RNA < 50 copies/mL, with the exception of 1 subject whose baseline plasma HIV-1 RNA value was 50 copies/mL . This subject was eligible for enrolment per the inclusion criteria, as this subject had HIV-1 RNA < 50 copies/mL at screening visits.

The median baseline CD4 cell count overall was 770 cells/µL, with 92.9% of subjects having a baseline CD4 cell count ≥ 500 cells/µL.

The median (Q1, Q3) number of years since diagnosis of HIV-1 infection was 14 (12, 15) years. The only mode of infection in all subjects was vertical transmission. At baseline, 78.6% (11 of 14) of subjects overall were asymptomatic, 14.3% (2 of 14) of subjects had a historic diagnosis of AIDS, and 7.1% (1 of 14) had symptomatic HIV-1 infection.

Table **GS-US-216-0128: Demographics and Baseline Characteristics, Cohort 1 Part A, ATV + COBI-Treated Subjects**

Characteristic	Cohort 1 Part A: Age 12 to < 18 Years ATV + COBI (N = 14)
Age (years)	
N	14
Mean (SD)	14 (2.0)
Median	14
Q1, Q3	12, 16
Min, Max	12, 17
Sex at Birth	
Male	10 (71.4%)
Female	4 (28.6%)
Race	
Asian	8 (57.1%)
Black	2 (14.3%)
Caucasian	4 (28.6%)
Other	0
Ethnicity	
Hispanic or Latino	4 (28.6%)
Not Hispanic or Latino	10 (71.4%)
Baseline Body Weight (kg)	
N	14
Mean (SD)	54.6 (13.43)
Median	52.7
Q1, Q3	46.5, 63.3
Min, Max	32.3, 81.4
HIV-1 RNA Categories (copies/mL)	
< 50	13 (92,9%)
≥ 50	1 (7,1%)
CD4 Cell Count (cells/μL)	
N	14
Mean (SD)	796 (308,5)

Table **GS-US-216-0128: Demographics and Baseline Characteristics, Cohort 1 Part A, ATV + COBI-Treated Subjects**

Characteristic	Cohort 1 Part A: Age 12 to < 18 Years ATV + COBI (N = 14)
Median	770
Min, Max	486,1765
Mode of Infection (HIV Risk Factors)	
Vertical transmission	14 (100%)
HIV Disease Status	
Asymptomatic	11 (78,6%)
Symptomatic HIV Infection	1 (7,1%)
AIDS	2 (14,3%)

Note: all patients were AgHBs and AbHCV negative

Numbers analysed

All 22 subjects who received at least 1 dose of study drug were included in the Safety, Full, and PK Analysis Sets, as well as the Intensive PK Analysis Set for COBI.

	Cohort 1 Part A: Age 12 to < 18 Years		
	ATV/co (N = 14)	DRV/co (N = 8)	Total (N = 22)
Subjects Enrolled	14	8	22
Subjects in Safety Analysis Set	14 (100.0%)	8 (100.0%)	22 (100.0%)
Subjects in Full Analysis Set	14 (100.0%)	8 (100.0%)	22 (100.0%)
Subjects in Intensive PK Analysis Set for ATV	14 (100.0%)	0	14 (63.6%)
Subjects in Intensive PK Analysis Set for DRV	0	8 (100.0%)	8 (36.4%)
Subjects in Intensive PK Analysis Set for COBI	14 (100.0%)	8 (100.0%)	22 (100.0%)
Subjects in PK Analysis Set	14 (100.0%)	8 (100.0%)	22 (100.0%)

The participant flow, the baseline data and the numbers analysed are considered described adequately by the CHMP committee.

Outcomes and estimation

The results of the efficacy analyses in virologically suppressed paediatric subjects at Week 24 and Week 48 using the USFDA-defined snapshot algorithm demonstrate that the rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were as follows for those who were coadministered ATV + COBI:

- Week 24: 64.3% (9 of 14 subjects)

Four subjects had HIV-1 RNA ≥ 50 copies/mL at Week 24 but remained in the study at the investigators' discretion and subsequently re-suppressed HIV-1 RNA to < 50 copies/mL at Week 48. One ATV + COBI-treated subject had missing Week 24 data, but was on study drug.

At Week 48, with the four subjects having re-suppressed to HIV-1 RNA to <50 copies/mL, 92.9% (13 of 14 subjects) in Cohort 1 Part A had HIV-1 RNA < 50 copies/mL using the US FDA defined snapshot algorithm.

One subject had HIV-1 RNA ≥ 50 copies/mL at Week 48, remained viraemic at the Week 48 retest visit (HIV-1 RNA ≥ 50 copies/mL by snapshot analysis), and beyond Week 48. This subject was discontinued from study drug regimen at Week 108 due to noncompliance with study drug.

The results of the efficacy analyses at Weeks 12, 24 and 48 using the M = E analysis demonstrated that the rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were as follows for those who were coadministered ATV + COBI:

- Week 12: 100.0% (14 of 14 subjects)
- Week 24: 69.2% (9 of 13 subjects)
- Week 48: 92.9% (13 of 14 subjects)

Ancillary analyses

Individual Subjects with Virologic Failure

For those who were coadministered ATV + COBI, the Resistance Analysis Population contained 3 subjects in Cohort 1 Part A who experienced protocol-defined virologic failure during the first 48 weeks of the study. Post-baseline genotypic and phenotypic data were available for 1 subject and showed no resistance in protease or reverse transcriptase. The other 2 subjects had no postbaseline data due to assay failure.

Immunologic Change

In this virologically suppressed paediatric study population with high baseline mean CD4 cell count and CD4%, there were no clinically relevant changes from Baseline in CD4 cell counts and CD4% for Cohort 1 Part A at Interim Analysis 1.

CD4 Cell Counts (Median [min, max]):

- Baseline: 770 (486, 1765) cells/μL
- Week 24: 721 (384, 1234) cells/μL
- Week 48: 605 (473, 1490) cells/μL

At Week 48, the median change from Baseline in CD4+ cell count was -60 cells/μL.

CD4% (Median [min, max]):

- Baseline: 33.3% (22.8%, 44.7%)
- Week 24: 30.5% (23.0%, 48.7%)
- Week 48: 33.9% (22.4%, 53.0%)

At Week 48, the median change from Baseline in CD4+% was -0.3%.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well

as the benefit risk assessment (see later sections).

Summary of Efficacy for trial GS-US-216-0128

Title: 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 Paediatric Subjects			
Study identifier	GS-US-216-0128		
Design	Open-label		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks not applicable up to 5 years	
Hypothesis	Cobicistat-boosted ATV or DRV will be safe, well tolerated, will have pharmacokinetics comparable to adults and will demonstrate antiviral activity when used with a background therapy in HIV-1-infected, treatment experienced, virologically suppressed infants and children.		
Treatments groups	Cohort 1: ≥ 12 years to < 18 years of age	ATV + Cobi + BR. 48 weeks, 14 patients (DRV + Cobi + BR. 48 weeks, 8 patients)	
	Cohort 2: ≥ 6 year to < 12 years of age	Group not analysed	
	Cohort 3: ≥ 3 years to < 6 years	Group not analysed	
	Cohort 4: ≥ 3 months to < 3 years	Group not analysed	
Endpoints and definitions	efficacy endpoint	HIV-1 RNA < 50 c/ml	percentage of subjects with HIV-1 RNA <50 c/mL at Weeks 24 and 48 (snapshot approach).
	efficacy endpoint	HIV-1 RNA < 50 c/ml	percentage of subjects with HIV-1 RNA <50 c/mL at Weeks 12, 24 and 48, and every 12 weeks after Week 48 Using Missing = Excluded (M=E) Analysis.
	efficacy endpoint	CD4+	change from baseline in CD4 cell count (cells/µl) and CD4 percentage at Weeks 24 and 48, and every 12 weeks after Week 48
Database lock	01 June 2018		
Results and Analysis			
Analysis description	**Interim Analysis**		
Analysis population and time point description	The Full Analysis Set (FAS) population: all randomized subjects who received at least one dose of study treatment and had baseline data for those analyses that require baseline data.		
Descriptive statistics and estimate variability	Treatment group		Cohort I for ATV + CO
	Number of subjects		14
	HIV-1 RNA < 50 c/ml week 48 (FAS) (snapshot approach)		13/14 (92.9%)
	95% CI		(66.1%; 99.8)
	HIV-1 RNA < 50 c/ml week 48 (FAS) (M=E)		13/14 (92.9%)
	95% CI		(66.1%; 99.8)
	CD4+ (cells/uL) Mean change from baseline week 48 (FAS)		-30
	SD		331.1
	CD4+ (%) Mean change from baseline week 48 (FAS)		-0.2%
	SD		3.94%

2.4.2. Discussion on clinical efficacy

To support the current variation, the applicant has submitted, as interim report, one ongoing study (GS-US-216-0128) that evaluated PK, safety, and efficacy data of atazanavir coadministered with cobicistat in paediatric patients aged ≥ 12 to < 18 years weighing at least 35 kg. Although Study GS-US-216-0128 is evaluating paediatric subjects who are receiving ATV + COBI or DRV + COBI, the data submitted focuses on the ATV + COBI data from the Interim Analysis 1 of Cohort 1 Part A, consisting of paediatric subjects 12 to < 18 years of age weighing ≥ 25 kg.

Design and conduct of clinical studies

A total of 22 subjects were included of whom 14 subjects received ATV + COBI. Eligible subjects were antiretroviral treatment-experienced, virologically suppressed HIV-1 subjects aged 3 months to < 18 years on a stable antiretroviral regimen comprising 2 nucleoside reverse transcriptase inhibitors (NRTIs) and either ATV/r once daily (QD) or DRV/r QD or twice daily (BID) for ≥ 3 months prior to screening; plasma HIV-1 RNA concentrations (at least 2 consecutive measurements obtained at least 4 weeks apart) at an undetectable level according to the assay being used, but not more than 75 copies/mL; HIV-1 RNA < 50 copies/mL at screening; estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2 (as calculated using the Schwartz formula; $eGFR_{Schwartz}$); and adequate hematologic and hepatic function.

Efficacy data and additional analyses

The virologic response rate, defined as the number and percentage of subjects with plasma viral load < 50 HIV 1 RNA copies/mL at Week 48 (per FDA Snapshot approach, FAS population) was 92.9% (13/14) in Cohort 1. The results were consistent with M=E analysis.

The Resistance Analysis Population contained 3 subjects treated with ATV + COBI in Cohort 1 Part A who experienced protocol-defined virologic failure during the first 48 weeks of the study. Post-baseline genotypic and phenotypic data were available for 1 subject and showed no resistance in protease or reverse transcriptase. The other 2 subjects had no postbaseline data due to assay failure.

In this virologically suppressed paediatric study population with high baseline mean CD4 cell count and CD4%, there were no clinically relevant changes from Baseline in CD4 cell counts and CD4% for Cohort 1 Part A at Interim Analysis 1.

During clinical study GS-US-216-0128, it was anticipated that a number of adolescent patients may have difficulties to swallow the whole tablets due to the large size of Evotaz fixed-dose combination tablets (19 mm x 10.4 mm).

The applicant does not recommend the splitting or crushing of the fixed-dose tablet, as it would result in the unpleasant taste and likely a lack of compliance with an increased risk for a loss in the overall total administered dose. The MAH is encouraged to conduct an age appropriate formulation development as per the PIP. Nevertheless, the currently approved adult ATV/COBI fixed-dose combination tablet is considered acceptable use in adolescents 12 years to 18 years, weighing at least 35 kg.

2.4.3. Conclusions on the clinical efficacy

Based on efficacy analyses at Week 24 and Week 48 using the USFDA defined snapshot algorithm, the rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were 64.3% at Week 24 and 92.9% at Week

48 for ATV + COBI, and high rates of virologic suppression were maintained beyond Week 48. There were no clinically relevant changes in CD4 cell counts and CD4%. No subjects developed treatment-emergent drug resistance substitutions in protease or reverse transcriptase.

The results from the submitted study showed an acceptable efficacy of the combination of atazanavir with cobicistat, although the sample size is limited. These results could be considered applicable to the fixed dose combination of these two substances.

Although it would be preferable to allow the splitting or crushing of tablets for adolescents (or adults) with difficulty in swallowing tablets, the CHMP agreed on the acceptability of the use in adolescents of the current approved adult ATV/COBI fixed-dose combination tablet formulation.
Additionally, considering that other authorised antiretrovirals indicated for the treatment of adolescents are available as tablets with size similar to the size of Evotaz. Some of these tablets are also authorized to be swallowed whole and nothing is mentioned in their prescribing information regarding patients with difficulty in swallowing tablets.

Nevertheless, regarding the unpleasant taste of ATV and COBI, CHMP noted that other two cobicistat-containing medicinal products which can be split into two pieces to be taken together after splitting, among the other authorised antiretrovirals indicated for the treatment of adolescents with size similar to the size of Evotaz.

In conclusion, the CHMP suggested to endeavour the development of acceptable age-appropriate formulation(s) for younger paediatric populations, as outlined in the recently approved RfM03 to the PIP for Evotaz (EMA/PDCO/444877/2020).

2.5. Clinical safety

Introduction

The MAH submitted the safety data of ATV + COBI in HIV-1-infected, treatment-experienced, virologically suppressed paediatric subjects 12 to < 18 years weighing ≥ 25 kg participating in Cohort 1 Part A of Study GS-US-216-0128.

Patient exposure

The median (Q1, Q3) exposure to ATV + COBI in the paediatric population from Cohort 1 Part A studied in GS-US-216-0128 was 160.0 (110.6, 181.3) weeks, with 100% (14 of 14) of subjects receiving study drug for ≥ 48 weeks.

Table 1 **GS-US-216-0128: Duration of Exposure to Study Drug, Cohort 1 Part A, ATV + COBI-Treated Subjects (Safety Analysis Set)**

	Cohort 1 Part A: Age 12 to < 18 Years
	ATV + COBI (N = 14)
Duration of Exposure to Study Drug (Weeks)[a]	
N	14
Mean (SD)	146.8 (50.23)
Median	160.0
Q1, Q3	110.6, 181.3
Min, Max	48.4, 207.4
Duration of Exposure to Study Drug[a]	
≥ 10 Days	14 (100.0%)
≥ 24 Weeks (168 days)	14 (100.0%)
≥ 48 Weeks (336 days)	14 (100.0%)
≥ 96 Weeks (672 days)	12 (85.7%)
≥ 144 Weeks (1008 days)	10 (71.4%)
≥ 192 Weeks (1344 days)	2 (14.3%)
≥ 204 Weeks (1428 days)	1 (7.1%)

ATV + COBI = atazanavir coadministered with cobicistat; N = number of subjects

[a] Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug. For subjects who had prematurely discontinued study drug, if the last dose date was completely missing or only year was known, the latest of study drug start and end dates or clinic and laboratory visit dates (excluding the 30-day follow-up visit date) was used to impute the last dose date.
For subjects who had not prematurely discontinued study drug, the data-cut date (01-Jun-2018) was used to impute the last dose date.

Adverse events

In Interim Analysis 1, 92.9% of all ATV + COBI-treated subjects (13 of 14) had at least 1 AE reported, the majority of which were Grade 1 or 2 in severity and not considered by the investigator to be related to study drug. Grade 3 AEs were reported for 14.3% of subjects (2 of 14; wrist fracture and substance abuse), none of which were considered related to study drug.

The following were the 3 most commonly reported AEs in subjects treated with ATV + COBI:

- Upper respiratory tract infection (50.0%, 7 of 14 subjects),
- Cough (21.4%, 3 of 14 subjects),
- Nasal congestion (21.4%, 3 of 14 subjects)

The overall incidence and types of common AEs were consistent with those expected in the study population.

GS-US-216-0128: Adverse Events Reported for at Least 1 Subject in Cohort 1, Part A, ATV + COBI-Treated Subjects (Safety Analysis Set)

Adverse Event by Preferred Term[a,b,c]	Cohort 1 Part A: Age 12 to < 18 Years ATV + COBI (N = 14)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	13 (92.9%)
Upper respiratory tract infection	7 (50.0%)
Cough	3 (21.4%)
Nasal congestion	3 (21.4%)
Acne	2 (14.3%)
Arthralgia	2 (14.3%)
Bronchitis	2 (14.3%)
Hyperbilirubinemia	2 (14.3%)
Myalgia	2 (14.3%)
Pharyngitis	2 (14.3%)
Proteinuria	2 (14.3%)
Skin abrasion	2 (14.3%)
Vomiting	2 (14.3%)
Abdominal pain	1 (7.1%)
Headache	1 (7.1%)
Metabolic acidosis	1 (7.1%)
Oropharyngeal pain	1 (7.1%)

- ATV + COBI = atazanavir coadministered with cobicistat; N = number of subjects

- [a] Adverse events were coded using MedDRA version 21.1.
- [b] Preferred terms are presented by descending order of the total frequencies.

Adverse events considered related to study drug by the investigator were reported for 28.6% (4 of 14) of ATV + COBI-treated subjects (dyspepsia, hyperbilirubinemia, jaundice, proteinuria, vomiting). No study drug-related AEs with ATV + COBI were reported in more than 1 subject each.

Serious adverse event/deaths/other significant events

Serious AEs were reported for 21.4% of all ATV + COBI-treated subjects (3 of 14; clavicle fracture and foot fracture for 1 subject; substance abuse and appendicitis for 1 subject each), and were not considered related to study drug. There were no drug-related serious AEs, and there were no deaths. No ATV + COBI-treated subjects had an event that might meet the definition of Category C events indicative of an AIDS-defining diagnosis reported during the study.

Laboratory findings

There were no clinically relevant changes from Baseline for median values of haematology or clinical chemistry (excluding some liver-related parameters). Median values were within the relevant reference ranges.

All subjects (100%; 14 of 14) receiving ATV + COBI had at least 1 laboratory abnormality. The abnormalities reported were Grade 1 or 2 in severity for 28.5% of subjects (4 of 14); Grade 3 for 64.3% of subjects (9 of 14); and a transient Grade 4 laboratory abnormality (creatine kinase increased) was reported for 1 subject.

Grade 3 abnormalities were reported as follows: Grade 3 hyperbilirubinemia (57.1%, 8 of 14 subjects), Grade 3 haematuria by quantitative assessment (14.3%, 2 of 14 subjects; both female), Grade 3 alanine aminotransferase (ALT) increased (7.1%, 1 of 14 subjects), Grade 3 amylase increased (7.1%, 1 of 14 subjects), Grade 3 bicarbonate decreased (7.1%, 1 of 14 subjects), and Grade 3 fasting low-density lipoprotein (LDL) increased (7.1%, 1 of 14 subjects).

The subject who had a Grade 4 creatine kinase level had a normal baseline creatine kinase level of 151 U/L (reference range, 18 – 198 U/L) that increased to 5784 U/L at Week 8, decreased to normal levels from Weeks 12 to 24, then remained above normal (range, 208 to 370 U/L) from Weeks 32 to 108 (ie, last visit [subject was prematurely discontinued from the study drug combination and study at the investigator's discretion]). Aspartate aminotransferase (AST) levels also transiently increased to 134 U/L at Week 8 in this subject, after which they decreased to normal levels.

Most laboratory abnormalities were isolated and transient occurrences. No subject had an SAE associated with a clinical laboratory abnormality.

Safety in special populations

No new information is submitted.

Safety related to drug-drug interactions and other interactions

No relevant data on this topic could be retrieved from the currently evaluated trial.

Discontinuation due to adverse events

No ATV + COBI treated subjects has AEs leading to premature discontinuations.

2.5.1. Discussion on clinical safety

The Week-48 interim analysis data from Study GS-US-216-0128 is based on the exposure of 14 patients who received ATV + COBI in Cohort 1 [aged ≥12 to <18 years]. Atazanavir coadministered with cobicistat, was generally safe and well tolerated in the studied HIV-1 infected, ART-experienced paediatric population (aged ≥12 to <18 years).

There were no newly identified clinically relevant safety findings in subjects analysed.

Serious AEs were reported for 21.4% of all ATV + COBI-treated subjects (3 of 14; clavicle fracture and foot fracture for 1 subject; substance abuse and appendicitis for 1 subject each), and were not considered related to study drug. There were no drug-related serious AEs, and there were no deaths.

There were no clinically relevant changes from Baseline for median values of haematology or clinical chemistry (excluding some liver-related parameters). Median values were within the relevant reference ranges.

Taking the low sample size into account, the safety profile of atazanavir coadministered with cobicistat appears to be consistent with the established safety profile in adults.

2.5.2. Conclusions on clinical safety

From the limited information provided by the MAH, there are no particular concerns to highlight from the use of the combination of atazanavir with cobicistat in children from 12 to 18 years of age.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan (RMP) version 8.0 dated 18 August 2020 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8.0 dated 18 August 2020 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

Although it can be agreed that no changes are made within the current procedure, the MAH is requested to revise the extensive Summary of Safety Concerns at the next regulatory opportunity, to be in line with the current version of GVP Module V.

The CHMP endorsed this advice.

The CHMP endorsed the RMP version 8.0 with the following content:

Safety concerns

Table SVIII: Summary of safety concerns

Important identified risks	• PR interval prolongation (both paediatric and adult populations) (ATV) • Hyperbilirubinemia (ATV) • Nephrolithiasis (ATV) • Severe skin reactions (ATV) • Cholelithiasis (ATV) • Angioedema (ATV) • IRIS (ATV) • CKD (ATV)

Table SVIII: Summary of safety concerns

Important potential risks	• QT prolongation (ATV) • Kernicterus (ATV) • Acute renal failure (adults) (ATV) • Interstitial nephritis (ATV) • Concurrent use of drugs whose co-administration with COBI is contraindicated (COBI) • Medication error leading to overdose in case of concurrent use of ATV/COBI with any components, including ATV, COBI, or with FDC products that contain COBI
Missing information	• Safety in pregnancy (ATV and COBI) • Safety in geriatric population (ATV and COBI) • Safety in lactation (COBI) • Safety in patients with cardiac conduction disorders (COBI) • DDI (ATV and COBI)

Pharmacovigilance plan

Table Part III.3: On-going and planned additional pharmacovigilance activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestone(s)	Due Date(s)
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
APR/ Category 3Ongoing	To detect major teratogenic effects involving any of the Registry drugs, including ATV/COBI, to which pregnant women are exposed	Missing information; Pregnancy (ATV and COBI); Terato-genicity of Registry drugs, including ATV/COBI	Bi-annual update	Interim reports are issued by the APR in June and December of each year and the most current data available are included in PSUR/PBRER submissions

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
PR interval prolongation (both paediatric and adult populations)	Routine risk minimisation measures: SmPC Sections 4.4, 4.5, and 5.3.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Hyperbilirubinemia	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Nephrolithiasis	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Severe skin reactions	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Cholelithiasis	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Angioedema	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
IRIS	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
CKD	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
QT prolongation	Routine risk minimisation measures: SmPC Sections 4.4, 4.8, and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Kernicterus	Routine risk minimisation measures: SmPC Sections 4.1 and 4.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Acute renal failure (adults)	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Interstitial nephritis	Routine risk minimisation measures: SmPC Section 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Concurrent use of drugs whose co-administration with COBI is contraindicated	Routine risk minimisation measures: SmPC Sections 4.3 and 4.5	Routine pharmacovigilance activities beyond adverse reactions

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Medication error leading to overdose in case of concurrent use of ATV/COBI with any components, including ATV, COBI, or with FDC products that contain COBI	Routine risk minimisation measures: SmPC Sections 4.4 and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Safety in pregnancy (ATV and COBI)	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: APR
Safety in geriatric population (ATV and COBI)	Routine risk minimisation measures: SmPC Sections 4.8 and 5.2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Safety in lactation (COBI)	Routine risk minimisation measures: SmPC Sections 4.6 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
Safety in patients with cardiac conduction disorders (COBI)	Routine risk minimisation measures: SmPC Sections 4.3, 4.4, and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None
DDI (ATV and COBI)	Routine risk minimisation measures: SmPC Sections 4.3, 4.4, and 4.5	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

2.7. Update of the Product information

As consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated to include the language on the use of EVOTAZ in combination with other antiretroviral agents in the treatment of HIV-1 infection in adolescent patients aged ⩾ 12 to < 18 years, weighing ⩾ 35 kg without known mutations associated with resistance to atazanavir. The Package Leaflet has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial corrections.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- This extension of indication does not introduce any relevant changes to the approved PIL and for this reason a new user consultation is not required;
- The key safety messages are essentially the same for this new indication; as explained by the MAH, the route of administration, the pharmaceutical form and the posology remain unchanged. The only differences are related to the text of the therapeutic indication in order to reflect the new population;
- Thera are also no changes with regards to the design and layout of the PIL
- The MAH has submitted the results of the user consultation with target patient groups on the PIL in the context of the MAA (EC decision issued on 13 July 2015) and it was considered that the PIL met the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

The above presented reasons fully justify the rational for not performing a new user consultation.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HIV-1 infection is a life-threatening and serious disease that is of major public health interest. There are approximately 34 million people living with HIV-1. The infection, if left untreated or sub-optimally treated, is characterized by deterioration in immune function, the subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death. Infants and children infected with HIV-1 tend to progress more rapidly than adults to symptomatic disease. Therapeutic strategies for the treatment of adults and children with HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART). Several antiretroviral drugs are approved for the treatment of HIV-1 infection in children who are naïve to treatment. Current DHHS paediatric treatment guidelines

recommend combination therapy for children, including either a NNRTI or PI/r, plus a dual NRTI backbone for initial treatment.

3.1.2. Available therapies and unmet medical need

First-line antiretroviral therapy in paediatric patients is based upon the same principle of combination therapy for adults but consists of fewer approved options available for treatment. The recommended first-line 2-NRTI backbone is dependent upon age and the availability of the formulation.

Cobicistat (150 mg once daily [QD] tablet) is currently indicated as a pharmacokinetic (PK) enhancer of atazanavir (ATV) 300 mg once daily or darunavir (DRV) 800 mg once daily as part of antiretroviral (ARV) combination therapy in HIV-1 infected adults. Cobicistat provides patients with a potent, convenient, well-tolerated, and practical PK enhancer of ATV and DRV containing ARV regimens in the treatment of HIV-1 infected adults. Cobicistat in combination with ATV or DRV with 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) is one regimen recommended by both the US Department of Health and Human Services guidelines for the treatment of HIV-1 in adults {Department for Health and Human Services (DHHS) 2018}, the International Antiviral Society – USA Panel {Saag 2018} and the European AIDS Clinical Society guidelines; Additionally, COBI-boosted DRV with 2 NRTIs is a recommended regimen and COBI-boosted ATV is an alternative regimen for the treatment of HIV-1 in adults {European AIDS Clinical Society (EACS) 2018}.

EVOTAZ is an oral immediate-release, film-coated fixed-dose tablet containing 300 mg ATV and 150 mg COBI indicated in the United States (US), European Union (EU) and other countries for use in combination with other antiretroviral agents for the treatment of human immunodeficiency virus 1 (HIV-1) infection in adults.

Considering that the indication for cobicistat (as an individual active substance) was recently extended to cover the use of COBI (150 mg) as a pharmacokinetic (PK) enhancer for the HIV-1 protease inhibitors (PIs) ATV (300 mg) or darunavir (DRV) (800 mg) in combination with other antiretroviral agents in the treatment of HIV-1 infection in paediatric patients aged ≥ 12 to < 18 years weighing at least 35 kg co-administered with ATV or at least 40 kg co-administered with DRV (EMEA/H/C/002572/II-0051; EC Decision 09-Mar-2020), the MAH submitted the same data to support the extension of indication to include the use of Evotaz in combination with other antiretroviral agents in the treatment of HIV-1 infection in paediatric patients aged ≥ 12 to < 18 years, weighing ≥ 35 kg.

3.1.3. Main clinical studies

The current application is based on the interim results from the ongoing paediatric Study GS-US-216-0128. This study is an ongoing, open-label, multicenter, multicohort, two-part study to evaluate the PK, safety, efficacy, and antiviral activity of ATV + COBI or DRV + COBI administered with a background regimen (BR) in HIV-1-infected, treatment experienced, virologically suppressed paediatric subjects.

3.2. Favourable effects

Based on efficacy analyses at Week 24 and Week 48 using the USFDA defined snapshot algorithm, the rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were 64.3% at Week 24 and 92.9% at Week 48 for ATV + COBI, and high rates of virologic suppression were maintained beyond Week 48. There were no clinically relevant changes in CD4 cell counts and CD4%. No subjects developed treatment-emergent drug resistance substitutions in protease or reverse transcriptase.

3.3. Uncertainties and limitations about favourable effects

No data was obtained from the use of the fixed dose combination in this patient population. The bioequivalence of the approved fixed-dose tablet Evotaz (ATV/COBI; 300 mg/150 mg) to the coadministration of the single components of 300 mg ATV + 150 mg COBI was demonstrated in the adult Phase 1 registrational study (Study AI424511).

3.4. Unfavourable effects

No clinically relevant safety signals have been identified with the coadministration of approved doses of ATV and COBI to adolescent subjects weighing ≥ 35 kg. No new warnings or precautions are warranted based on the data described.

3.5. Uncertainties and limitations about unfavourable effects

The Week 48 analysis data from Study GS-US-216-0128 is based on the exposure of 14 adolescents (small sample size). There are no other limitations and uncertainties in regard to the unfavourable effects that might have an impact on the benefit-risk balance.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The efficacy and safety of cobicistat in association with atazanavir in the treatment of HIV-1 was also demonstrated for adolescent subjects.

3.6.2. Balance of benefits and risks

In HIV infected adolescent subjects weighing ≥ 35 kg the benefits driven by the use of Evotaz as part of combination ART could outweigh the risks associated with its use.

3.6.3. Additional considerations on the benefit-risk balance

The generation of additional data regarding acceptability (swallowability) or an evaluation on the splitting of the Evotaz fixed-dose combination tablets was not considered to be warranted for this application. The currently approved adult formulation is considered appropriate for use in adolescents 12 years to 18 years, weighing at least 35 kg. Evotaz currently "is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults without known mutations associated with resistance to atazanavir." The present Type II-038 variation for Evotaz proposes to extend the indication to paediatric patients who are "adolescents aged 12 years to 18 years, weighing at least 35 kg" (henceforth simply referred to as adolescents). The currently marketed fixed-dose formulation of Evotaz is an oval, biconvex, bilayer pink film-coated tablet, 19 × 10.4 mm in size, debossed with 3641 on one side and with a plain face on the other side. It is not scored to facilitate splitting. It contains two drug substances, 300 mg atazanavir (ATV) (as sulfate) and 150 mg cobicistat (COBI) (on silicon dioxide). It also contains the following excipients: stearic acid, microcrystalline cellulose, sodium starch glycolate, crospovidone, hydroxypropyl cellulose, magnesium stearate, croscarmellose sodium and Opadry Pink (a film-coating material containing titanium dioxide, talc, triacetin, red iron oxide, and hypromellose). The Opadry film coat is inactive. The tablets are supplied in a high-density polyethylene bottle with a desiccant, child-resistant cap with heat induction seal activated.

The film-coated bilayer tablet of the currently marketed formulation confers acceptable palatability to the ATV and COBI components in a fixed-dose presentation. Taste evaluations of age-appropriate formulations of ATV and COBI as individual components, conducted by a trained taste panel, showed that each component had a very strong and lingering bitterness and a strong initial burnt aromatic. The combination of ATV with COBI presented with an even more intense taste compared to each of the components alone (EMA/PDCO/153723/2017). As such, the splitting or crushing of the fixed-dose tablet would result in the exposure of both ATV and COBI components to the oral mucosa when administered, leading to a very unpleasant taste and likely a lack of compliance. Furthermore, the bilayer design may cause fragmentation when attempting to split the tablet, thereby increasing the risk for a loss in the overall total administered dose. In addition, the MAH believes that the currently approved adult ATV/COBI fixed-dose combination tablet is acceptable for adolescents on the basis that similarly sized tablet products are approved in the EU for adolescents. The MAH provided a table with a summary of tablet sizes (presented in descending order by tablet length), similar to the size of Evotaz, for other fixed-dose tablets authorised in the EU for the treatment of HIV in the adolescent patient population.
The MAH will monitor for reported issues regarding the use of Evotaz tablets in the adolescent patient population in accordance with routine pharmacovigilance surveillance measures. In the meantime, the MAH continues to endeavour the development of acceptable age appropriate formulation(s) for younger paediatric populations, as outlined in the recently approved RfM03 to the PIP for Evotaz (EMA/PDCO/444877/2020).

3.7. Conclusions

The overall B/R of Evotaz in the additional age group for whom indication is sought is considered to be positive.

4. Recommendations

Outcome

Based on the arguments of the MAH and all the supporting data on quality, safety and efficacy, the CHMP in its final opinion considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the use of EVOTAZ in combination with other antiretroviral agents in the treatment of HIV-1 infection in adolescent patients aged ≥ 12 to < 18 years, weighing ≥ 35 kg without known mutations associated with resistance to atazanavir; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial corrections.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0009/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Evotaz -H-C-003904-II-0038'.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.