30 January 2020
EMA/88315/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tybost

International non-proprietary name: cobicistat

Procedure No. EMEA/H/C/002572/II/0051

Marketing authorisation holder (MAH): Gilead Sciences Ireland UC

Note

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

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List of abbreviations

abbreviation	description of abbreviated term
3TC	lamivudine
ABC	abacavir
ADR	Adverse Drug Reaction
AE	adverse event
AIDS	acquired immune deficiency syndrome
ART	antiretroviral treatment
ARV	antiretroviral
ATV	atazanavir
AZT	zidovudine
COBI	cobicistat
CSR	clinical study report
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DRV	darunavir
EACS	European AIDS Clinical Society
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
ECG	electrocardiogram
eGFRcr	estimated glomerular filtration rate based on serum creatinine
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
GVP	Guideline on good pharmacovigilance practices
pharmacovigilance practices	
HBV	hepatitis B virus
HDL	high-density lipoprotein
HIV(-1)	human immunodeficiency virus (type 1)
MAH	Marketing Authorisation Holder
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
PI	protease inhibitor

PEC	predicted environmental concentration
PK	pharmacokinetic(s)
PL	Package Leaflet
PRT	proximal renal tubulopathy
PV	pharmacovigilance
RAM	resistance-associated mutation
RMP	Risk Management Plan
rtv	low-dose ritonavir
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
TAF	tenofovir alafenamide
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TFV	tenofovir

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Gilead Sciences Ireland UC submitted to the European Medicines Agency on 3 July 2019 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 and IIIB

Extension of Indication to modify the approved therapeutic indication for Tybost to include a new population (adolescents aged 12 years and older, weighing at least 35 kg) for the treatment of HIV-1. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC and sections 1,2,3 of the Product leaflet are updated accordingly. The updated RMP version 4.1 is also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics 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/0060/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0060/2017 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 applicant 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 applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur : Bruno Sepodes Co-Rapporteur : N/A

Timetable	Actual dates
Submission date	3 July 2019
Start of procedure	20 July 2019
CHMP Rapporteur Assessment Report	13 September 2019
PRAC Rapporteur Assessment Report	13 September 2019
PRAC members comments	25 September 2019
PRAC Outcome	3 October 2019
CHMP members comments	07 October 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 October 2019
Request for Supplementary Information	17 October 2019
MAH's responses submitted to the CHMP on	20 December 2019
Re-start of procedure	01 January 2020
Rapporteur's preliminary assessment report on the MAH's responses	15 January 2020
Rapporteur's updated assessment report on the MAH's responses	23 January 2020
CHMP opinion:	30 January 2020

2. Scientific discussion

2.1. Introduction

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} and the International Antiviral Society – USA Panel {Saag 2018}. In addition, per European AIDS Clinical Society guidelines, COBI-boosted DRV (DRV/co) with 2 NRTIs is a recommended regimen and COBI-boosted ATV (ATV/co) is an alternative regimen for the treatment of HIV-1 in adults {European AIDS Clinical Society (EACS) 2018}.

COBI 150 mg has been studied extensively in adults with HIV-1 infection. COBI 150 mg is the pharmacoenhancing component for EVG in the approved EVG/COBI/FTC/TDF single-tablet regimen (Stribild®) for the treatment of treatment-naïve adults and paediatric patients aged 12 years and older weighing ≥ 35 kg. In the EU, the Stribild indication contains a restriction for patients without known mutations associated with resistance to any of the 3 ARV agents in Stribild who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil. COBI 150 mg is approved as a component of EVG/COBI/FTC/tenofovir alafenamide fumarate (TAF) in adult and paediatric patients with body weight at least 25 kg (Genvoya®). Furthermore, Genvoya is approved in the EU for adults and adolescents aged from 12 years with a body weight of at least 35 kg and children aged from 6 years and with a body weight of at least 25 kg for whom alternative regimens are unsuitable.

Moreover, COBI 150 mg is a component in the DRV/COBI/FTC/TAF fixed-dose combination approved in the EU for adolescents 12 years and older weighing ≥ 40 kg (Symtuza®).

The provided information in this submission is intended to support a paediatric indication for COBI as a PK enhancer of the HIV-1 protease inhibitors ATV and DRV in paediatric patients weighing ≥ 35 kg. Data from Study GS-US-216-0128 is provided.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

The present variation aims to modify the approved therapeutic indication to include new population (adolescents aged 12 years and older, weighing at least 35 kg) for the treatment of HIV-1.

The MAH requested an exemption for updating the ERA considering that the previous PEC calculations (2015) have been estimated based on forecast sales figures, that covered the period of 2015-2020 and included a reserve / margin of error, which is higher than the small increase in sales. Therefore, it could comprise a possible extend of the use due to the extension of indication.

Considering the published epidemiological data for human immunodeficiency virus-1 (HIV-1) in adults and adolescents, it was not understandable the reason why the previous PEC calculations were estimated based on forecast sales figures.

An increase in environmental exposure is expected for this medicinal product – new indication and new patient population (12 to 18 years old). Therefore, the PEC values for both active substances (based on prevalence data) should be calculated and then summed to the previous PECs to reach the total PEC. Moreover, the environmental risk assessment should be updated.

2.2.2. Discussion on non-clinical aspects

Upon request the MAH calculated a new predicted environmental concentration value (PEC) including HIV prevalence of paediatrics (0.01%) and adults (0.9%)) and then summed to the previous PEC to reach the total PEC. Moreover, an environmental risk assessment was updated for cobicistat.

Based on these prevalence values, the new PEC surface water was 0.675 µg.L-1 from contribution of adults, and 0.0075 µg.L-1 from contribution of paediatrics giving a total of 0.68 µg.L-1. It was calculated for the different environmental compartments. In addition, ERA has been updated. The new risk quotient for sediment, surfacewater and groundwater was less than one.

2.2.3. Conclusion on the non-clinical aspects

The environmental risk assessment has been updated based on new PEC values.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of cobicistat.

Considering the above data, 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.

Table 1 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	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/co or DRV/co administered with a BR through 48 weeks. • Evaluate the safety, tolerability, and efficacy of ATV/co or DRV/co administered with a BR through 48 weeks. Secondary objective: • Evaluate the safety, tolerability, and antiviral activity of long-term treatment of ATV/co or DRV/co 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 additional 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/r or DRV/r), 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 CSR; Cohort 1 Part A

ATV/co = cobicistat-boosted atazanavir; ATV/r = ritonavir-boosted atazanavir; BR = background regimen; COBI = cobicistat; CSR = clinical study report; DRV/co = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; HIV-1 = human immunodeficiency virus 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 Period:

16 January 2014 (First Subject Screened)

30 May 2018 (Last Subject Observation for this Report)

Methodology:

This is an ongoing open-label, multicenter, multicohort, two-part study (Part A and B) evaluating the PK, safety, efficacy, and antiviral activity of ATV/co or DRV/co administered with a background regimen (BR) in HIV-1 infected treatment-experienced, virologically suppressed paediatric subjects. A total of approximately 100 paediatric subjects, ages 3 months to < 18 years, of either sex are being enrolled 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:

Table 2 Enrolment by cohort

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 predose and at 1, 2, 3, 4, 5, 8, and 12 hours postdose 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 AUCtau for ATV and DRV at Day 10. The secondary PK endpoints were the PK parameters of Ctau, Cmax, and CL/F for ATV and DRV, and AUCtau, Ctau, Cmax, CL/F, and Vz/F for COBI at Day 10.

Sparse trough PK samples were collected at baseline (predose) and 20 to 28 hours postdose 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 reassayed due to concentrations above the quantifiable limit.

Darunavir

Determination of Darunavir in Human Plasma was made by a validated LC-MS/MS method. This method was linear between 20 ng/mL and 10000 ng/mL. Dilution Integrity was determined with a concentration of 20000 ng/mL diluted 20-fold. Analysis of samples began on 23 Apr 2015 (date of first extraction) and concluded on 03 Feb 2017 (date of last injection). A total of 963 days transpired between the first sample collection date and the last extraction date. All study samples were analyzed within the established long-term stability of 1635 days at -70°C. The %CV of the QCs for darunavir at 60, 800, and 9000 ng/mL ranged from 3.4% to 8.7% while %RE ranged from -5.1% to -0.3%. Seven samples were reassayed 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 reassayed because they were impacted by carryover and one sample was reassayed due to a concentration above the quantifiable limit.

Statistical Methods:

Pharmacokinetic parameters for ATV and DRV, each 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 DRV and Day 10 for ATV, DRV, 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 or DRV 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.

A one-way analysis of variance (ANOVA) model was fitted to the natural logarithmic transformed values of AUCtau (as the primary parameter) and Cmax and Ctau (as the secondary parameters, if available) for ATV and DRV 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 or DRV versus RTV-boosted ATV or DRV was also evaluated. An ANOVA model was fitted to the natural logarithmic transformed values of AUCtau, Cmax, and Ctau for ATV and DRV 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 AUCtau, Ctau, and Cmax, 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%.

SUMMARY OF RESULTS:

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. Plasma profiles were as follows:

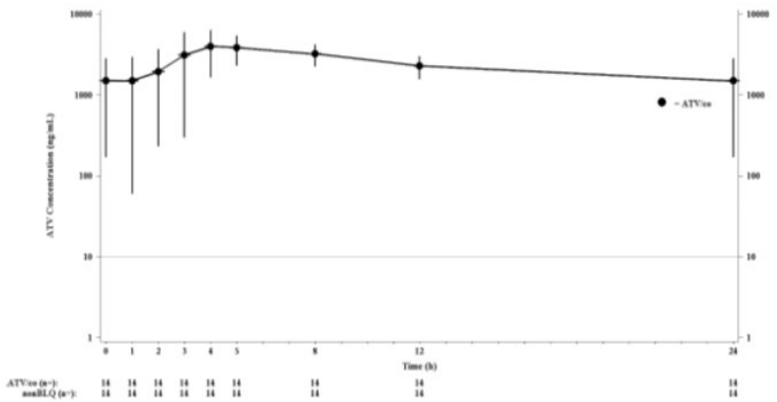


Figure 1 GS US 216 0128:Mean (SD) Plasma ATV Concentration vs Time(Semilogarithmic Scale), Cohort 1 Part A(Intensive PK Analysis Set for ATV), (ATV boosted by COBI)

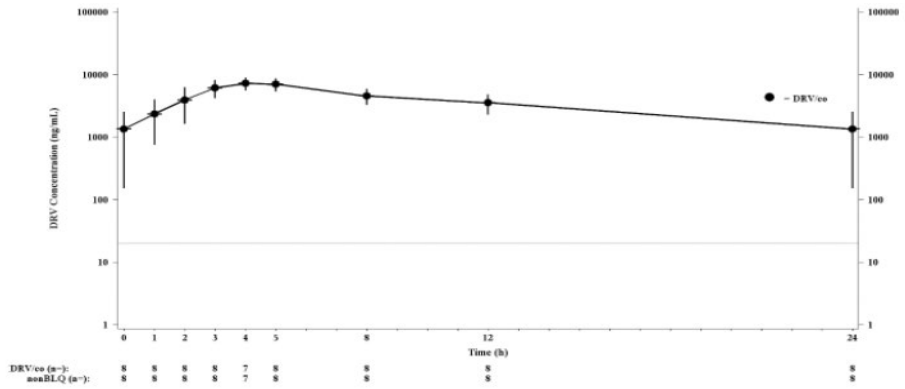


Figure 2 GS US 216 0128:Mean (SD) Plasma DRV Concentration vs Time(Semilogarithmic Scale), Cohort 1 Part A(Intensive PK Analysis Set for DRV), (DRV boosted by COBI)

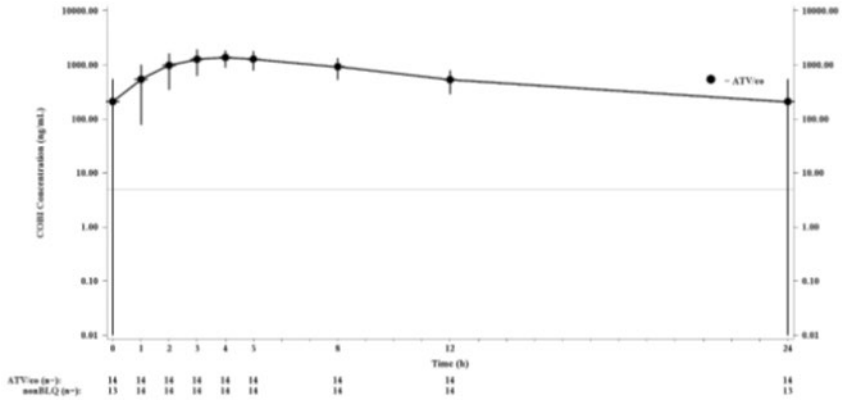


Figure 3 GS US 216 0128:Mean (SD) Plasma Cobicistat Concentration vs Time(Semilogarithmic Scale) following administration of ATV/co, Cohort 1 Part A,(Intensive PK Analysis Set for CoBI)

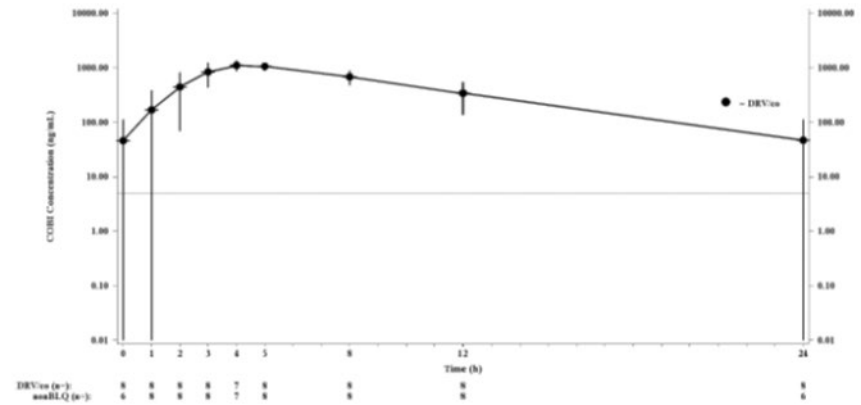


Figure 4 GS US 216 0128:Mean (SD) Plasma Cobicistat Concentration vs Time(Semilogarithmic Scale) following administration of DRV/co, Cohort 1 Part A,(Intensive PK Analysis Set for CoBI)

For ATV and DRV, the lower and upper bounds of the 95% CIs for the geometric mean of CL/F relative to the geometric mean for the respective analytes were within the FDA-specified boundary of 60% to 140%. For COBI, the lower and upper bounds of the 95% CIs of CL/F and Vz/F relative to the geometric mean were within 60% to 140%. These results confirm the precision of these parameters for each respective analyte. As such, the sample sizes for ATV/co and DRV/co selected for this study population are appropriate to confirm the doses that were evaluated.

For ATV, AUCtau, Cmax and Ctau 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, AUCtau, and Cmax were similar and Ctau was 16% lower with COBI relative to RTV. These differences were not considered clinically relevant as they were similar to those observed following treatment with RTV-boosted ATV, which is approved for use in this population {REYATAZ® 2018}, {REYATAZ 2018}. The safety profile of ATV boosted with RTV in pediatrics has been shown to be comparable to adults, and no exposure-safety relationship was observed, with the exception of increased indirect bilirubin with increasing ATV exposures, consistent with ATVs inhibition of uridine 5'-diphospho-glucuronosyltransferase 1A1 (UGT1A1). Further, exposures of ATV in adolescents with COBI were within the safe and efficacious ranges of exposures observed historically in adults are supported by the observed safety data in the study population.

For DRV, Cmax was similar and AUCtau and Ctau were 17% and 52% lower, respectively, in adolescents receiving COBI-boosted DRV compared to those observed in adults.

With respect to exposures of DRV boosted by COBI compared to those boosted by RTV in adolescents, Cmax was similar, and AUCtau and Ctau were 11% and 50% lower, respectively with COBI relative to RTV.

These differences were considered acceptable as the DRV Ctau values in adolescents were within the range of historical data in adults with DRV-boosted COBI. Mean DRV Ctau was approximately 25-fold above the protein-adjusted EC50 against wild-type HIV-1 virus (55 ng/mL) and no exposure-efficacy relationship was observed for COBI-boosted DRV in the Phase 3 Study GS-US-216-0130. Further, exposure-efficacy analyses of Phase 3 studies of RTV-boosted DRV demonstrated that a 50% reduction in DRV trough concentrations would not impact the mean predicted virological response. The COBI 150 mg dose with DRV is further supported by the high rate of virologic suppression maintained in the current study population.

For COBI, steady-state PK parameters following the administration of COBI-boosted ATV (mean COBI AUCtau [CV%] = 14851.9 [49.0] h•ng/mL) or COBI-boosted DRV (mean COBI AUCtau [CV%] = 9248.4 [34.3] h•ng/mL) to virologically suppressed HIV-1 infected adolescents were similar to historical data in adults from the Tybost® program.

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, DRV, and COBI PK was evaluated in adolescents 12 to < 18 years of age in Study GS-US-216-0128. Exposures of ATV, DRV, and COBI versus baseline age in Cohort 1 Part A are shown in the following figures for AUCtau (Cmax and Ctau figures were also included "Adhoc-tables" in the clinical module).(See below Figure 5 to Figure 8)

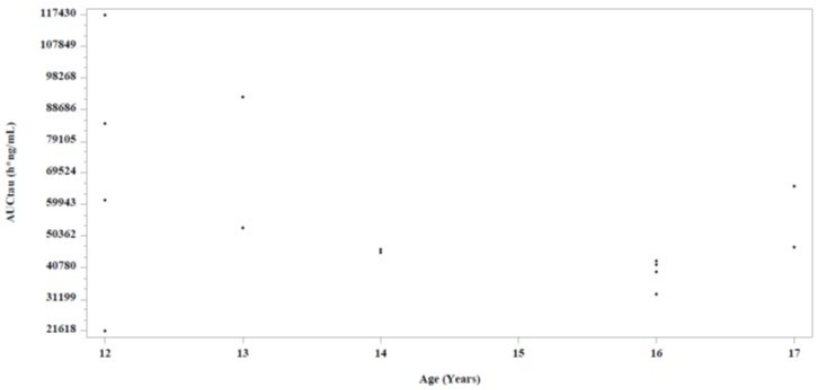


Figure 5 Scatter Plot of ATV AUCtau (boosted by COBI) vs Baseline Age,(Intensive PK Analysis Set for ATV).Study GS US 216 0128, Cohort 1 Part A. Age 12 to < 18 years

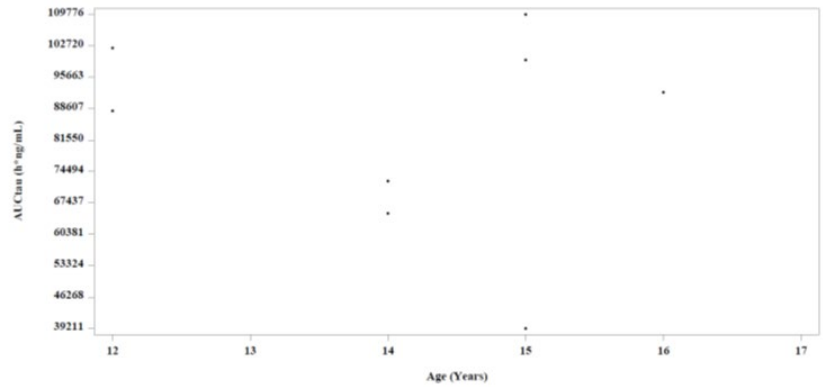


Figure 6 Scatter Plot of DRV AUCtau (boosted by COBI) vs Baseline Age,(Intensive PK Analysis Set for DRV).Study GS US 216 0128, Cohort 1 Part A. Age 12 to < 18 years

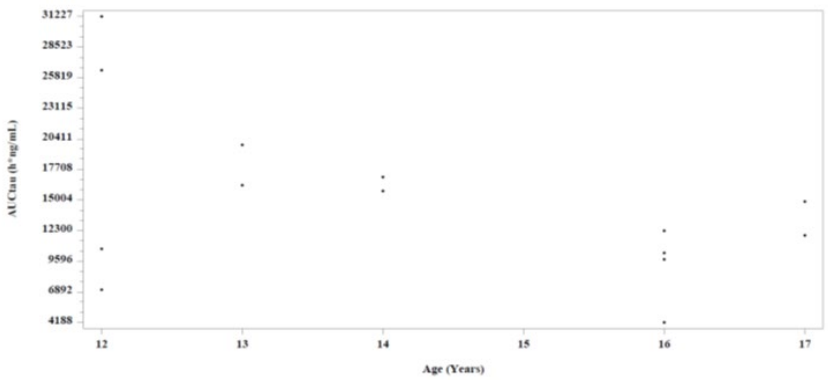


Figure 7 Scatter Plot of COBI AUCtau (with ATV) vs Baseline Age,(Intensive PK Analysis Set for COBI).Study GS US 216 0128, Cohort 1 Part A. Age 12 to < 18 years

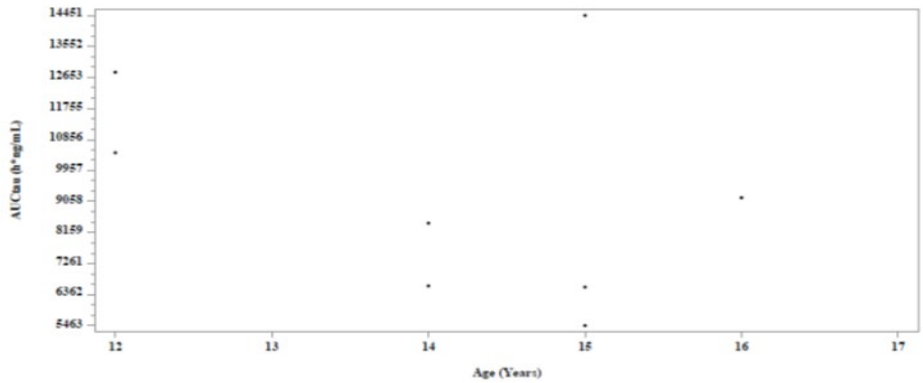


Figure 8 Scatter Plot of COBI AUCtau (with DRV) vs Baseline Age,(Intensive PK Analysis Set for COBI).Study GS US 216 0128, Cohort 1 Part A. Age 12 to < 18 years

Body Weight

The impact of body weight on ATV, DRV, and COBI PK was evaluated in paediatric subjects in Study GS-US-216-0128 with weight 32.3 to 81.4 kg. Exposures of ATV, DRV and COBI versus baseline body weight in Cohort 1 Part A are shown in the following figures for AUCtau (for Cmax and Ctau figures were also included "Adhoc-tables" in the clinical module). (See below Figure 9 to Figure 12)

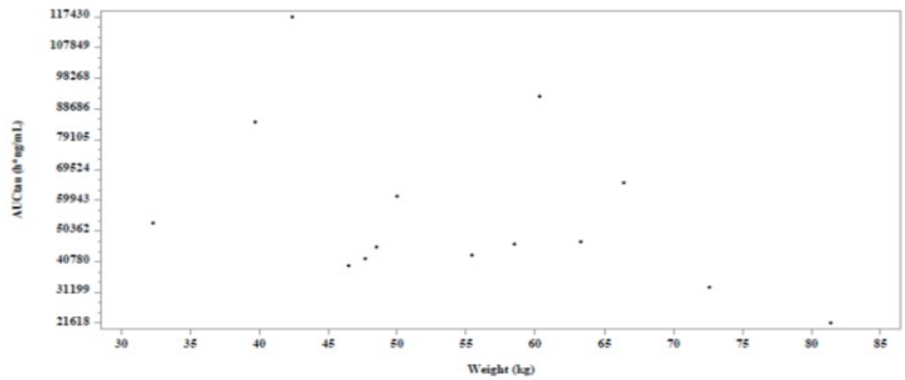


Figure 9 Scatter Plot of ATV AUCtau (boosted by COBI) vs Baseline Weight,(Intensive PK Analysis Set for ATV).Study GS US 216 0128, Cohort 1 Part A. Age 12 to < 18 years

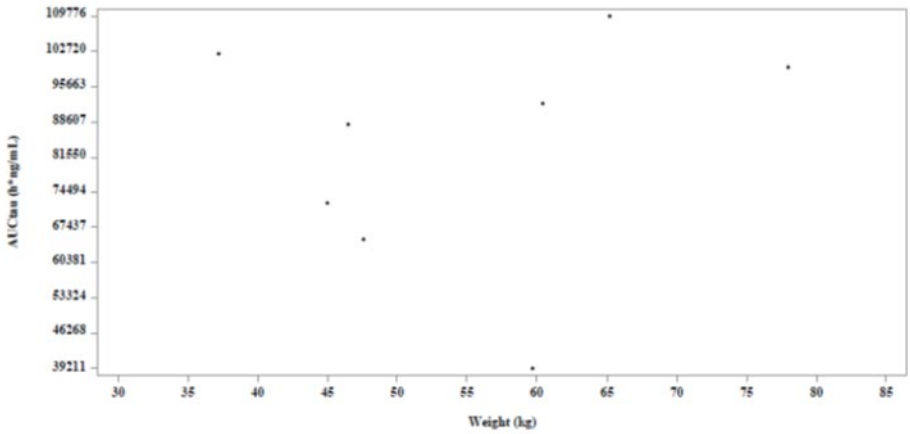


Figure 10 Scatter Plot of DRV AUCtau (boosted by COBI) vs Baseline Weight,(Intensive PK Analysis Set for DRV).Study GS US 216 0128, Cohort 1 Part A. Age 12 to < 18 years

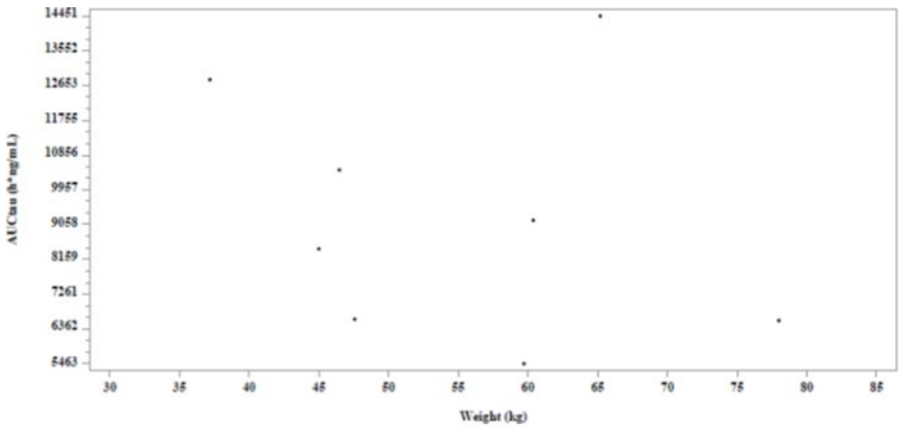


Figure 11 Scatter Plot of COBI AUCtau (with DRV) vs Baseline Weight,(Intensive PK Analysis Set for COBI).Study GS US 216 0128, Cohort 1 Part A. Age 12 to < 18 years

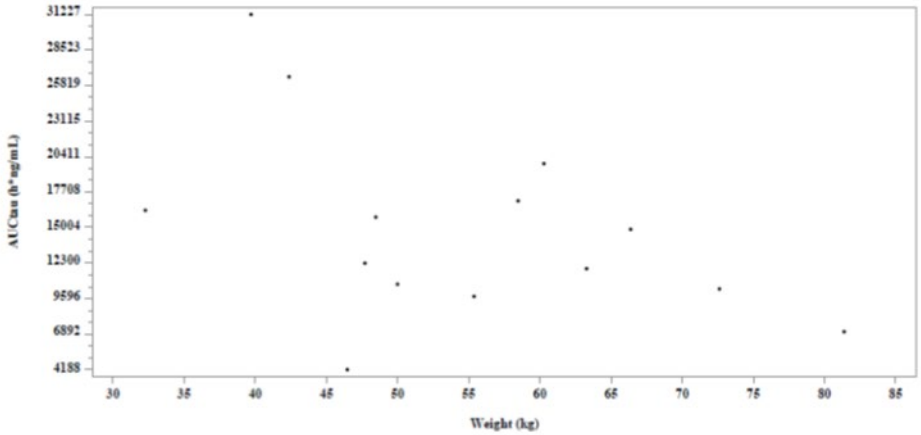


Figure 12 Scatter Plot of COBI AUCtau (with ATV) vs Baseline Weight,(Intensive PK Analysis Set for COBI).Study GS US 216 0128, Cohort 1 Part A. Age 12 to < 18 years

Pharmacokinetic interaction studies

Pharmacokinetics of ATV in HIV-1 Infected Adolescents

Plasma exposures of ATV in adolescents weighing ≥ 35 kg receiving ATV/co were compared to intensive PK data from adults 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 AUCtau, Cmax, and Ctau 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 (see table below).

Table 3 GS US 216 0128: Statistical comparisons of Atazanavir Plasma PK parameter estimates between adolescents and adults.* Cohort 1 Part A, *(Intensive PK Analysis Set for ATV)

ATV PK Parameter	Mean (%CV)		%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)[a]	56523.2 (45.8)	44845.1 (52.1)	129.26 (100.99, 165.45)
C_{max} (ng/mL)	4765.7 (46.0)	3902.9 (45.8)	123.67 (97.93, 156.17)
C_{tau} (ng/mL)[a]	1512.5 (88.6)	755.6 (84.7)	171.16 (100.21, 292.34)

ATV = atazanavir; %CV = percentage coefficient of variation; CI = confidence interval; GLSM = geometric least-squares mean; PK = pharmacokinetic(s)
Intensive PK parameters for the reference group were from COBI-boosted ATV treated adults in Studies GS-US-216-0105, and GS-US-216-0114
a Concentration at predose (0 hour) was used as surrogate for concentration at 24 hour for the purposes of estimating AUC_{tau} and C_{tau}.
Source: GS-US-216-0128 Interim 1 Clinical Study Report, Tables 15.10.1.2.1 and 15.10.1.4.1

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 pediatric patients treated with ATV/r, which is approved for use in this population (steady-state geometric mean of ATV AUCtau in pediatric subgroups 5 to < 10 kg to ≥ 35 kg ranged from 32503 to 55687 ng*h/mL; {REYATAZ® 2018}).

Exposures of ATV boosted by COBI (on Day 10) in adolescents were compared to those boosted by RTV (on Day -1) in the same group of participants. With respect to exposures of ATV boosted by COBI compared to those boosted by RTV in adolescents, AUCtau and Cmax were similar; the %GLSM ratios and associated 90% CIs were within 70% to 143%. Atazanavir Ctau was 16% lower in adolescents with COBI relative to with RTV (next table below).

Table 4 GS US 216 0128: 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)

ATV PK Parameter	Mean (%CV)		%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)[a]	56523.2 (45.8)	57746.3 (51.2)	98.68 (83.31, 116.90)
C_{max} (ng/mL)	4765.7 (46.0)	5295.7 (47.6)	90.93 (75.01, 110.23)
C_{tau} (ng/mL)[a]	1512.5 (88.6)	1565.6 (94.5)	83.81 (53.01, 132.51)

ATV = atazanavir; ATV/co = cobicistat-boosted atazanavir; ATV/r = ritonavir-boosted atazanavir; %CV = percentage coefficient of variation; CI = confidence interval; COBI = cobicistat; GLSM = geometric least-squares mean; PK = pharmacokinetic(s); RTV = ritonavir
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.
a Concentration at predose (0 hour) was used as surrogate for concentration at 24 hour for the purposes of estimating AUC_{tau} and C_{tau}.
Source: GS-US-216-0128 Interim 1 Clinical Study Report, Tables 15.10.1.2.1 and 15.10.1.5.1

The lower ATV Ctau in adolescents with COBI relative to with RTV was not considered clinically important as mean ATV Ctau was higher compared to the ATV/co-treated adult historical control group (Table 4) 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 Ctau 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 Cmin were 37643 h•ng/mL and 653 ng/mL, respectively; {REYATAZ® 2018}). This was not considered clinically important 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 ({EVOTAZ 2018, REYATAZ® 2018, Tybost 2018}).

Pharmacokinetics of DRV in HIV-1 Infected Paediatric Adolescents

Plasma exposures of DRV in adolescents weighing ≥ 35 kg receiving DRV/co were compared to population PK data from subjects receiving DRV/co in the Phase 3 Study GS-US-216-0130 (N = 298; AUCtau and Ctau were available). To compare DRV Cmax between adolescents and adults, exposures of DRV in adolescents were compared to intensive PK data from subjects receiving DRV/co in Study GS-US-216-0130 (N = 60). All subjects received COBI 150 mg.

The GLSM ratio and associated 90% CIs for DRV AUCtau and Ctau were outside the 70% to 143% boundary and were 17% and 52% lower, respectively, in adolescents receiving DRV/co compared with adults (next table below). With respect to DRV Cmax, exposures were similar in adolescents and adults (T/R 100.01 IC90% 85.82 – 116.54).

Table 5 GS US 216 0128: Statistical Comparisons of Pharmacokinetic parameter estimates between test and historical reference treatments for DRV ,(Intensive PK Analysis Set for DRV), Cohort 1 Part A: Age 12 to < 18 years.

	Treatment				Statistical Comparison			
	Test		Reference		Ratio		90% Confidence Interval	Model
Parameters	n	GLS Mean	n	GLS Mean	Test/Reference	(%)	(%)	rMSE
Analyte: DRV, Adolescents in GS-US-216-0128 (Test) vs. Adults from Study GS-US-216-0130 PopPK (Reference)								
AUCtau (h*ng/mL)	8	79968.68	298	96542.32	Test/Reference	82.83	(67.86,101.11)	0.338
Ctau (ng/mL)	8	824.09	298	1722.27	Test/Reference	47.85	(23.96,95.57)	1.180
Analyte: DRV, Adolescents in GS-US-216-0128 (Test) vs. Adults from Study GS-US-216-0130 Intensive PK (Reference)								
AUCtau (h*ng/mL)	8	79968.68	59	77534.43	Test/Reference	103.14	(83.47,127.44)	0.338
Cmax (ng/mL)	8	7422.41	60	7421.82	Test/Reference	100.01	(85.82,116.54)	0.260
Ctau (ng/mL)	8	824.09	59	947.24	Test/Reference	87.00	(42.25,179.13)	1.180

The lower DRV exposures in adolescents relative to adults were considered acceptable as the DRV Ctau values in adolescents were within the range of those observed previously with DRV-boosted COBI in adults {PREZCOBIX 2018} {Tybost 2018}; they were similar to those observed in an intensive PK substudy (N=60) in DRV/co treated adults in Phase 3 (mean [CV%] DRV Ctau= 1310.7 [74.0] ng/mL, GS-US-216-0130). Importantly, the mean DRV Ctau in DRV/co-treated adolescents was approximately 25-fold above the protein-adjusted EC50 against wild-type HIV-1 virus (55 ng/mL) and no exposure-efficacy relationship was observed for DRV/co in the Phase 3 Study GS-US-216-0130 (Pharmacokinetic and Pharmacodynamic Analyses of Darunavir at Week 24 in Study GS-US-216-0130, {Boffito 2011}).

Exposures of DRV boosted by COBI (on Day 10) in adolescents were compared to those boosted by RTV (on Day -1) in the same group of participants. For exposures of DRV boosted by COBI compared to those boosted by RTV in adolescents, AUCtau and Ctau were 11% and 50% lower, respectively, with COBI relative to RTV. Darunavir Cmax was similar; the %GLSM ratios and associated 90% CI were within 70% to 143% (see Table 6).

Table 6 GS US 216 0128: Statistical Comparisons of Pharmacokinetic parameter estimates between COBI-boosted DRV and RTV -boosted DRV in adolescents, Cohort 1 Part A. (Intensive PK Analysis Set for DRV).

	Mean (%CV)		
DRV PK Parameter	DRV/co Day 10 (Test, N = 8)	DRV/r Day -1 (Reference, N = 8)	%GLSM Ratio (90% CI) Test/Reference
AUC_{tau} (h•ng/mL)[a]	83540.3 (27.9)	95669.8 (35.3)	88.97 (67.98, 116.45)
C_{max} (ng/mL)	7591.3 (20.1)	8247.5 (36.4)	95.73 (78.18, 117.22)
C_{tau} (ng/mL)[a]	1364.8 (88.7)	2099.5 (97.7)	49.65 (23.15, 106.48)

%CV = percentage coefficient of variation; CI = confidence interval; COBI = cobicistat; DRV = darunavir; DRV/co = cobicistat-boosted darunavir; DRV/r = ritonavir-boosted darunavir; GLSM = geometric least-squares mean; PK = pharmacokinetic(s); RTV = ritonavir

PK parameters for the test group were from Day 10 intensive PK assessment when DRV was boosted by COBI.

PK parameters for the reference group were from Day -1 intensive PK assessment when DRV was boosted by RTV.

a Concentration at predose (0 hour) was used as surrogate for concentration at 24 hour for the purposes of estimating AUC_{tau} and C_{tau}.

Source: GS-US-216-0128 Interim 1 Clinical Study Report, Tables 15.10.1.2.2 and 15.10.1.5.2

Darunavir AUC boosted with RTV or COBI in adolescents in this study was similar to what has been reported previously with DRV/r in paediatric patients ≥ 35 kg, and DRV Ctau (equivalent to C0) with COBI was lower in patients in this study (mean steady-state DRV AUC and C0 were 84390 h•ng/mL and 2141 ng/mL, respectively; {PREZISTA 2018b}). The lower DRV Ctau in adolescents with COBI relative to RTV was consistent with historical data in adults treated with DRV/co and was not considered clinically relevant; DRV Ctau was ~32% lower when DRV was co-administered with COBI versus with RTV in adults {Tybost 2018}.

Pharmacokinetics of COBI 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). Exposures of COBI in adolescents receiving DRV/co were compared to intensive PK data from subjects receiving DRV/co in the Phase 3 Study GS-US-216-0130 (N = 60).In adolescents receiving ATV/co, COBI AUCtau and Ctau were 37% and 181% higher, respectively, relative to adults (see table below). The Cmax of COBI was similar in adolescents and adults; the %GLSM ratios and associated 90% CI were within 70% to 143%.

Table 7 **GS US 216 0128: Statistical Comparisons of Cobicistat plasma PK parameter estimates between adolescent and adults following *administration of COBI-boosted ATV* .Cohort 1 Part A. (Intensive PK Analysis Set for COBI).**

COBI PK Parameter	Mean (%CV)		%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)[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)

ATV = atazanavir; %CV = percentage coefficient of variation; CI = confidence interval; COBI = cobicistat; GLSM = geometric least-squares mean; PK = pharmacokinetic(s)
PK parameters for the test group were from Day 10 intensive PK assessment when ATV was boosted by COBI.
Intensive PK parameters for the reference group were from COBI-boosted ATV treated adults in Studies GS-US-216-0105 and GS-US-216-0114
a Concentration at predose (0 hour) was used as surrogate for concentration at 24 hour for the purposes of estimating AUC_{tau} and C_{tau}.
Source: GS-US-216-0128 Interim 1 Clinical Study Report, Tables 15.10.1.2.3, req10043.2, and req10043.3

In adolescents receiving DRV/co, COBI AUCtau and Ctau were 25% and 166%, higher, respectively,relative to adults. The Cmax of COBI was similar in adolescents and adults; the % GLSM ratios and associated 90% CI were within 70% to 143%.

Table 8 **GS US 216 0128: Statistical Comparisons of Cobicistat plasma PK parameter estimates between adolescent and adults following administration of COBI-boosted DRV. Cohort 1 Part A. (Intensive PK Analysis Set for COBI).**

COBI PK Parameter	Mean (%CV)		%GLSM Ratio (90% CI) Test/Reference
	Adolescents in Study GS-US-216-0128 (Test, N = 8)	Adults in Studies GS-US-216-0130 (Reference, N = 60)	
AUC_{tau} (h•ng/mL)[a]	9248.4 (34.3)	7596.3 (48.1)[b]	125.18 (100.75, 155.53)
C_{max} (ng/mL)	1121.4 (18.5)	991.4 (33.4)	116.77 (102.12, 133.51)
C_{tau} (ng/mL)[a]	82.7 (85.6)	32.8 (289.4)[b]	265.54 (116.32, 606.18)

%CV = percentage coefficient of variation; CI = confidence interval; COBI = cobicistat; DRV = darunavir; GLSM = geometric least-squares mean; PK = pharmacokinetic(s)
PK parameters for the test group were from Day 10 intensive PK assessment when DRV was boosted by COBI.
Intensive PK parameters for the reference group were from COBI-boosted DRV treated adults in Study GS-US-216-0130
a Concentration at predose (0 hour) was used as surrogate for concentration at 24 hour for the purposes of estimating AUC_{tau} and C_{tau}.
b N = 59
Source: Table 15.10.1.2.3, req10043.4 and GS-US-216-0130 Week 24 Clinical Study Report, Section 15.1, GS-US-216-0128 Interim 1 Clinical Study Report, Tables 6.2.2.3 and 6.3.2.1

The higher COBI exposures (AUCtau and Ctau) 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 pediatric HIV patients {GENVOYA® 2018, STRIBILD® 2018, Tybost 2018}.

On the other hand, after request, a revalidation of the bioanalytical method was performed, including an additional medium Quality Control (QC) sample at 30-50% of the range maximum in three precision and accuracy runs. The results confirmed that the intra- and between run accuracy and precision of all the QC samples meet the bioanalytical acceptance criteria.

Pharmacokinetics using human biomaterials

No new information is submitted.

2.3.3. Pharmacodynamics

No new information is submitted.

2.3.4. PK/PD modelling

No new information is submitted.

2.3.5. Discussion on clinical pharmacology

The clinical Study with the 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 Pediatric Subjects" is an ongoing study were the PK of the combination of Cobicistat-boosted Atazanavir (ATV/co) or Cobicistat-boosted Darunavir were studied. 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. This application is concerning only 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. 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.

Based on the several plots of PK exposure parameters vs age for DRV, ATV and COBI, it seems that age between 12 and 18 years did not have a clinically meaningful impact on the exposure of any analyte. This is consistent with historical paediatric data of ATV and DRV 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 DRV, ATV and COBI, a trend with exposure and body weight was observed for all analytes. This trend follows historical paediatric data of ATV and DRV with RTV, and of COBI within Genvoya and Stribild. No dose adjustment is considered needed as the exposures of ATV, DRV, and COBI in adolescents are within the range of adult exposures associated with safety and efficacy.

A higher ATV exposure of the paediatric population was observed, 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 AUCtau and Cmax. A slightly 16% lower Ctau was observed in adolescents with COBI relative to with RTV. This is, however, above the historical data on adults.

Similar exposure for DRV AUCtau and Cmax of the paediatric population was observed when compared with the adult historical data. However, for Ctau a lower exposure was concluded. Same conclusions were obtained in the day -1 to Day 10 comparison (DRV/r vs DRV/co). So, although similarity in AUCtau and Cmax can be observed in all comparisons, Ctau seems to be slightly lower in the test treatment. However, this lower Ctau is still within the range of Ctau values in the adult population and above the protein-adjusted EC50 against wild-type HIV-1 virus (55 ng/mL).

In adolescents receiving ATV/co or DRV/co, COBI AUCtau and Ctau 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 with GENVOYA (with even higher GLSM AUCtau, but slightly lower GLSM Ctau). The range of observed values is within the range of safety exposures in other COBI containing medicines.

During the procedure the MAH provided statistical analysis excluding a patient with less than 40 kg and taking only 600 mg of darunavir. Overall, conclusions remain the same, with similar exposure for DRV AUCtau and Cmax of the paediatric population but a lower Ctau was concluded. Still this lower Ctau is within the range of Ctau values in the adult population and above the protein-adjusted EC50 against wild-type HIV-1 virus (55 ng/mL). Since the new PK analysis with DRV only includes patients with more than 40 kg, the SmPC was updated accordingly.

2.3.6. Conclusions on clinical pharmacology

No clinically relevant differences in ATV or DRV 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, and exposures of COBI were 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 and COBI 150 mg-boosted DRV in paediatric patients weighing ≥ 40 kg.

2.4. Clinical efficacy

2.4.1. Main study

The COBI pediatric clinical development program consists of one ongoing study (GS-US-216-0128), supporting the proposed change to add paediatric patients weighing ≥ 35 kg to the approved COBI (150 mg) prescribing information.

Study 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 Pediatric Subjects

Methods

This is an ongoing open-label, multicenter, multicohort, two-part study (Part A and B) evaluating the PK, safety, efficacy, and antiviral activity of ATV/co or DRV/co administered with a BR in HIV-1 infected treatment-experienced, virologically suppressed paediatric subjects.

A total of approximately 100 paediatric subjects, ages 3 months to < 18 years, of either sex are being enrolled 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 protease inhibitor (PI), ATV or DRV, following confirmation of appropriate COBI exposure and PI exposures from the corresponding age cohort in Part A.

The remaining approximately 21 subjects are enrolled in any cohort as follows:

-Cohort 1: 12 years to <18 years old

-Cohort 2: 6 years to <12 years old

-Cohort 3: 3 years to < 6 years old

-Cohort 4: 3 months to < 3 years old

Parts A and B:

In each cohort, if the minimum number of either ATV/co or DRV/co subjects complete their Day 10 intensive PK visit before the other, then the data from that treatment may proceed to be analysed. Upon acceptable COBI and PI safety and PK data through Day 10, Part B of that cohort and Part A of the subsequent cohort will proceed to be opened for that treatment. Part A for the treatment that has not completed enrolment will remain open until the minimum number of subjects complete their Day 10 intensive PK visit.

Only Cohort 1 Part A is subject to analysis in this report.

Study participants

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.

Treatments

Subjects receive 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 during 48 weeks plus an additional 5 year, long term extension.

Upon request, the MAH explained that protocol amendment 4 was installed to specify that DRV will be administered as either tablets or oral suspension depending upon subject's weight and ability to swallow tablets. This option was added in case a subject enrolled in the study and was already taking DRV suspension. A subject enrolled while taking darunavir tablet would not have been switched to the

suspension. In Cohort 1, Part A no subjects have taken DRV suspension since none were enrolled taking this formulation. Furthermore, no data on acceptability of the DRV tablets was collected as this is not an objective of the study.

Outcomes/endpoints

The efficacy endpoints for Interim Analysis 1 were as follows:

-The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using the US Food and Drug Administration (FDA)-defined snapshot algorithm

-The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 12, 24 and 48, and every 12 weeks after Week 48 Using Missing = Excluded (M = E) Analysis

-The change from baseline in CD4 cell count (cells/µl), and CD4 percentage at Weeks 24 and 48, and every 12 weeks after Week 48

Objectives

The primary objectives of this 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 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 background regimen (BR) through 48 weeks in HIV-1 infected antiretroviral treatment-experienced paediatric subjects 3 months to <18 years of age

The secondary objective of this study is as follows:

-To evaluate the safety, tolerability, and antiviral activity of ATV/co or DRV/co, each administered with a BR, during long-term treatment (minimum 5 years) treatment in HIV-1 infected antiretroviral treatment-experienced paediatric subjects 3 months to < 18 years of age

Sample size

At least 100 paediatric subjects ages 3 months to < 18 years were planned to be enrolled into this study. For Part A, a minimum of 54 evaluable subjects are planned to be enrolled. For Part B, a minimum of 46 evaluable subjects were planned to be enrolled.

A sample size of 14 evaluable ATV subjects and 8 evaluable DRV subjects provided at least 86% and 90% power, respectively, to show that COBI-boosted ATV or DRV AUCtau in pediatric subjects was similar to AUCtau in adult subjects. For the above sample size computations, inter-subject standard deviations (natural log scale) of 0.38 h•ng/mL for ATV AUCtau (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 AUCtau (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.

In addition, a sample size of 14 evaluable ATV subjects provided > 99% power to target a 95% confidence interval (CI) within 60% and 140% of the geometric mean estimate of CL/F, assuming a percentage coefficient of variation (%CV) of 31.8% for ATV clearance (based on Study GS-US-216-0110). A sample size of 8 evaluable DRV subjects also provided at least 78% power to target a 95% CI within 60% and 140% of

the geometric mean estimate of CL/F, assuming a %CV of 35.7% for DRV clearance (based on population PK data from Study GS-US-216-0130).

Table 9 Study GS-US-216-0128, Interim 1 CSR (Cohort 1 Part A). Baseline characteristics

Characteristic	**Cohort 1 Part A: Age 12<18 Years**		
	ATV/co (N=14)	DRV/co (N=8)	Total (N=22)
Age (years)			
N	14	8	22
Mean (SD)	14 (2.0)	14 (1.5)	14(1.8)
Median	14	15	14
Min, Max	12,17	12,16	12,17
Sex at birth			
Male	10 (71,4%)	4 (50%)	14 (63,6%)
Female	4 (28,6%)	4 (50%)	8 (36,4%)
Race			
Asian	8 (57,1%)	0	8 (36,4%)
Black	2 (14,3%)	3 (37,5%)	5 (22,7)
White	4 (28,6%)	3 (37,5%)	7 (31,8%)
Other	0	2 (25%)	2 (9,1%)
Ethnicity			
Hispanic or latino	4 (28,6%)	3 (37,5%)	7 (31,8%)
Not hispanic or latino	10 (71,4%)	5 (56,5%)	15 (68,2%)
HIV-1 RNA Categories (copies/mL)			
<50	13 (92,9%)	8 (100%)	21 (95,5%)
>=50	1 (7,1%)	0	1 (4,5%)
CD4 Cell Count (cells/µL)			
N	14	8	22
Mean (SD)	796 (308,5)	1327 (679,3)	989 (530,1)
Median	770	1069	799
Min, max	486,1765	658, 2416	486, 2416
CD4 Cell Count Categories (cells/µL)			

>=350 to 500	1 (7,1%)	0	1 (4,5%)
>= 500	13 (92,9%)	8 (100%)	21 (95,5%)
Mode of Infection (HIV Risk Factors)			
Vertical transmission	14 (100%)	8 (100%)	22 (100%)
HIV Disease Status			
Asymptomatic	11 (78,6%)	8 (100%)	19 (86,4%)
Symptomatic HIV Infection	1 (7,1%)	0	1 (4,5%)
AIDS	2 (14,3%)	0	2 (9,1%)

Note: all patients were AgHBs and AbHCV negative

Randomisation

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

Blinding (masking)

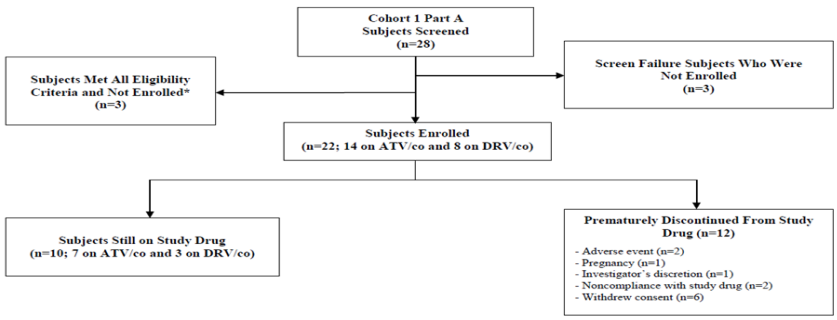
N/A. This is an open-label study

Statistical methods

The software used for all summary statistics and statistical analyses was SAS Version 9.4 (SAS Institute, Cary, NC, USA). nQuery Advisor® Version 6.0 (Statistical Solutions, Cork, Ireland) was used for the sample size and power calculation. Phoenix WinNonlin® Version 6.4 and Version 7.0 (Certara USA, Princeton, NJ, USA) was used for intensive PK analyses for Cohort 1.

Results

Participant flow



*For 3 subjects who met all eligibility criteria and not enrolled, the reasons (N) were: withdrew consent (1); and Other (2). Screen failure subjects are the subjects who did not meet the eligibility criteria.

Figure 13 Participant flow

Recruitment

First subject screened was 16 January 2014, first subject enrolled was 11 June 2014. Last subject enrolled for this report was 25 November 2015. Last subject last observation for this report was 30 May 2018. Database finalization was 4 January 2019.

Baseline data

See table above (Study GS-US-216-0128, Interim 1 CSR (Cohort 1 Part A))

Outcomes and estimation

Primary efficacy endpoint

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24

At Week 24, the percentages of subjects in Cohort 1 Part A with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm were as follows:

-ATV/co: 64.3% (9 of 14 subjects)

-DRV/co: 75.0% (6 of 8 subjects)

-Overall: 68.2% (15 of 22 subjects)

All 4 subjects in the ATV/co group who had HIV-1 RNA ≥ 50 copies/mL at Week 24 remained in the study at the investigators' discretion and subsequently resuppressed to HIV-1 RNA < 50 copies/mL at Week 48. Three subjects did not have virologic data in the Week 24 window; 1 subject in the ATV/co group had missing data during the window but was on study drug; 2 subjects in the DRV/co group discontinued study drug due to AE or other reasons, and their last available HIV-1 RNA was < 50 copies/mL.

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48

At Week 48, the percentages of subjects in Cohort 1 Part A with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm were as follows:

-ATV/co: 92.9% (13 of 14 subjects)

-DRV/co: 75.0% (6 of 8 subjects)

- Overall: 86.4% (19 of 22 subjects)

One subject in the ATV/co group had HIV-1 RNA ≥ 50 copies/mL at Week 48 and remained viremic 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 at Week 108 due to noncompliance with study drug. This subject met the protocol-defined criteria for VF through Week 48. Two subjects in the DRV/co group did not have virologic data in the Week 48 window; both subjects discontinued study drug due to AE or other reasons, and their last available HIV-1 RNA was < 50 copies/mL.

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 12, 24 and 48, and every 12 weeks after Week 48 Using Missing = Excluded (M = E) Analysis

The number and percentages of subjects in Cohort 1 Part A with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 determined using the M = E imputation method was as follows:

-Week 12: overall 100.0% (21 of 21 subjects)

-Week 24: ATV/co, 69.2% (9 of 13 subjects); DRV/co, 100.0% (7 of 7 subjects); overall, 80.0% (16 of 20 subjects)

-Week 48: ATV/co, 92.9% (13 of 14 subjects); DRV/co, 100.0% (6 of 6 subjects); overall, 95.0% (19 of 20 subjects)

The change from baseline in CD4 cell count (cells/µl), and CD4 percentage at Weeks 24 and 48, and every 12 weeks after Week 48

CD4 cell counts decreased following initiation of study drug. Mean (SD) baseline CD4 cell counts were as follows: ATV/co, 796 (308.5) cells/µL; DRV/co, 1327 (679.3) cells/µL; overall, 989 (530.1) cells/µL. Mean (SD) changes from baseline in CD4 cell count were as follows:

-Week 24: ATV/co, -29 (266.1) cells/µL; DRV/co, -494 (532.7) cells/µL; overall, -169 (413.2) cells/µL

-Week 48: ATV/co, -30 (331.1) cells/µL; DRV/co, -411 (558.8) cells/µL; overall, -144 (435.1) cells/µL

CD4% decreased following initiation of study drug. Mean (SD) baseline CD4% were as follows: ATV/co, 34.1% (6.63%); DRV/co, 42.0% (10.81%); overall, 37.0% (9.03%). Mean (SD) changes from baseline in CD4% were as follows:

-Week 24: ATV/co, -2.1% (4.83%); DRV/co, -3.5% (3.07%); overall, -2.5% (4.34%)

-Week 48: ATV/co, -0.2 (3.94%); DRV/co, -5.2% (6.81%); overall, -1.7% (5.33%)

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).

Table 10 Summary of the efficacy results from the main studies

Virologic Outcome at Week 48 Using the USFDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 Copies/mL, Cohort 1 Part A (Full Analysis Set)			
Parameter	48 weeks		
	ATV/co (N=14)	**DRV/co (N=8)**	**Total (N=22)**
HIV-1 RNA < 50 copies/mL	13 (92,9%)	6 (75%)	19 (86,4%)
HIV-1 RNA ≥ 50 copies/mL	1 (7,1%)	0	1 (4,5%)
No Virologic Data in Week 48 Window	0	2 (25%)	2 (9,1%)
Discontinued Study Drug Due to	0	1(12,5%)	1 (4,5%)

AE/Death and Last Available HIV-1 RNA < 50 copies/mL			
Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA < 50 copies/mL	0	1(12,5%)	1(12,5%)
Number and Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 Using the Missing = Excluded Imputation Method, Cohort 1 Part A (Full Analysis Set)			
Subjects with HIV-1 RNA < 50 copies/mL, n (%)[b]			
At Week 12	14/14 (100%)	7/7 (100%)	21/21 (100%)
At Week 24	9/13 (69,2%)	7/7 (100%)	16/20 (80%)
At Week 48	13/14 (92,9%)	6/6 (100%)	19/20 (95%)

[a] "Other reasons" included subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

[b]The denominator for percentages was the number of subjects in the Full Analysis Set with nonmissing HIV-1 RNA at each visit.

Virology Analyses in Subjects Experiencing Virologic Failure through Week 48 and Included in the Resistance Analysis Population

Of the 22 subjects in the Cohort 1 Part A FAS, 3 subjects (14.0%) receiving ATV/co met the VF and Resistance Analysis Population (RAP) inclusion criteria through Week 48. 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 in PR or RT, and subsequently resuppressed 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 resuppressed 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).

Summary of main study

The following table summarizes the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11 Summary of efficacy for trial GS-US-216-0128, Interim 1 CSR (Cohort 1 Part A)

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 Pediatric Subjects			
Study identifier	GS-US-216-0128		
Design	Multicenter, Open-label, Multicohort		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks Not applicable 5 year extension
Hypothesis	Primary: Co is effective and safe when co-administered whith ATV/co or DRV/co with a BR through 48 weeks in HIV-1 infected antiretroviral treatment-experienced virologically suppressed pediatric subjects 3 months to < 18 years of age Secondary: Co is effective and safe when co-administered whith ATV/co or DRV/co with a BR during long-term in HIV-1 infected antiretroviral treatment-experienced virologically suppressed pediatric subjects 3 months to < 18 years of age		
Treatments groups	ATV/co + BR		ATV/co + BR, 48 weeks , N=14
	DRV/co + BR		DRV/co + BR, 48 weeks , N=8
Endpoints and definitions	Efficacy endpoint	HIV-1 RNA < 50 copies/mL	The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using the US Food and Drug Administration (FDA)-defined snapshot algorithm
		HIV-1 RNA < 50 copies/mL	The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 12, 24 and 48, and every 12 weeks after Week 48 Using Missing = Excluded (M = E) Analysis
		CD4	The 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	30 May 2018		
Results and Analysis			

<table>
<tr><td>Analysis description</td><td colspan="4">Primary Analysis
<u>HIV-1 RNA<50 cops/ml</u>
At Week 48, the percentages of subjects in Cohort 1 Part A with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm were as follows:
-ATV/co: 92.9% (13 of 14 subjects)
-DRV/co: 75.0% (6 of 8 subjects)
-Overall: 86.4% (19 of 22 subjects)
One subject in the ATV/co group had HIV-1 RNA ≥ 50 copies/mL at Week 48 and remained viremic 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 at Week 108 due to noncompliance with study drug. This subject met the protocol-defined criteria for VF through Week 48. Two subjects in the DRV/co group did not have virologic data in the Week 48 window; both subjects discontinued study drug due to AE or other reasons, and their last available HIV-1 RNA was < 50 copies/mL.

The number and percentages of subjects in Cohort 1 Part A with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48 determined using the M = E imputation method was as follows:
-Week 12: overall 100.0% (21 of 21 subjects)
-Week 24: ATV/co, 69.2% (9 of 13 subjects); DRV/co, 100.0% (7 of 7 subjects); overall, 80.0% (16 of 20 subjects)
-Week 48: ATV/co, 92.9% (13 of 14 subjects); DRV/co, 100.0% (6 of 6 subjects); overall, 95.0% (19 of 20 subjects)

<u>CD4</u>
CD4 cell counts decreased following initiation of study drug. Mean (SD) baseline CD4 cell counts were as follows: ATV/co, 796 (308.5) cells/µL; DRV/co, 1327 (679.3) cells/µL; overall, 989 (530.1) cells/µL. Mean (SD) changes from baseline in CD4 cell count were as follows:
-Week 24: ATV/co, -29 (266.1) cells/µL; DRV/co, -494 (532.7) cells/µL; overall, -169 (413.2) cells/µL
-Week 48: ATV/co, -30 (331.1) cells/µL; DRV/co, -411 (558.8) cells/µL; overall, -144 (435.1) cells/µL CD4% decreased following initiation of study drug. Mean (SD) baseline CD4% were as follows: ATV/co, 34.1% (6.63%); DRV/co, 42.0% (10.81%); overall, 37.0% (9.03%). Mean (SD) changes from baseline in CD4% were as follows:
-Week 24: ATV/co, -2.1% (4.83%); DRV/co, -3.5% (3.07%); overall, -2.5% (4.34%)
-Week 48: ATV/co, -0.2 (3.94%); DRV/co, -5.2% (6.81%); overall, -1.7% (5.33%)</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="4">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.</td></tr>
<tr><td rowspan="2">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>ATV/co</td><td>DRV/co</td><td>Total</td></tr>
<tr><td>Number of subjects</td><td>14</td><td>8</td><td>22</td></tr>
</table>

	The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US Food and Drug Administration (FDA)-defined snapshot algorithm	13 (92,9%)	6 (75%)	19 (86,4%)
	Number and Percentage of Subjects with HIV-1 RNA < 50 copies/mL at Week 48 Using the Missing = Excluded Imputation Method, Cohort 1 Part A (Full Analysis Set)	13/14 (92,9%)	6/6 (100%)	19/20 (95%)
	The change from baseline in CD4 cell count (cells/µl), and CD4 percentage at week 48.	-30 (331.1) cells/µL -0.2 (3.94%)	-411 (558.8)cells/µL -5.2% (6.81%)	-144 (435.1)cells/µL -1.7% (5.33%)
Notes	This report describes Interim Analysis 1 of the study that included all data collected up to 01 June 2018 (data-cut date) from adolescent subjects (12 to < 18 years of age) in Cohort 1 Part A only)			

Design and conduct of clinical studies

In general, the design of the study including the patient selection criteria, statistical method, the endpoints are acceptable. For the primary outcome, the cut-off of <50 copies/ml at 48 weeks was used. This was considered acceptable. Although the use of cobicistat is done as a booster with ATV and DRV no direct comparison with the already approved booster in children – ritonavir - was made.

Efficacy analyses used the FAS which included all subjects who received at least 1 dose of study drug.

The proportions of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 were evaluated using both the US FDA-defined snapshot algorithm and M = E analyses. The 95% confidence intervals (CIs) for these percentages were constructed using the Clopper-Pearson Exact method. CD4 cell count and CD4% data, including change from baseline, were summarized using observed, on-treatment data (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug).

Efficacy data and additional analyses

The proportion of subjects achieving HIV RNA <50 copies/mL at Week 48 by the FDA Snapshot approach was 92.9% and 75% for the ATV/co and DRV/co, respectively. The proportion of subjects achieving HIV RNA <50 copies/mL at Week 48 by the Missing = Excluded Imputation Method approach was 92.9% and 100 % for the

ATV/co and DRV/co, respectively. The population treated with cobicistat, although the numbers were very small shows an acceptable efficacy in this age group population.

In terms of CD4 counts, at week 48 there was a decrease of 30 cells/mL in the ATV/co group and -411 in the DRV/co group, in total -144 cells/mL. In terms of CD4 percentage at week 48 it was -0,2% (3.94%) and -5,2% in the ATV/co and DRV/co respectively., overall -1,7% (5,33%).

Of the 22 subjects in the Cohort 1 Part A FAS, 3 subjects (14.0%) receiving ATV/co met the VF and Resistance Analysis Population (RAP) inclusion criteria through Week 48. 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 in PR or RT, and subsequently resuppressed to HIV-1 RNA < 50 copies/mL at Week 48 while continuing study drugs. No data was obtained in the two remaining subjects in the RAP, who both experienced confirmed VF at Week 48. Neither had data on resistance available.

2.4.2. Discussion on clinical efficacy

This application concerns the use of one tablet of cobicistat of 150 mg or 2 tablets of 75 mg in combination with Atazanavir or Darunavir plus a background regimen of other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced virologically suppressed paediatric subjects >12 years to < 18 years of age. The intention is to propose cobicistat as a treatment efficient booster in children (as ritonavir the other approved booster in children has some AE issues). One 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 was provided in support of this application.

In general, the design of the study including the patient selection criteria, statistical method, the endpoints are acceptable. For the primary outcome, the cut-off of <50 copies/ml at 48 weeks was used. This was considered acceptable. Although the use of cobicistat is done as a booster with ATV and DRV no direct comparison with the already approved booster in children – ritonavir - was made.

In the studies that have been submitted in support of the use of Cobicistat in adolescents, its efficacy as a boosted with ATV or DRV, was overall acceptable although sample size was limited.

2.4.3. Conclusions on the clinical efficacy

Cobicistat has been demonstrated to be effective for use in children as from 12 to 18 years by achieving HIV-1 RNA < 50 copies/mL at week 48 using the NC=F approach as defined by FDA "snapshot" approach and Missing = Excluded Imputation Method approach. The MAH will continue the part B of this study to have data in long term use. Also new data will emerge to the use of cobicistat in children bellow 12 years. The benefit risk for the proposed new posology is considered to be positive with the data available.

2.5. Clinical safety

Introduction

No information on the safety profile of the drug was provided. The MAH only provides clinical safety data from an interim analysis of Study GS-US-216-0128, to support the proposed paediatric indication for Tybost® (cobicistat [COBI]) as a pharmacokinetic (PK) enhancer of the human immunodeficiency virus type-1 (HIV-1) protease inhibitors (PIs) atazanavir (ATV) and darunavir (DRV) in paediatric patients weighing ≥ 35 kg. For this reason, an integrated analysis was not performed.

Patient exposure

The median (Q1, Q3) exposure to COBI (150 mg) in the paediatric population from Cohort 1 Part A studied in GS-US-216-0128 was 147.7 (87.7, 180.4) weeks, with approximately 90% (20 of 22) of subjects receiving study drug for ≥ 48 weeks. Most subjects (63.6%) were male. Subjects were 12 to 17 years of age (median, 14 years). A summary of demographic and baseline characteristics of subjects is presented in the previous section on safety.

Adverse events

In Cohort 1 Part A study GS-US-216-0128 Interim Analysis 1, 95.5% of subjects 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. Serious AEs were reported for 22.7% of subjects and were not considered related to study drug. There were no treatment emergent deaths. Grade 3 or 4 AEs were reported for 13.6% of subjects, none of which were considered related to study drug. Two subjects (9.1%) had AEs leading to premature study drug discontinuation. No subject had an event that might meet the definition of Category C events indicative of an AIDS-defining diagnosis reported during the study.

Table 12 Overall Summary of adverse events for trial GS-US-216-0128, Interim 1 CSR (Cohort 1 Part A)

	Study GS-US-216-0128 Cohort 1 Part A: Age 12 to < 18 Years		
	ATV/co (N = 14)	**DRV/co (N = 8)**	**Total (N = 22)**
Subjects Experiencing Any Treatment-Emergent Adverse Event	13 (92.9%)	8 (100.0%)	21 (95.5%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	10 (71.4%)	3 (37.5%)	13 (59.1%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	2 (14.3%)	1 (12.5%)	3 (13.6%)
Subjects Experiencing Any Treatment-Emergent Study Drug Related Adverse Event	4 (28.6%)	2 (25.0%)	6 (27.3%)
Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Event	0	2 (25.0%)	2 (9.1%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event	0	0	0
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	3 (21.4%)	2 (25.0%)	5 (22.7%)
Subjects Experiencing Any Treatment-Emergent Study Drug-Related Serious Adverse Event	0	0	0

	Study GS-US-216-0128 Cohort 1 Part A: Age 12 to < 18 Years		
	ATV/co (N = 14)	**DRV/co (N = 8)**	**Total (N = 22)**
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	0	2 (25.0%)	2 (9.1%)
Subjects who had Treatment-Emergent Death[a]	0	0	0

a Treatment emergent death refers to a death occurring between the first dose date and the last dose date plus 30 days (inclusive).

Adverse events were coded using MedDRA version 21.1.

Severity grades were defined by the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

Source: Interim 1 CSR GS-US-216-0128, Table 26

The most commonly reported adverse events were: upper respiratory tract infection (54,2%, N=12), cough (22.7%, N=5) and nasal congestion (22.7%, N=5). None was considered by the investigator related to the study drug.

Adverse events considered related to study drug by the investigator were reported for 27.3% (6 of 22) of subjects. Among study drug-related AEs, only hyperlipidaemia and nausea (9.1%, 2 subjects each) were reported in more than 1 subject each. Both subjects were receiving DRV/co; both cases of nausea were Grade 1 in severity and both cases of hyperlipidaemia were Grade 2 in severity. One subject with hyperlipidaemia entered the study with low-density lipoprotein (LDL) that was higher than normal range (baseline value, 119 mg/dL). The other subject with hyperlipidaemia had normal baseline LDL levels and prematurely discontinued study drug due to the AE.

Table 13 GS-US-216-0128: All Study Drug-Related Adverse Events, Cohort 1 Part A (Safety Analysis Set)

	Cohort 1 Part A: Age 12 to < 18 Years		
Adverse Event by Preferred Term[a,b,c]	**ATV/co (N = 14)**	**DRV/co (N = 8)**	**Total (N = 22)**
Number of Subjects Experiencing Any Treatment-Emergent Study Drug-Related Adverse Event	4 (28.6%)	2 (25.0%)	6 (27.3%)
Hyperlipidaemia	0	2 (25.0%)	2 (9.1%)
Nausea	0	2 (25.0%)	2 (9.1%)
Decreased appetite	0	1 (12.5%)	1 (4.5%)
Dyspepsia	1 (7.1%)	0	1 (4.5%)
Hyperbilirubinaemia	1 (7.1%)	0	1 (4.5%)

Adverse Event by Preferred Term[a,b,c]	Cohort 1 Part A: Age 12 to < 18 Years		
	ATV/co (N = 14)	DRV/co (N = 8)	Total (N = 22)
Jaundice	1 (7.1%)	0	1 (4.5%)
Proteinuria	1 (7.1%)	0	1 (4.5%)
Vomiting	1 (7.1%)	0	1 (4.5%)

ATV/co = cobicistat-boosted atazanavir; DRV = cobicistat-boosted darunavir; 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.

c Multiple AEs were counted only once per subject per preferred term.

d Relatedness to study drug was assessed by the investigator.

Source: Interim 1 CSR GS-US-216-0128, Table 28

Serious adverse event/deaths/other significant events

Serious AEs, considered unrelated to study drug by the investigator, were reported for 22.7% (5 of 22) of subjects. These included: clavicle fracture and foot fracture (both traumatic) in 1 subject receiving ATV/co; substance abuse in 1 subject receiving ATV/co; bipolar disorder in 1 subject receiving DRV/co; appendicitis in 1 subject receiving ATV/co; and chest pain in 1 subject receiving DRV/co. No SAE was reported for > 1 subject. The SAE of chest pain led to premature study drug discontinuation (on posterior analysis the patient had a first-degree AV block and was taking ABC/3TC DRV).

No treatment-emergent deaths were reported in Interim Analysis 1.

Adverse events that led to premature study drug discontinuation besides the one already mentioned in the SAE section were reported for 1 subject receiving DRV/co. It had hyperlipidaemia (Grade 2, considered related to study drug) and acanthosis nigricans (Grade 1, unrelated).

Laboratory findings

Most subjects (90.9%; 20 of 22) had at least 1 laboratory abnormality in Interim Analysis 1. The maximum toxicity was Grade 1 or 2 for 36.4% (8 of 22) of subjects; Grade 3 for 50.0% (11 of 22) of subjects. Grade 3 abnormalities were reported as follows: Grade 3 hyperbilirubinemia (36.4%, 8 of 22 subjects; all receiving ATV/co), Grade 3 haematuria by quantitative assessment (18.2%, 4 of 22 subjects; all female), Grade 3 alanine aminotransferase (ALT) increased (4.5%, 1 of 22 subjects), Grade 3 amylase increased (4.5%, 1 of 22 subjects), Grade 3 bicarbonate decreased (4.5%, 1 of 22 subjects), and Grade 3 fasting LDL increased (5.0%, 1 of 20 subjects).

A Grade 4 laboratory abnormality (creatine kinase increased) was reported for 1 subject. This subject 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 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.

Overall, most laboratory abnormalities were isolated and transient occurrences. Clinical laboratory abnormalities that were reported as AEs included hyperbilirubinemia in 2 subjects (both ATV/co), hyperlipidaemia in 2 subjects (both DRV/co), proteinuria in 2 subjects (both ATV/co), metabolic acidosis in 1 subject (ATV/co), and haematuria in 1 subject (DRV/co). No subject had an SAE associated with a clinical laboratory abnormality. One subject receiving DRV/co prematurely discontinued study drug due to an AE of hyperlipidaemia considered related to study drug by the investigator.

Safety in special populations

No new information is submitted.

Safety related to drug-drug interactions and other interactions

No new information is submitted.

Discontinuation due to adverse events

Adverse events that led to premature study drug discontinuation besides the one already mentioned in the SAE section were reported for 1 subject receiving DRV/co. It had hyperlipidaemia (Grade 2, considered related to study drug) and acanthosis nigricans (Grade 1, unrelated).

One subject had a confirmed pregnancy on Day 1012 (ie, Week 144). Study drugs (ATV/co) were discontinued with the last dose administered on Day 1012, and the subject was prematurely discontinued from the study on Day 1014. The estimated delivery date was Day 1236. Follow-up information for this subject indicated that she had an induced abortion.

Post marketing experience

No post marketing experience was submitted.

2.5.1. Discussion on clinical safety

The most commonly reported adverse events were upper respiratory tract infection (54,2%, N=12), cough (22.7%, N=5) and nasal congestion (22.7%, N=5). None was considered by the investigator related to the study drug. Adverse events considered related to study drug by the investigator were reported for 27.3% (6 of 22) of subjects. Among study drug-related AEs, only hyperlipidaemia and nausea (9.1%, 2 subjects each) were reported in more than 1 subject each.

Grade 3 laboratory abnormalities were reported as follows: hyperbilirubinemia (36.4%, 8 of 22 subjects; all receiving ATV/co), haematuria by quantitative assessment (18.2%, 4 of 22 subjects; all female), alanine aminotransferase (ALT) increased (4.5%, 1 of 22 subjects), amylase increased (4.5%, 1 of 22 subjects), bicarbonate decreased (4.5%, 1 of 22 subjects), and fasting LDL increased (5.0%, 1 of 20 subjects).

A Grade 4 laboratory abnormality (creatine kinase increased) was reported for 1 subject.

Laboratory adverse events that led to premature study drug discontinuation were reported for 1 subject receiving DRV/co. It had hyperlipidaemia (Grade 2, considered related to study drug).

2.5.2. Conclusions on clinical safety

From the limited information provided by the applicant, there are no particular concerns to highlight from the use of 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 and updated RMP (version 5.0) with this application for Tybost to include the relevant information related to the extension of the indication for the treatment of adolescents aged 12 years and older, weighing at least 35 kg, based on data from Cohort 1 Part A of Study GS-US-216-0128.

The main proposed RMP changes are the following:

- Product overview: updated indication
- Part II – Safety Specification: updated epidemiology and clinical trial data with information from study supporting the extension of indication; post-authorisation exposure was brought up to date
- Parts III-VI – no changes
- Part VII- Annexes: Administrative data updated

Changes proposed are endorsed.

The MAH did not propose changes in the list of safety concerns, the pharmacovigilance plans, or the risk minimisation measures plan, this is considered acceptable.

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

The PRAC considered that the risk management plan version 5.0 is acceptable.

The CHMP endorses the conclusions on the RMP assessment without any change.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. 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.

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 1.1 million people in the United States (US) living with HIV-1 (34 million people worldwide). The infection, if left untreated or suboptimally 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 NNRTI or PI/r or an integrase inhibitor, plus a dual NRTI backbone for initial treatment.

3.1.2. Available therapies and unmet medical need

Ritonavir (RTV, r), an agent originally approved as a HIV-1 protease inhibitor used in adults and children with HIV-1 infection, is an efficient mechanism-based inhibitor of CYP3A and is used at low dose to boost HIV-1 PIs such as lopinavir (LPV), darunavir (DRV), atazanavir (ATV) and the HIV-1 integrase inhibitor, elvitegravir (EVG), all CYP3A substrates.

Liabilities of low-dose RTV include gastrointestinal adverse events (AE) that are problematic for some patients even at lower boosting doses; the potential for metabolic complications including elevations in serum cholesterol and triglycerides; and insulin resistance in some patients. In addition, low-dose RTV has the potential to select for PI-resistant virus when used as a pharmaco-enhancer in regimens that do not contain a fully active PI. Furthermore, the paediatric RTV liquid preparation is poorly palatable, making it difficult for some children to tolerate, even at low boosting doses. Therefore, the development of new pharmaco-enhancers as part of HIV therapy for children represents an unmet medical need.

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, COBI-boosted DRV (DRV/co) with 2 NRTIs is a recommended regimen and COBI-boosted ATV (ATV/co) is an alternative regimen for the treatment of HIV-1 in adults {European AIDS Clinical Society (EACS) 2018}.

3.1.1. Main clinical studies

An ongoing 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 was provided in support of this application.

As is an ongoing study only Interim Analysis 1 of the study that included all data collected up to 01 June 2018 (data-cut date) from adolescent subjects (12 to < 18 years of age) in Cohort 1 Part A is included in this analysis.

The study was designed to evaluate the antiretroviral activity and safety of Cobicistat in combination with ATV or DRV each in combination with BR, as measured by the proportion of subjects achieving HIV-1 RNA < 50 copies/mL) at Week 48 using the NC=F approach as defined by FDA "snapshot" approach and Missing = Excluded Imputation Method approach. In addition, a PK bridging is also possible as 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.

3.2. Favourable effects

The COBI 150 mg dose was generally well tolerated by pediatric subjects through a median duration of exposure of 147.7 weeks, as demonstrated by the absence of SAEs considered related to study drug and the low incidence of AEs leading to study drug discontinuation.

Based on efficacy analyses at Week 24 and Week 48 using the US FDA defined snapshot algorithm, the rates of virologic suppression (HIV-1 RNA < 50 copies/mL) were 68% at Week 24 and 86% at Week 48, 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

The number of subjects <12 years and >18 years included in this analysis was only 22. Only 8 subjects were included in the DRV/co arm. Although the results provided support the indication there's uncertainty in the use of Cobicistat in the real-life setting.

3.4. Unfavourable effects

Adverse events considered related to study drug by the investigator were reported for 27.3% (6 of 22) of subjects. Among study drug-related AEs, only hyperlipidaemia and nausea (9.1%, 2 subjects each) were reported in more than 1 subject each.

A Grade 4 laboratory abnormality (creatine kinase increased) was reported for 1 subject.

Laboratory adverse events that led to premature study drug discontinuation were reported for 1 subject receiving DRV/co. This subject had hyperlipidaemia (Grade 2, considered related to study drug).

No new safety findings were related in this study report.

3.5. Uncertainties and limitations about unfavourable effects

There are no limitations and uncertainties about unfavourable effects that have an impact on the benefit-risk balance

3.6. Effects Table

Table 14 Effects Table for Cobicistat use in children≥12 and less than 18 years weighting≥35Kg

Effect	Short description	Unit	ATV/co	DRV/co	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary efficacy endpoint	The proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48	% n	92,9 % (13/14)*	75% (6/8)*	HIV-1 RNA ≥ 50 copies/mL at Week 48 by snapshot analysis; long term use; low number of patients	GS-US-216-0128: Cohort 1 Part A
Primary efficacy endpoint	The proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48	% n	92,9 % (13/14)	100% (6/6)	HIV-1 RNA ≥ 50 copies/mL at Week 48 using the M = E analysis; long term use; low number of patients	GS-US-216-0128: Cohort 1 Part A
Unfavourable Effects**						
Treatment-emergent study drug related AE		n/N (%)	4/14 (28.6%)	2/8 (25.0%)	low number of patients	Study GS-US-2016-0128: Cohort 1 Part A

* ATV/co :1 patient had HIV-1 RNA ≥ 50 copies/mL at Week 48 and remained viraemic at the Week 48 retest visit (HIV-1 RNA ≥ 50 copies/mL by snapshot analysis).

DRV/Co: 2 patients did not have virologic data in the Week 48 window; both subjects discontinued study drug due to AE or other reasons, and their last available HIV-1 RNA was < 50 copies/mL.

**Note: No new safety issues were found within the data presented.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Evidence of clinical efficacy is provided from a single study (GS-US-216-0128: Cohort 1 Part A) in treatment-experienced subjects 12 to < 18 years of age weighing ≥ 35 kg (only one subject weighted less than 35 Kg). The primary analysis was based on the proportion of subjects achieving HIV-1 RNA <50 copies/mL at Week 48 by FDA and using the M = E analysis.

Regarding the PK bridging, a higher ATV exposure of the paediatric population was observed, 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 AUCtau and Cmax. A slightly 16% lower Ctau was observed in adolescents with COBI relative to with RTV. This is, however, above the historical data on adults. Similar exposure for DRV AUCtau and Cmax of the paediatric population was observed when compared with the adult historical data. However, for Ctau a lower exposure was concluded in a comparison against popPK data (if comparison is made based only in Rich-sampled subjects, the T/R ratio 0f 87% is observed). Therefore, although similarity

in AUCtau and Cmax can be observed in all comparisons, Ctau seems to be slightly lower in the test treatment. However, this lower Ctau is still within the range of Ctau values in the adult population and above the protein-adjusted EC50 against wild-type HIV-1 virus (55 ng/mL). Finely, in adolescents receiving ATV/co or DRV/co, COBI AUCtau and Ctau 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 with GENVOYA (with even higher GLSM AUCtau, but slightly lower GLSM Ctau). The range of observed values is within the range of safety exposures in other COBI containing medicines.

There is no data on long term use and low number of patients was included. It's an ongoing study, so, more data will be available. No new safety issues were found within the data presented.

3.7.2. Balance of benefits and risks

Cobicistat has demonstrated its efficacy for the use in subjects ≥12 and <18 years weighting ≥35Kg in combination with ATV and at least 40 kg in combination with DRV.

There are no significant concerns to note regarding the unfavourable effects that have a negative impact on the benefit risk of Cobicistat in the proposed indications.

3.7.3. Additional considerations on the benefit-risk balance

- Not applicable

3.8. Conclusions

The overall B/R of Cobicistat is positive in the provided indication.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP 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 and IIIB

To modify the approved therapeutic indication to include new population (adolescents aged 12 years and older, weighing at least 35 kg) for the treatment of HIV-1. As a consequence, sections 4.1, 4.2, 4.5, 4.8,5.1,5.2 of the SmPC and sections 1,2,3 of the PL are updated accordingly. The updated RMP version 5 is also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

Risk management plan (RMP)

The 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.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Amendments to the marketing authorisation

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0060/2017 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

Extension of Indication to modify the approved therapeutic indication for Tybost to include the adolescent population aged 12 years old and older weighing at least 35kg when Tybost is used in combination with ATV and at least 40 kg when it is used in combination with Darunavir.
As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC and sections 1,2,3 of the Product leaflet have been updated accordingly. An updated RMP version 5 was agreed during the procedure.

Summary

Please refer to Scientific Discussion 'Tybost-H-C-002572-II-51'