EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/425517/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prezista

International non-proprietary name: darunavir

Procedure No. EMEA/H/C/000707/II/0107

Note

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

Table of contents

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
$eGFR_{cr}$	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
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
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
TLOVR	time to loss of virologic response

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 2 April 2020 an application for a variation.

The following variation was requested:

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

Extension of indication for PREZISTA (darunavir) (800 mg) in combination with COBI (150 mg) for the treatment of HIV-1 infection in adolescents (aged 12 years and older with body weight at least 40 kg). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC and section 3 of the PL are being updated accordingly. The updated RMP version 27.1 has also been submitted.

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

Information on paediatric requirements

The application does not fall under the agreed PIP for PREZISTA (Decision P/138/2010, dated 30 July 2010). The PIP was considered completed as indicated in the compliance statement (dated 9 December 2011) and in the CHMP Opinion (dated 25 July 2013).

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	2 April 2020
Start of procedure:	25 April 2020
CHMP Rapporteur Assessment Report	19 June 2020
PRAC Rapporteur Assessment Report	19 June 2020
PRAC members comments	01 July 2020
Updated PRAC Rapporteur Assessment Report	02 July 2020
PRAC Outcome	09 July 2020
CHMP members comments	13 July 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 July 2020
Opinion	23 July 2020

2. Scientific discussion

2.1. Introduction

The Marketing Authorization Holder, Janssen-Cilag International NV, submitted a Type II Variation to extend the use of PREZISTA (darunavir) (800 mg) in combination with COBI (150 mg) for the treatment of HIV-1 infection in adolescents (aged 12 years and older with body weight at least 40 kg).

The use of PREZISTA, in combination with cobicistat, in adolescent patients is supported by the results of Study GS-US-216-0128, in HIV-1 infected ART-experienced, virologically suppressed adolescent subjects taking darunavir (DRV) (800 mg) and cobicistat (COBI) (150 mg) as single components.

The new proposed use is also in line with the approved use of COBI (150 mg) tablets (Tybost) in adolescents in the EU (EMEA/H/C/002572/II/0051) and with the approved use of the DRV/COBI 800/150 mg fixed-dose combination (REZOLSTA) in adolescents in the EU (EMEA/H/C/002819/II/0033).

Study GS-US-216-0128 was already assessed in above-mentioned procedures for Tybost and Rezolsta. Therefore, where applicable, the assessment of study GS-US-216-0128 done for Rezolsta is presented in this AR for Prezista.

The application does not fall under the agreed PIP for PREZISTA (Decision P/138/2010, dated 30 July 2010). The PIP was considered completed as indicated in the compliance statement (dated 9 December 2011) and in the CHMP Opinion (dated 25 July 2013).

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Table 1: Tabulated Overview of Study GS-US-216-0128

Study (Phase, Status)	Number of Subjects and Treatment	Main Endpoints
GS-US-216-0128 (Phase 2/3, ongoing)	N=8[a,b] DRV[b] and COBI (150 mg) once daily + ARV background regimen[c]	PK of DRV and COBI at Day 10; Incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities

AE = adverse event; ART = antiretroviral treatment; ARV = antiretroviral; ATV = atazanavir; COBI = cobicistat; CSR = clinical study report; DRV = darunavir; HIV-1 = human immunodeficiency virus type 1; N = number of subjects; NRTI = nucleoside reverse transcriptase inhibitors; PK = pharmacokinetics; PI = protease inhibitor.

[a] In Study GS-US-216-0128, an additional arm investigating the combination ATV+COBI was evaluated (N=14). The full intent-to-treat population for the study included 22 subjects. Data from the ATV+COBI arm are not discussed in this summary document.

[b] DRV doses were administered according to applicable Prescribing Information. Only the 7 subjects who received DRV 800 mg + COBI 150 mg are discussed in this summary document.

[c] For all subjects, the ARV background regimen had to include 2 NRTIs and might contain additional ARV agents except for the following disallowed agents: saquinavir, indinavir, nelfinavir, double PI regimens, raltegravir, elvitegravir, efavirenz, nevirapine, delavirdine, maraviroc, etravirine, rilpivirine, dolutegravir, and investigational ARV agents.

Prezista (darunavir) is available as oral suspension 100 mg/ml for this extension and as film-coated tablets of 400 and 800 mg.

2.3.2. Pharmacokinetics

The appropriateness of the combined use of DRV 800 mg and COBI 150 mg once daily in adolescents aged ≥12 years is confirmed by the results from the adolescent cohort of the ongoing Phase 2/3 Study GS-US-216-0128 in HIV-1 infected, ART-experienced, virologically suppressed children. Adolescents in this cohort received DRV (800 or 675 mg) plus COBI (150 mg once daily) in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs).

2.3.2.1. Main study GS-US-216-0128

Study GS-US-216-0128 is an ongoing open-label, multicohort, two-part, Phase 2/3 study to evaluate the PK, safety, and efficacy of COBI-boosted atazanavir (ATV) or COBI-boosted DRV in treatment-experienced, virologically suppressed, HIV-1 infected, pediatric subjects. Eligible subjects are on a stable ARV regimen including 2 NRTIs and either ATV/rtv once daily, or DRV/rtv once daily or twice daily as per product label for a minimum of 3 months prior to the Screening visit. The primary objectives of this study are to evaluate the steady-state PK and confirm the dose of ATV and COBI or DRV and COBI in HIV-1 infected, antiretroviral treatment (ART)-experienced, virologically suppressed, pediatric subjects 3 months to <18 years of age and to evaluate the safety, tolerability, and efficacy of COBI-boosted ATV or

COBI-boosted DRV, each co-administered with a background regimen through 48 weeks in HIV-1 infected, ART-experienced, virologically suppressed, pediatric subjects 3 months to <18 years of age. The secondary objective of this study is to evaluate the safety, tolerability, and antiviral activity of long-term treatment with COBI-boosted ATV or COBI-boosted DRV, each co-administered with a background regimen, in HIV-1 infected, ART-experienced, virologically suppressed, pediatric subjects 3 months to <18 years of age.

For the scope of this submission, only data from subjects receiving COBI-boosted DRV in Cohort 1 (≥12 to <18 years of age) Part A (evaluating the steady-state PK and confirming the dose of DRV and COBI) will be discussed.

Subjects and Methods

A total of 8 treatment-experienced, virologically suppressed, HIV-1 infected, adolescent subjects (aged ≥12 to <18 years and weighing ≥35 kg) were included in the DRV+COBI group in Cohort 1 Part A of the study. Subjects received the recommended dose of COBI for HIV-1 infected adults (150 mg once daily) in combination with approved doses for DRV based on body weight according to the applicable prescribing information (800 mg once daily [body weight ≥40 kg; N=7] or 675 mg once daily [body weight ≥30 kg to <40 kg; N=1]), and a background regimen, for 48 weeks. For all subjects, the background regimen had to include 2 NRTIs. The background regimen could contain additional ARV agents except for the following disallowed agents: saquinavir, indinavir, nelfinavir, double PI regimens, raltegravir, EVG, efavirenz, nevirapine, delavirdine, maraviroc, etravirine, rilpivirine, dolutegravir, and investigational ARV agents.

An intensive PK evaluation was performed on Day -1 (for DRV) and Day 10 (for DRV and COBI) for subjects enrolled in Cohort 1 Part A. Pharmacokinetic blood samples were collected at pre-dose and up to 12 hours post-dose on Day -1 (for DRV) and Day 10 (for DRV and COBI). Intensive PK blood samples were collected at pre-dose and 1, 2, 3, 4, 5, 8, and 12 hours post-dose on Day -1 (for ATV or DRV) and Day 10 (for ATV or DRV and COBI). The pre-dose (0 hours) concentration was also used as a surrogate for the concentration at the end of the dosing interval (24 hours) for the purpose of estimating AUCtau and Ctau. The primary PK endpoint was AUC from time of administration up to the end of the dosing interval (AUCtau) for DRV on Day 10. The secondary PK endpoints were plasma concentration at the end of the dosing interval (Ctau), Cmax, and apparent clearance (CL/F) for DRV, and AUCtau, Ctau, Cmax, CL/F, and apparent volume of distribution of the drug (Vz/F) for COBI on Day 10.

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

- Intensive PK data (AUCtau, Ctau, and Cmax) from adults receiving COBI-boosted DRV in Study GS-US-216-0130 (N=60).
- Population PK data (AUCtau and Ctau) from adults receiving COBI-boosted DRV in Study GS-US-216-0130 (N=298).

In addition, exposures of DRV boosted by COBI in adolescents (on Day 10) were compared with those boosted by rtv (on Day -1) in the same pediatric subjects to confirm that exposures of boosted DRV with COBI were comparable to those approved in paediatrics with rtv. All subjects were receiving DRV boosted by COBI or rtv once daily at least 10 days prior to the intensive PK visits.

Exposures of COBI were compared with historical data with COBI-boosted DRV from Study GS-US-216-0130 (intensive PK data; N=60).

Bioanalytical Methods

Plasma concentrations of DRV and COBI, as well as other ARVs were determined using validated liquid chromatographic - mass spectrometry/mass spectrometry methods. Details are provided in the respective clinical study reports (CSRs).

DRV was analysed using analytical method QPS 42-0902, validated at QPS (Newark, Delaware, United States) under the responsibility of Gilead Sciences Inc. The calibrated range for DRV was 20 to 10000 ng/mL; the inter-run precision ranged from 3.4% to 8.7%; the inter-run accuracy ranged from -9.6% to -0.3%. The QC concentrations were 60, 800 and 9000 ng/mL.

COBI (GS-9350) was measured using analytical method QPS 60-1343, validated at QPS (Newark, Delaware, United States) under the responsibility of Gilead Sciences Inc. The calibrated range for COBI was 5 to 2500 ng/mL; the inter-run precision ranged from 5.2% to 113.0%; the inter-run accuracy ranged from -5.8% to 74.0%. The large precision and accuracy values are attributed to outliers for QC 15 and QC 100 in one run that appear to have been inadvertently switched. All QC data points from accepted runs were included in the statistical calculations. The QC concentrations were 15, 100, 1000 and 2000 ng/mL.

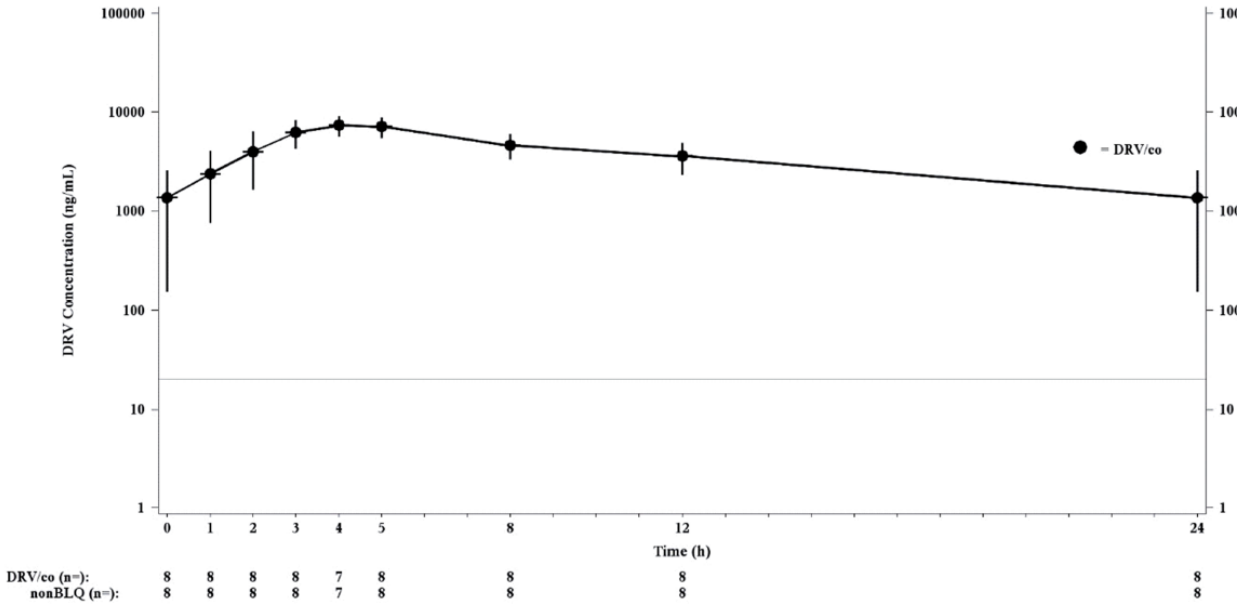
Demographics - dosing

Demographics of the 8 subjects included in the PK dataset are given in Table 11 (See section 2.4.1 Main Study). This table shows that mean body weight at baseline was 55 kg (min 37 kg; max 78 kg). One subject of the eight subjects included was weighing 37 kg (< 40 kg. male, 12-yr old) and received a DRV dose of 600 mg (instead of the planned protocol dose of 675 mg), the others received a DRV dose 800 mg. At the time of enrolment, this subject weighing 37 kg was on a stable antiretroviral regimen including 2 nucleoside reverse transcriptase inhibitors and ritonavir-boosted DRV 600 mg. The subject was able to maintain virologic suppression with the DRV 600 mg dose, and therefore the dose of DRV remained unchanged when the subject began on Study GS-US-216-0128. This subject's data have been excluded from the primary statistical comparisons.

From the 7 subjects receiving the 800 mg DRV dose, 1 subject was 16-yr old, 3 subjects were 15-yr old, two subjects were 14-yr old, and one subject was 12-yr old, which means the adolescent age range of 12-18 yrs old was reasonably covered.

Results: Pharmacokinetics of DRV

All PK parameters were calculated using conventional non-compartmental methods using actual times of blood sampling. The mean (SD) steady-state plasma concentration vs time profile for DRV following administration of COBI-boosted DRV to virologically suppressed, HIV-1 infected adolescents ≥35 kg on Day 10 (N=8) is shown in Figure 1. Maximal plasma concentrations of DRV were achieved at approximately 4.50 hours post-dose (median tmax) (Table 2).



BLQ = below the lower limit of quantitation; DRV/co = darunavir boosted by cobicistat.
Solid reference line indicates lower limit of quantitation (20.0 ng/mL).

Figure 1: Mean (SD) Plasma DRV Concentrations vs Time (Semi-logarithmic Scale), Cohort 1 Part A (Intensive PK Analysis Set for DRV [DRV Boosted by COBI]) (Study GS-US-216-0128)

Steady-state PK parameters for DRV following the administration of DRV and COBI (Day 10) in HIV-1 infected adolescents ≥35 kg are presented in Table 2.

Table 2: COBI-boosted DRV Steady-state Plasma PK Parameters (Study GS-US-216-0128 Cohort 1 Part A; Intensive PK Analysis Set for DRV)

	Mean (%CV); t_{max}, $t_{1/2}$: Median (Q1; Q3)
DRV PK Parameter	**COBI-boosted DRV (Day 10)**
N	8
AUC_{tau} (h.ng/mL)[a]	83,540.3 (27.9)
C_{max} (ng/mL)	7,591.3 (20.1)
C_{tau} (ng/mL)[a]	1,364.8 (88.7)
t_{max} (h)	4.50 (4.00, 5.00)
$t_{1/2}$ (h)	7.80 (4.00, 12.11)

AUC_{tau} = area under the plasma concentration-time curve from time of administration up to the end of the dosing interval; C_{max} = maximum plasma concentration; COBI = cobicistat; C_{tau} = plasma concentration at the end of the dosing interval; CV = coefficient of variation; DRV = darunavir; N = number of subjects; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; $t_{1/2}$ = terminal half-life; t_{max} = time to reach maximum plasma concentration.

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

The lower and upper bounds of the 95% CI of CL/F relative to the geometric mean for DRV were within the FDA-specified boundary of 60% to 140% (Table 3).

Table 3: DRV (Day 10, With COBI) CL/F (Study GS-US-216-0128 Cohort 1 Part A; Intensive PK Analysis Set for DRV)

DRV PK Parameter	CL/F (L/h)
N	8
Mean (%CV)	10.3 (43.9)
Geometric mean	9.7
95% CI/Geometric mean	0.728, 1.374

CI = confidence interval; CL/F = apparent clearance; COBI = cobicistat; CV = coefficient of variation; DRV = darunavir; N = number of subjects; PK = pharmacokinetic(s).
PK parameters were from Day 10 intensive PK assessment when DRV was boosted by COBI.

When compared with historical PK data for DRV administered as DRV+COBI 800/150 mg once daily in treatment-naïve and treatment-experienced, HIV-1 infected adults (Study GS-US-216-0130 PK substudy), DRV AUCtau and Cmax were similar, and the DRV Ctau was 29% lower, respectively, in adolescents receiving COBI-boosted DRV than in adults (Table 4). When compared with the overall adult population PK data for DRV in Study GS-US-216-0130, DRV AUCtau and Ctau were 20% and 61% lower, respectively, in adolescents receiving COBI-boosted DRV, and the geometric least-squares mean (GLSM) ratio and associated 90% CIs were outside the 70% to 143% boundaries (Table 4).

The lower DRV exposures in adolescents relative to adults were not considered clinically relevant, as the DRV Ctau values in adolescents were within the overall range of those observed previously with COBI-boosted DRV in adults. Importantly, the mean DRV Ctau was approximately 20-fold above the protein-adjusted half-maximal effective concentration 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 and Phase 3 D/C/F/TAF studies. 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.

Table 4: Statistical Comparisons of DRV Plasma PK Parameter Estimates Between Adolescents (Study GS-US-216-0128 Cohort 1 Part A) and Adults (Study GS-US-216-0130)

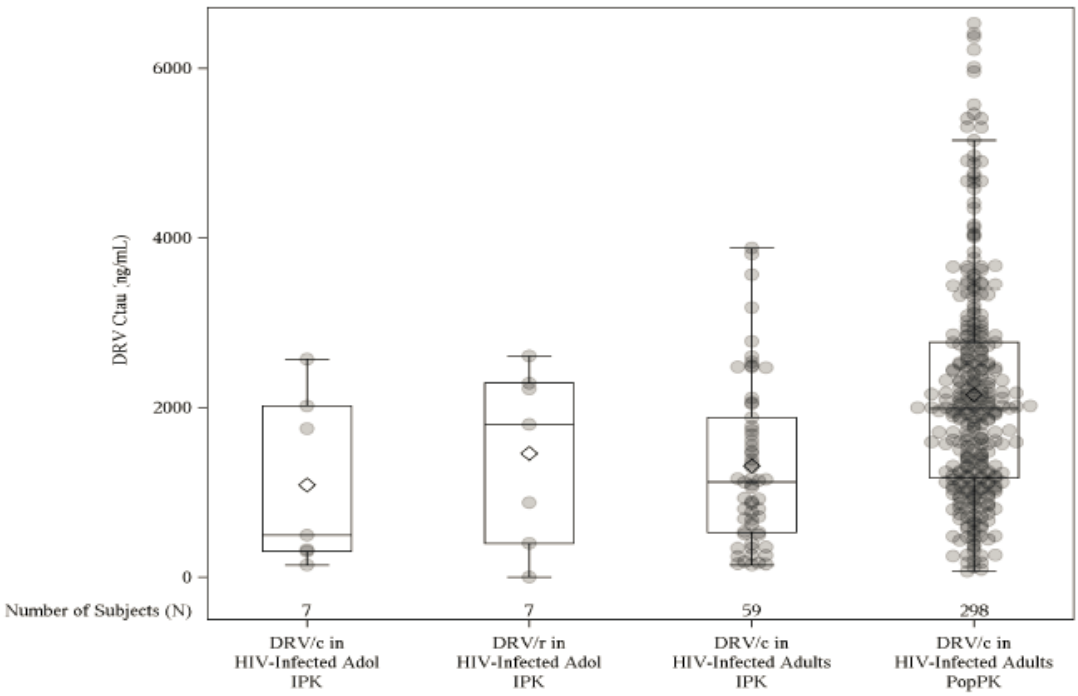
DRV PK Parameter	Mean (%CV) GLSM: Adults in Study GS-US-216-0130, Week 24 (Reference)	Mean (%CV) GLSM: Adolescents in Study GS-US-216-0128, Day 10 (Test)[a]	%GLSM Ratio (Test/Reference)	90% CI
N	60[b]	7		
AUC_{tau} (h.ng/mL)[c]	81,645.9 (32.2) 77,534.4	80,876.8 (29.5) 77,216.5	99.59	79.03 - 125.50
C_{max} (ng/mL)	7, 663.2 (25.1) 7,421.8	7,505.7 (21.7) 7,318.8	98.61	83.06 - 117.07
C_{tau} (ng/mL)[c]	1,310.7 (74.0) 947.2	1,086.9 (91.6) 675.6	71.33	34.28 - 148.41
N	298[d]	7		
AUC_{tau} (h.ng/mL)[c]	100,152 (32.0) 96,542.3	80,876.8 (29.5) 77,216.5	79.98	64.21 - 99.63
C_{tau} (ng/mL)[c]	2,043 (61.5) 1,722.3	1,086.9 (91.6) 675.6	39.23	19.44 - 79.18

AUC_{tau} = area under the plasma concentration-time curve from time of administration up to the end of the dosing interval; CI = confidence interval; C_{max} = maximum plasma concentration; COBI = cobicistat; C_{tau} = plasma concentration at the end of the dosing interval; CV = coefficient of variation; DRV = darunavir; GLSM = geometric least-squares mean; N = number of subjects; PK = pharmacokinetic(s).

a. PK parameters for the test group were from Day 10 intensive PK assessment when DRV was boosted by COBI.
b. Intensive PK data from subjects receiving COBI-boosted DRV in Study GS-US-216-0130; N=59 for AUC_{tau} and C_{tau}.
c. Concentration at predose (0 hours) was used as surrogate for concentration at 24 hours for the purposes of estimating AUC_{tau} and C_{tau}.
d. Population PK data from subjects receiving COBI-boosted DRV in Study GS-US-216-0130 (only AUC_{tau} and C_{tau} were available).

Source: Mod5.3.5.2/GS-US-216-0130-W24-CSR/Tab10-1, Tab6.3.5.1, and data on file (GS-US-216-0128 ad-hoc analysis table req10367.1.1 and table req10367.9).

Boxplots comparing the Ctau values of DRV at steady state are presented in the following graph, which allows the same conclusions to be drawn as above.



DRV/c = darunavir boosted with cobicistat; DRV/r = darunavir boosted with ritonoavir; Adol = adolescents.
IPK = intensive pharmacokinetics; PopPK = population pharmacokinetics.
One subject, who weighed <40 kg at baseline and received DRV 600 mg, was excluded from analysis.
Lines are medians and interquartile ranges; dots are individual values; diamonds are means.
DRV/COBI and DRV/r in HIV-Infected adolescent IPK data are from Study GS-US-216-0128, and adult IPK and PopPK data are from Study GS-US-216-0130.

Figure 2: Boxplots of Plasma DRV PK parameter Ctau from Studies Study GS-US-216-0128 and GS-US-216-0130

Exposures of DRV boosted by COBI (on Day 10) in adolescents were also compared to those boosted by rtv (on Day -1) in the same group of subjects (Table 5). All subjects were receiving DRV boosted by COBI or rtv once daily at least 10 days prior to the intensive PK visits. The AUCtau and Ctau were 9% and 51% lower, respectively, with COBI relative to rtv. Darunavir Cmax was similar.

Table 5: Statistical Comparisons of PK Parameter Estimates Between COBI-boosted DRV and rtv-boosted DRV in Adolescents (Study GS-US-216-0128 Cohort 1 Part A)

	Mean (%CV) GLSM			
DRV PK Parameter	rtv-boosted DRV Day -1 (Reference)[a]	COBI-boosted DRV Day 10 (Test)[b]	%GLSM Ratio (Test/Reference)	90% CI
N	7	7		
AUC_{tau} (h.ng/mL)[c]	90,375.2 (36.2) 85,012.0	80,876.8 (29.5) 77,216.5	90.83	66.27 - 124.50
C_{max} (ng/mL)	8,125.7 (39.6) 7,578.2	7,505.7 (21.7) 7,318.8	96.58	76.05 - 122.65
C_{tau} (ng/mL)[c]	1,456.6 (70.4) 1,374.2	1,086.9 (91.6) 675.6	49.17	19.80 - 122.10

AUC_{tau} = area under the plasma concentration-time curve from time of administration up to the end of the dosing interval; CI = confidence interval; C_{max} = maximum plasma concentration; COBI = cobicistat; C_{tau} = plasma concentration at the end of the dosing interval; CV = coefficient of variation; DRV = darunavir; GLSM = geometric least-squares mean; N = number of subjects; PK = pharmacokinetic(s); rtv = low-dose ritonavir.

a. PK parameters for the reference group were from Day -1 intensive PK assessment when DRV was boosted by rtv.
b. PK parameters for the test group were from Day 10 intensive PK assessment when DRV was boosted by COBI.
c. Concentration at predose (0 hours) was used as surrogate for concentration at 24 hours for the purposes of estimating AUC_{tau} and C_{tau}.

Source: data on file (GS-US-216-0128 ad-hoc analysis table req10367.1.2 and table req10367.9).

Results: Pharmacokinetics of COBI

Steady-state PK parameters for COBI following the administration of DRV+COBI to virologically suppressed, HIV-1 infected adolescents on Day 10 are presented in Table 6. Maximal plasma concentrations of COBI were achieved at 4.00 hours post-dose (median tmax).

Table 6: COBI Steady-state Plasma PK Parameters (Study GS-US-216-0128 Cohort 1 Part A; Intensive PK Analysis Set for COBI)

	Mean (%CV); t_{max}, $t_{1/2}$: Median (Q1; Q3)
COBI PK Parameter	COBI (as Booster for DRV) (Day 10)
N	8
AUC_{tau} (h.ng/mL)[a]	9,248.4 (34.3)
C_{max} (ng/mL)	1,121.4 (18.5)
C_{tau} (ng/mL)[a]	82.7 (85.6)
t_{max} (h)	4.00 (4.00, 5.00)
$t_{1/2}$ (h)	2.93 (2.45, 4.71)

AUC_{tau} = area under the plasma concentration-time curve from time of administration up to the end of the dosing interval; C_{max} = maximum plasma concentration; COBI = cobicistat; C_{tau} = plasma concentration at the end of the dosing interval; CV = coefficient of variation; DRV = darunavir; N = number of subjects; PK = pharmacokinetic(s); Q1 = first quartile; Q3 = third quartile; $t_{1/2}$ = terminal half-life; t_{max} = time to reach maximum plasma concentration.

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

The lower and upper bounds of the 95% CIs of CL/F and Vz/F relative to the geometric mean for COBI following administration of DRV+COBI were within the FDA-specified boundary of 60% to 140% (Table 7).

Table 7: COBI CL/F and Vz/F (Study GS-US-216-0128 Cohort 1 Part A; Intensive PK Analysis Set for DRV)

COBI PK Parameter	CL/F (L/h)	V_z/F (L)
N	8	8
Mean (%CV)	17.9 (33.2)	86.2 (27.1)
Geometric mean	17.1	83.1
95% CI/Geometric mean	0.752, 1.330	0.775, 1.290

CI = confidence interval; CL/F = apparent clearance; COBI = cobicistat; CV = coefficient of variation; DRV = darunavir; N = number of subjects; PK = pharmacokinetic(s); V_z/F = apparent volume of distribution of the drug.

When compared with historical intensive PK data for COBI administered as DRV+COBI 800/150 mg once daily in treatment-naïve, and treatment-experienced, HIV-1 infected adults (Study GS-US-216-0130 intensive PK sub-study; N=60), COBI AUCtau, Cmax and Ctau were 19%, 16% and 28% higher, respectively, in adolescents receiving DRV+COBI relative to adults (Table 8).

The higher COBI exposures in adolescents relative to adults were not considered clinically relevant as they were within the overall range of exposures associated with robust PK boosting and safety established in the Rezolsta, Symtuza, Tybost, and Genvoya programs in adult and paediatric HIV patients. There was a large degree of variability in COBI Ctau in adolescents and adults, which reduced the precision of this estimate. This was attributed to the variability in the time of collection of the pre-dose PK sample at the intensive PK visit (collected approximately 8.5 to 28 hours post-dose; pre-dose samples were used as a surrogate for Ctau.

Table 8: Statistical Comparisons of COBI Plasma PK Parameter Estimates Between Adolescents (Study GS-US-216-0128 Cohort 1 Part A) and Adults (Study GS-US-216-0130)

	Mean (%CV) GLSM			
COBI PK Parameter	Adults in Study GS-US-216-0130, Week 24 (Reference)	Adolescents in Study GS-US-216-0128, Day 10 (Test)[a]	%GLSM Ratio (Test/Reference)	90% CI
N	60[b]	7		
AUC_{tau} (h.ng/mL)[c]	7,596.3 (48.1) 7,021.7	8,741.1 (34.9) 8,330.2	118.6	94.88 - 148.34
C_{max} (ng/mL)	991.4 (33.4) 944.8	1,115.9 (20.0) 1,095.4	115.9	99.85 - 134.61
C_{tau} (ng/mL)[c]	32.8 (289.4) 17.2	28.3 (157.2) 22.0	128.1	50.97 - 322.00

AUC_{tau} = area under the plasma concentration-time curve from time of administration up to the end of the dosing interval; CI = confidence interval; C_{max} = maximum plasma concentration; COBI = cobicistat; C_{tau} = plasma concentration at the end of the dosing interval; CV = coefficient of variation; DRV = darunavir; GLSM = geometric least-squares mean; N = number of subjects with data; PK = pharmacokinetic(s).

a. PK parameters for the test group were from Day 10 intensive PK assessment when DRV was boosted by COBI.
b. N=59 for AUC_{tau} and C_{tau}.
c. Concentration at predose (0 hours) was used as surrogate for concentration at 24 hours for the purposes of estimating AUC_{tau} and C_{tau}.

Source: Mod5.3.5.2/GS-US-216-0130-W24-CSR/Tab10-2 and data on file (GS-US-216-0128 ad-hoc analysis table req10367.1.3 and table req10367.7).

2.3.3. Discussion on clinical pharmacology

The appropriateness of the combined use of DRV 800 mg and COBI 150 mg once daily in adolescents aged ≥12 years is confirmed by the results from the adolescent cohort of the ongoing Phase 2/3 Study GS-US-216-0128 in HIV-1 infected, ART-experienced, virologically suppressed children. Adolescents in this cohort received DRV (800 or 675 mg) plus COBI (150 mg once daily) in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs).

The applicant concluded that no clinically relevant differences in DRV 800 mg exposures with COBI 150 mg once daily were observed in HIV-1 infected, virologically suppressed adolescents compared with adults, and also exposures of COBI were within the safe and efficacious ranges associated with robust PK boosting in the Rezolsta, Symtuza, Tybost, and Genvoya programs. The PK data support the use of COBI 150 mg-boosted DRV (800 mg) in adolescents weighing at least 40 kg.

In general, this conclusion was supported by the CHMP, as Table 4 shows that the PK parameters AUCtau, Cmax and Ctau for DRV were on average at the same level for the adolescents and adults using the intensive PK data. For COBI, Table 8 shows that AUCtau and Cmax were similar between adolescents and adults, only mean Ctau for the adolescents was 28% higher than for the adults, which means that the boosting effect is at least maintained in comparison to the adults. There are no safety issues expected with this exposure level.

From the 7 subjects receiving the 800 mg DRV dose, 1 subject was 16-yr old, 3 subjects were 15-yr old, two subjects were 14-yr old and one subject was 12-yr old, which means the adolescent age range of 12-18 yrs old was reasonably covered.

In general, the precision of the PK parameter estimates AUC and Cmax were sufficient both for DRV and COBI, allowing conclusions to be drawn on the comparison with N=8 adolescent subjects and probably also ultimately when the group is reduced to 7 adolescents. There was a large degree of variability in Ctau both for DRV and COBI, but both in adolescents and adults, which reduced the precision of this estimate. This was attributed to the variability in the time of collection of the pre-dose PK sample at the intensive PK visit on Day 10 (collected approximately 8.5 to 28 hours after the previous dose on Day 9).

CHMP noted that the adolescents PK parameters on Ctau tends to be inexplicably lower than in adults, but that might not have significant impact.

2.3.4. Conclusions on clinical pharmacology

Results from study GS-US-216-0128 showed that the PK parameters AUCtau, Cmax and Ctau for DRV were on average at the same level for the adolescents and adults using the intensive PK data. For COBI it was shown that AUCtau and Cmax were similar between adolescents and adults, only mean Ctau for the adolescents was 28% higher than for the adults, which means that the boosting effect is at least maintained in comparison to the adults. There are no safety issues expected with this exposure level.

Therefore, Prezista (darunavir) at a dose of 800 mg, co-administered with COBI 150 mg given once daily is appropriate for use in adolescents aged ⩾12 years and weighing at least 40 kg.

2.4. Clinical efficacy

2.4.1. Main study

GS-US-216-0128: 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:

Table 9: Description of the cohorts classification for Study GS-US-216-0128

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.

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.

Study participants

Main inclusion criteria for participation in cohort 1 of the study were:

- HIV-1 infected, treatment-experienced, virologically suppressed, male and female subjects 12 years to < 18 years (according to requirements of enrolling cohort) at the Day 1 visit
- Able to provide written assent if having the ability to read and write. Parent or legal guardian able to provide written informed consent prior to any screening evaluation and willing to comply with study requirements

- Body weight ≥ 25 kg at screening
- Adequate renal function: eGFR ≥ 90 mL/min/1.73 m2, Adequate hematologic function defined as absolute neutrophil count ≥ 500 cells/mm3, Hemoglobin ≥ 8.5 g/dL, Platelets ≥ 50,000/mm3, Adequate hepatic function defined as Transaminases (AST and ALT) ≤ 5 x upper limit of normal (ULN) and Total bilirubin ≤ 1.5 mg/dL or a normal direct bilirubin
- Plasma HIV-1 RNA concentrations (at least 2 consecutive measurements obtained at least 4 weeks apart) at an undetectable level according to the assay being used, but not more than 75 copies/mL. HIV-1 RNA < 50 copies/mL at the screening visit.
- Stable antiretroviral regimen including 2 NRTI and either ATV/r QD, or DRV/r QD or BID as per product label for a minimum of 3 months prior to the Screening visit. Treatment-experienced paediatric subjects taking DRV/r must have had no history of DRV resistance associated mutations.

Main exclusion criteria for participation in cohort 1 of the study were:

- Screening CD4 cell count < 200 cells/µl
- An AIDS-defining condition with onset within 30 days prior to screening. A history of, or ongoing, malignancies other than cutaneous Kaposi sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Subjects with biopsy-confirmed cutaneous KS were eligible, but must not have received any systemic therapy for KS within 30 days of Day 1, and were not anticipated to require systemic therapy during the study
- An ongoing serious infection requiring systemic antibiotic therapy at the time of screening. Evidence of active pulmonary or extra-pulmonary tuberculosis (TB) disease, within 3 months of the Screening visit. Active HCV infection. Positive hepatitis B virus (HBV) surface antigen or other evidence of active HBV infection.
- Pregnant or lactating subjects
- Subjects receiving ongoing therapy with any medication that was not to be taken with COBI, a component of the background regimen, or drugs not to be used with RTV.

Treatments

COBI

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

DRV

DRV is administered as either tablets or oral suspension depending upon subject's body weight and ability to swallow tablets. DRV suspension was not administered to any subject in Cohort 1.

The recommended daily dosage of DRV is given, based on body weight, according to the prescribing information provided in the product monograph and should not exceed the recommended adult dosage.

Objectives

The primary objectives, related to DRV/co, of this ongoing study, are as follows:

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

The secondary objective, related to DRV/co, of this ongoing study, is as follows:

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

Outcomes/endpoints

The efficacy endpoints were:

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using the US 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 based on Missing = Excluded [M = E] analysis
- The change from baseline in CD4 cell count and percentage at Weeks 24 and 48, and every 12 weeks after Week 48

Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory tests (including renal, hepatic, and fasting glucose and lipid parameters), physical examinations, Tanner stage assessments, and vital signs.

Sample size

A sample size of 8 evaluable DRV subjects provided at least 90% power to show that COBI-boosted DRV AUCtau in paediatric subjects was similar to AUCtau in adult subjects. For the above sample size computation, inter-subject standard deviations (natural log scale) of 0.3 h•ng/mL for DRV AUCtau (based on population PK data from 298 adult subjects in Study GS-US-216-0130) 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.

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).

Randomisation

Not applicable since study GS-US-216-0128 was not a randomised study.

Blinding

Not applicable since this is an open-label study.

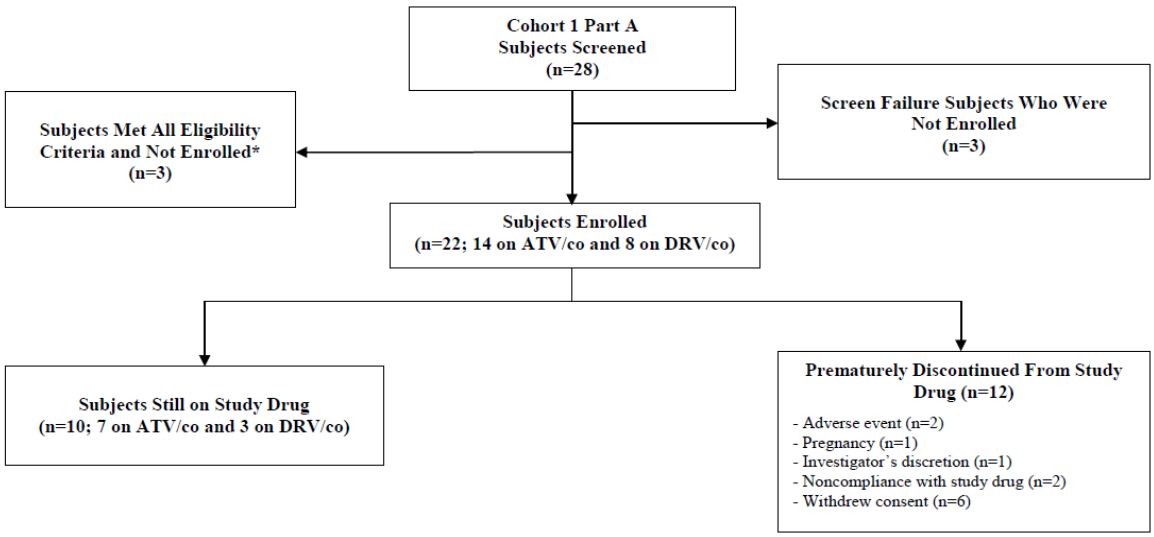
Statistical methods

Efficacy analyses used the Full Analysis Set (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 summarised 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).

Adverse event and clinical laboratory data were summarised using descriptive statistics. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. Tanner stage assessments were used to evaluate the onset and progression of pubertal changes. Body weight, body weight Z-score, height, and height Z-score were summarised.

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 3: Subject disposition Cohort 1.

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 finalisation was 4 January 2019.

Conduct of the study

Protocol amendments

The original study protocol (dated 09 July 2013) was amended 6 times prior to this interim analysis.

Protocol amendment 1 and 2 were effective before the first subject was enrolled. Protocol amendment 6 became effective after the last subject last observation for this report. Important changes described in protocol amendment 3-6 are described below:

Protocol Amendment 3 (18 December 2014)

- Removed Day -10 and Day -1 visits
- Added trough PK on Day 1 pre-dose for Part A subjects
- For DRV/r BID subjects, switched to DRV/co QD on Day 1
- Revised pharmacokinetic analysis to align with other paediatric studies/guidance
- Updated the statistical comparisons and power computations to reflect the exposure comparison equivalency of COBI-boosted ATV or DRV in paediatric versus adult subjects

Protocol Amendment 4 (14 November 2016)

- Changed inclusion criteria for body weight at screening for the respective cohorts according to this plan: Cohort 1 ≥ 25 kg, Cohort 2 to consist of 2 groups (Group 1 ≥ 25 kg, Group 2 ≥ 15 kg to < 25 kg), Cohort 3 TBD, and Cohort 4 TBD
- Added 90 mg tablet of the test product (for Cohort 2 Group 2, ≥15 kg to <25 kg), and the option to give 1 x 150 mg tablet or 2 x 75 mg tablets (for Cohort 1 and Cohort 2 Group 1, ≥ 25 kg)
- Added ATV powder and DRV suspension to the description of each treatment as alternative options for subjects who were unable to swallow capsules or tablets, respectively
- Added language around potential for use of dispersible tablets as oral suspension for those who could not swallow tablets

Protocol Amendment 5 (19 January 2018)

- Included disallowed/discouraged use of direct oral anticoagulants based on the Tybost® Investigator's Brochure (IB) Edition 10. Included recommendations on atorvastatin and drospirenone usage based on the Tybost IB Edition 10
- Removed references to COBI 75 mg tablets due to availability of COBI 150 mg tablets

Protocol Amendment 6 (28 June 2018)

- Included disallowed/discouraged use of antipsychotics based on approved US prescribing information for Tybost. Updated language around drug interaction with corticosteroids to be broadened to include all routes of administration, excluding cutaneous, based on the Tybost IB Edition 11.

Protocol deviations

Table 10 provides information on important protocol deviations that occurred in subjects treated with DRV/COBI from Cohort 1 Part A. Protocol deviations were documented during routine monitoring visits.

Among the 8 subjects treated with DRV/COBI from Cohort I Part A, 4 important protocol deviations have been noted in 3 subjects. None of these important protocol deviations affected the overall quality or interpretation of the study data.

Table 10. Study GS-US-216-0128 (Open Label COBI Cohort 1A DRV) Important Protocol Deviation Log

Subject ID	Treatment Group	Study Visit	Date of Deviation	Deviation Category	Description
-	1A	Week 24	24 Nov 2015	Other Treatment Compliance Issue	Study drug compliance less than 70%; compliance was 53% between Week 16 and Week 24
-	1A	Week 48	16 May 2016	Other Treatment Compliance Issue	Study drug compliance less than 70%; compliance was 67.2% between Week 40 and Week 48
-	1A	Week 96	27 Sep 2017	Other Treatment Compliance Issue	Study drug compliance less than 70%; compliance was 66.6% between Week 84 and Week 96
-	1A	Day 10	16 Mar 2015	Missing Data	Dosing non-compliance identified after Day 10 IPK completed. Per protocol, Day 10 IPK should have been repeated upon 3 days of compliant dosing. The repeat IPK was not performed.

COBI: cobicistat; DRV: darunavir; ID: identifier; IPK: intensive pharmacokinetics.
Subject (PPD), who weighed <40 kg at baseline and received DRV 600 mg, was excluded from analysis.

Baseline data

In the Safety Analysis Set for Cohort 1 Part A, most subjects (overall 63.6%) were male Table 11. Median age (range) in the DRV/co arm was 15 (12 to 16) years. The study enrolled a virologically suppressed, HIV-1 infected population, and all subjects in the Safety Analysis Set for DRV/co Cohort 1 Part A had baseline plasma HIV-1 RNA < 50 copies/mL. The median (Q1, Q3) baseline CD4 cell count overall in the DRV/co group was 1069 (820, 1881) cells/μL, with 100% of subjects having a baseline CD4 cell count ≥ 500 cells/μL. The mode of infection in all subjects was vertical transmission. At baseline, all subjects in the DRV/co arm were asymptomatic.

Table 11. GS-US-216-0128: Demographic and Baseline Characteristics, Cohort 1 Part A (Safety Analysis Set)

	Cohort 1 Part A: Age 12 to < 18 Years		
Characteristic	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
Q1, Q3	12, 16	13, 15	12, 16
Min, Max	12, 17	12, 16	12, 17
Sex at Birth			
Male	10 (71.4%)	4 (50.0%)	14 (63.6%)
Female	4 (28.6%)	4 (50.0%)	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 (25.0%)	2 (9.1%)
Ethnicity			
Hispanic or Latino	4 (28.6%)	3 (37.5%)	7 (31.8%)
Not Hispanic or Latino	10 (71.4%)	5 (62.5%)	15 (68.2%)
Baseline Body Weight (kg)			
N	14	8	22
Mean (SD)	54.6 (13.43)	55.0 (13.25)	54.8 (13.05)
Median	52.7	53.7	52.7
Q1, Q3	46.5, 63.3	45.8, 62.8	46.5, 63.3
Min, Max	32.3, 81.4	37.2, 78.0	32.3, 81.4

Numbers analysed

All 8 subjects who received at least 1 dose of DRV/co were included in the Safety, Full, and PK Analysis Sets, as well as the Intensive PK Analysis Sets for COBI and DRV.

Outcomes and estimation

The efficacy endpoints were:

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

At Week 24, the percentage of subjects in Cohort 1 Part A with HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm was 75.0% (6 of 8 subjects). The remaining 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. Similar results were achieved at week 48 (**Table 12**).

Table 12. GS-US-216-0128: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA Cutoff at 50 Copies/mL, Cohort 1 Part A (Full Analysis Set)

	Cohort 1 Part A: Age 12 to < 18 Years		
	ATV/co (N = 14)	DRV/co (N = 8)	Total (N = 22)
HIV-1 RNA < 50 copies/mL at Week 48	13 (92.9%)	6 (75.0%)	19 (86.4%)
95% CI[a]	66.1% to 99.8%	34.9% to 96.8%	65.1% to 97.1%
HIV-1 RNA ≥ 50 copies/mL at Week 48	1 (7.1%)	0	1 (4.5%)
No Virologic Data in Week 48 Window	0	2 (25.0%)	2 (9.1%)
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 copies/mL	0	1 (12.5%)	1 (4.5%)
Discontinued Study Drug Due to Other Reasons[b] and Last Available HIV-1 RNA < 50 copies/mL	0	1 (12.5%)	1 (4.5%)

a The 95% CIs for percentage estimates of HIV-1 RNA < 50 copies/mL were obtained using the Clopper-Pearson Exact method.
b "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.
Week 48 window was between Days 309 and 378 (inclusive).
Source: Table 15.9.1.2

Excluding the subject with body weight below the 40 kg cut-off resulted in the following virologic outcome (Table 13).

Table 13. Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Algorithm) – Full Analysis Set (Cohort 1, Part A: Age 12 to <18 Years: Subjects Who Received DRV 800 mg)

	DRV/COBI (N=7)
HIV-1 RNA <50 copies/mL at Week 48	6 (85.7%)
95% CI	42.1% to 99.6%
HIV-1 RNA ≥ 50 copies/mL at Week 48	0
HIV-1 RNA ≥50 copies/mL	0
Discontinued Study Drug Due to Lack of Efficacy	0
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥50 copies/mL	0
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA ≥50 copies/mL	0
No Virologic Data in Week 48 Window	1 (14.3%)
Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA <50 copies/mL	0
Discontinued Study Drug Due to Other Reasons* and Last Available HIV-1 RNA <50 copies/mL	1 (14.3%)
Missing Data During Window but on Study Drug	0

AE: adverse event; CI: confidence interval; COBI: cobicistat; DRV: darunavir; HIV-1: human immunodeficiency virus type 1

One subject, who weighed <40 kg at baseline and received DRV 600 mg, was excluded from analysis.
Week 48 window is between Day 309 and 378 (inclusive).
The 95% CI for percentage estimate of HIV-1 RNA <50 copies/mL was obtained using the Clopper-Pearson exact method.
* Other reasons include 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.

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 12, 24, and 48, and every 12 weeks after Week 48 based on 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 were 100.0% at week 12 (8/8), week 24 (7/7), and week 48 (6/6).

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

Mean (SD) changes from baseline in CD4 cell count and percentages were:

- Week 24: -494 (532.7) cells/µL, -3.5% (3.07%)
- Week 48: -411 (558.8) cells/µL, -5.2% (6.81%)
- Week 120: -324 (225.0) cells/µL, -4.6% (6.72%)

Virology Resistance Analyses

HIV-1 historical genotypes with PR and RT data were available for 13 of 22 subjects (59.0%) in the Cohort 1 Part A FAS. Two subjects receiving DRV/co had a pretreatment primary PI-associated resistance substitution (Q58E or L90M) in their historical genotypes. Both subjects had HIV-1 RNA < 50 copies/mL at Week 48. None of the 8 subjects in the DRV/co Cohort 1 Part A FAS met the VF and Resistance Analysis Population (RAP) inclusion criteria through Week 48.

Ancillary analyses

Summary of main study

The following tables summarise 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 14: Summary of main 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				
Study identifier	GS-US-216-0128			
Design	Open-label phase 2/3 study			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks not applicable 5 years	
Hypothesis	No efficacy hypothesis listed			
Treatments groups	DRV/co		Darunavir tablet + cobicistat tablet, 48 weeks, n=8	
Endpoints and definitions	Secondary endpoint	% HIV-1 RNA < 50 copies/mL	Week 24, Week 48 FDA snapshot algorithm, Missing = Excluded [M = E] analysis	
	Secondary endpoint	CD4 cell count	Change from baseline (mean (SD))	
Database lock	4 January 2019 (database finalisation)			
Results and Analysis				
Analysis description	**Efficacy Analysis**			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Analysis timepoint		Week 24	Week 48
	Number of subject		8	8
	% HIV-1 RNA < 50 copies/mL		75.0% (6/8)	75.0% (6/8)
	Change in CD4 cell count		-494 (532.7) cells/µL	-324 (225.0) cells/µL

2.4.2. Discussion on clinical efficacy

Extensions of indication to include adolescents for antiretroviral agents are primarily based on demonstration of comparable exposure in adolescents vs. adults, and a specific demonstration of antiviral efficacy in paediatric patients is not required, as it is stated in the EMA Guideline on the clinical development of medicinal products for the treatment of HIV infection.

In this case, only information on Cohort 1 from study GS-US-216-0128, (subjects from 12 years to < 18 years old, who received DRV/COBI) was provided, as this is the data submitted in support of the

extension of indication for Prezista to include adolescents 12 to <18 years of age for the combination DRV/co.

Efficacy endpoints were the percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using the US FDA-defined snapshot algorithm.

Protocol amendment 4, describing DRV suspension as alternative options for subjects who were unable to swallow tablets and adding language around the potential for the use of dispersible tablets as an oral suspension for those who could not swallow tablets, is of interest, especially in light of the large tablet size.

The applicant explained that protocol amendment 4 was installed to specify that DRV will be administered as either tablets or oral suspension depending upon the 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 the acceptability of the DRV tablets was collected as this is not an objective of the study.

Additionally, body weight is an important parameter, given that DRV dosing in children is weight-based. In children (including adolescents) ≥30 to <40 kg, a 675mg DRV dose is recommended, in contrast to the 800 mg in the Rezolsta FDC tablet. In the current study, DRV and COBI were administered as single components, and dose adjustments based on weight were possible. Of note, one of the 8 patients in the DRV/co arm had a baseline body weight below 40 kg and hence received the 675 mg DRV dose (see PK session of this AR). The applicant was asked to provide the main efficacy and safety information for the 7 subjects treated with DRV 800 mg + COBI 150 mg, i.e. remove the subject with the lower body weight of 37 kg as this subject does not belong to the required age/body weight extension. Throughout the report, the updated information has been added to the originally provided information, where relevant.

The 'Other Reasons' for which one of the subjects prematurely discontinued the study was withdrew consent (last dose was taken at Day38). The applicant clarified that the reason was that the subject's guardian did not want to expose the subject to a non-Food and Drug Administration (FDA) approved drug.

The virologic success rate (HIV-1 RNA <50 copies/mL) at Week 48 in Study GS-US-216-0128 was 85.7% (6/7 subjects) using the FDA Snapshot Approach.

2.4.3. None of the subjects experienced protocol-defined virologic failure.Conclusions on the clinical efficacy

In this small study, the overall efficacy was considered acceptable by the CHMP.

2.5. Clinical safety

Introduction

The safety results from the 7 adolescent subjects weighing ≥40 kg who received the DRV 800 mg dose in Study GS-US-216-0128 are presented. The subject weighed <40 kg at screening is not included in the analyses.

Patient exposure

Six of the 7 subjects completed the 48 weeks of treatment. Median (Q1; Q3) exposure DRV (800 mg) and COBI (150 mg): 108.7 (49.3; 155.3) weeks.

Adverse events

Overall, AEs were reported for 7 (100%) subjects. Common AEs (≥2 [≥28.6%] subjects) were upper respiratory tract infection, cough, nasal congestion, myalgia, pharyngitis, vomiting, abdominal pain, headache, oropharyngeal pain, back pain, hyperlipidemia, nausea, post-traumatic stress disorder, and weight increased. Two (28.6%) subjects experienced study drug-related AEs: nausea and hyperlipidemia were reported for both subjects, decreased appetite was reported for 1 (14.3%) subject.

Serious adverse event/deaths/other significant events

There were no deaths.

One (14.3%) subject experienced a grade 4 AE (reported as a serious adverse event [SAE]) of bipolar disorder. No other SAEs were reported. There was no SAE or grade 3/4 AE considered related to study drug.

Laboratory findings

Lipid-related Events

Individual fasting metabolic laboratory parameters remained within normal ranges. Hyperlipidemia was reported as a grade 2 AE in 2 (28.6%) subjects and led to study drug discontinuation in 1 of the 2 subjects.

Renal Events

Glomerular Function

Serum creatinine mean and median values were increased at Day 10 and all other timepoints through Week 48, with eGFRcr values (based on serum creatinine using Schwartz formula) mirroring these changes.

Changes from baseline in serum creatinine and eGFRcr were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine and are not considered reflective of changes in actual glomerular filtration rate based on the observed stable values of cystatin C.

Other Events

There were no noteworthy findings for the other events of interest.

Discontinuation due to adverse events

One subject had 2 AEs that led to premature study drug discontinuation: Grade 2 hyperlipidemia that started on Day 173 and was considered related to study drug by the investigator, and Grade 1 acanthosis nigricans that started on Day 222 and was considered unrelated to study drug. This subject also had an SAE of bipolar disorder. The last dose day was Day 614 and last study day was Day 629.

Post marketing experience

Based on the total of 713,668,997 grams of DRV distributed (from launch to 31 December 2019), the estimated exposure is 24,257,590 person-months or 2,021,463 person-years.

At the time of finalisation of this SCS addendum, 17 Periodic Benefit Risk Evaluation Reports/Periodic Safety Update Reports (PBRERs/PSURs) have been generated for DRV covering the period from 23 June 2006 to 23 December 2019 and summarising the postmarketing safety data obtained by the applicant. These concluded that based on the review of nonclinical, clinical, epidemiologic information, scientific literature, and postmarketing data, DRV continues to demonstrate a favourable benefit-risk profile for its authorised indications.

2.5.1. Discussion on clinical safety

The safety of DRV in adolescents has been assessed before and is described in the Prezista (DRV) product information. The conclusion of the available data at that time was that the overall safety profile of in paediatric patients aged 12 to < 18 years and weighing at least 40 kg was similar to that observed in the adult population. There is no indication from the available data that DRV or COBI affects pubertal development or growth in adolescents.

One subject receiving DRV/co prematurely discontinued study drug due to an AE of hyperlipidemia, which was considered related to study drug by the investigator. Hyperlipidemia is a known AR with DRV/Cobi and is listed as 'common' in section 4.8 of the Prezista SmPC

The current study is considered too small to draw meaningful conclusions regarding the safety profile. However, the available safety data from this study did not reveal safety concerns that would preclude it's use in adolescents.

2.5.2. Conclusions on clinical safety

The safety of DRV in adolescents has been assessed before and is described in the Prezista (DRV) product information. The current study is considered too small to draw meaningful conclusions regarding the safety profile. However, the available safety data from this study did not reveal safety concerns that would preclude it's use in adolescents.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application (version 27.2).

The (main) proposed RMP changes were the following:

1. Indication in the EEA broadened for PREZISTA co-administered with COBI from "adult patients" to "adults and adolescents (aged 12 years and older, weighing ≥40 kg)".

2. The following safety concerns are removed in accordance with GVP V Rev 2:

Important identified risks

- Severe skin reactions
- Hepatotoxicity
- Hyperglycemia
- Lipid abnormalities
- Immune reconstitution inflammatory syndrome
- Development of drug resistance
- Overdose due to medication error
- Drug-drug interactions

Important potential risks

- Coronary artery events
- Off-label use of DRV/COBI in the pediatric population and in ARV treatment-experienced patients with HIV-1 RNA >100,000 copies/mL

Missing information

- Elderly (65 years and above)
- Subjects with severe hepatic impairment (Child-Pugh Class C
- Subjects with renal impairment
- Impact of palatability of the oral suspension on adherence and efficacy in treatment-experienced children >15 kg (DRV/rtv)
- Children <18 years of age (DRV/COBI)
- Long-term safety of DRV/COBI in adults (DRV/COBI)
- Subjects coinfected with HIV and HBV and/or HCV (DRV/COBI)

3. As the impact of palatability of the oral suspension on adherence and efficacy in treatment-experienced children >15 kg (DRV/rtv) is no longer considered missing information, the dose regimen follow-up questionnaire for DRV is removed from the pharmacovigilance plan.

4. As children <18 years of age (DRV/COBI) is no longer considered missing information, trial GS-US-216-0128 is removed from the pharmacovigilance plan.

The PRAC considered that the risk management plan version 27.2 is acceptable.

Safety concerns

Table SVIII.1:Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	Long-term safety data in children from 3 to <6 years of age (DRV/rtv)

Pharmacovigilance plan

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Long-term safety data in children from 3 to <6 years of age (DRV/rtv)	Routine risk minimization measures: • SmPC Section 4.8 • SmPC Section 5.1 • Legal status: restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Risk minimisation measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Missing information	
Long-term safety data in children from 3 to <6 years of age (DRV/rtv)	Routine risk communication: • SmPC Section 4.8 • SmPC Section 5.1 Other routine risk minimization measures beyond the Product Information: • Legal status: restricted medical prescription

Conclusion on the RMP

The changes to the RMP (version 27.2) are acceptable to the PRAC and CHMP.

2.7. Update of the Product information

As a result of this variation, the respective SmPCs are being updated as follows:

For Prezista 100 mg/ml oral suspension, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2

For Prezista 75, 150 and 600 mg film-coated tablets, section 4.5

For Prezista 400 and 800 mg film-coated tablets, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2.

In addition, and in order to align the SmPC with recommendations for other HIV products, the MAH has also taken the opportunity to update section 4.2 of the SmPC with regards to the administration of Prezista in case of vomiting in all presentations.

The Package Leaflet (PL) is updated accordingly.

Following Member States comments, the MAH updated the SmPC to delete of boceprevir and simeprivir in section 4.5, since both have been withdrawn from the EU market. In addition, the MAH was requested to update the DDI information on etravirine however, the MAH justified that the information was based on the information available on Intelence (etravirine) SmPC. This was endorsed by CHMP.

2.7.1. User consultation

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

- For PREZISTA, full user testing in compliance with the above-mentioned legislative requirements was performed on the initial patient leaflet for PREZISTA 300 mg filmcoated tablets (n=37 participants)(procedure EMEA/H/C/000707, approved on 12 February 2007) and on the patient leaflets for PREZISTA 75 mg and 150 mg tablets for use in adolescents (in combination with ritonavir) (n=20 participants, ages 14 through 18 years of age were tested)(procedures EMEA/H/C/000707/X/20 and EMEA/H/C/000707/X/21, approved on 23 June 2009),
- The proposed updated indication for PREZISTA, co-administered with cobicistat, is an extension of the target group of users (i.e. HIV-1 infected adults and paediatric subjects [⩾12 to < 18 years of age, weighing at least 40 kg]). No new tablet strength or formulation, or new route of administration is proposed.
- Safety analyses from the study in adolescent subjects did not identify new safety concerns compared to the known safety profile of DRV and COBI.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The 2018 annual report from the Joint United Nations Programme on HIV/AIDS on the global AIDS epidemic estimates that worldwide, approximately 160,000 (range: 110,000-260,000) children <15 years of age were newly infected with HIV-1 in 2017, down from 270,000 in 2010. An estimated 1.8 million adolescents (10-19 years) were living with HIV-1 in 2016 globally.

3.1.2. Available therapies and unmet medical need

The aim of ART in children is to achieve undetectable HIV RNA levels, to provide a high barrier to resistance development, to maintain viral suppression, and thus to allow normal immune function, whilst minimising drug toxicities.

Current paediatric and adolescent guidelines recommend the use of combination ART (cART) with at least 3 drugs, usually a dual or triple nucleoside reverse transcriptase inhibitor (NRTI) backbone together with either a ritonavir-boosted protease inhibitor (PI) or a nonnucleoside reverse transcriptase inhibitor (NNRTI). Albeit not finalised yet, the 2019 PENTA summary guideline that has been out for public consultation recommends for children >12 years of age the use of DRV boosted with either ritonavir or cobicistat, or DTG as preferred 3rd agent, in combination with an ABC+3TC or TAF+FTC/3TC backbone.

3.1.3. Main clinical studies

For an extension of indication to include adolescents, similar exposure in adolescents vs. adults forms the basis of approval. As it is assumed that the PK/PD relation for a direct acting antiviral is roughly similar regardless of the age of the patient, the efficacy of a dose that yields sufficiently similar exposure in children, compared to adults, would be inferred.

The applicant submitted the following study in support of the proposed use in HIV-1 infected adolescents (aged ≥12 to <18 years):

GS-US-216-0128 (DRV 800 or 675 mg in combination with COBI 150 mg [as single agents] in n=8 ART-experienced, virologically suppressed subjects).

3.2. Favourable effects

Results from study GS-US-216-0128 showed that the PK parameters AUCtau, Cmax and Ctau for DRV were on average at the same level for the adolescents and adults using the intensive PK data. For COBI it was shown that AUCtau and Cmax were similar between adolescents and adults, only mean Ctau for the adolescents was 28% higher than for the adults, which means that the boosting effect is at least maintained in comparison to the adults. There are no safety issues expected with this exposure level.

The virologic success rate (HIV-1 RNA <50 copies/mL) at Week 48 in Study GS-US-216-0128 was 85.7% (6/7 subjects) using the FDA Snapshot Approach.

None of the subjects experienced protocol-defined virologic failure.

3.3. Uncertainties and limitations about favourable effects

It should be considered that conclusions on favourable effects were drawn from a very low number of subjects.

3.4. Unfavourable effects

Two (28.6%) subjects experienced study drug-related AEs: nausea and hyperlipidemia were reported for both subjects, decreased appetite was reported for 1 (14.3%) subject.

3.5. Uncertainties and limitations about unfavourable effects

Study GS-US-216-0128 included only 8 patients on DRV/co. Excluding the subject with body weight below the 40 kg cut-off, the total number of patients resulted in only 7. This is considered too small to draw meaningful conclusions regarding the Prezista safety profile. However, for darunavir it was already concluded that the safety profile in adolescents is comparable to that in adults.

3.6. Effects Table

Table 15: Effects Table for Prezista in adolescent population (aged 12 years old and older with body weight at least 40 kg).

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PK DRV	AUC_{tau} ratio=1.00 Cmax ratio=0.99 Cmin ratio=0.71		Ratio of mean adolescent value over mean adult value	Study GS-US-2016-0130	Small sample size (n=7 patients)	Study GS-US-2016-0128
PK COBI	AUC_{tau} ratio=1.19 Cmax ratio=1.16 Cmin ratio=1.28		Ratio of mean adolescent value over mean adult value	Study GS-US-2016-0130	Small sample size (n=7 patients)	Study GS-US-2016-0128
Virologic response	Proportion of patients with confirmed viral load < 50 HIV-1 RNA copies/ml at week 48	n/N (%)	6/7 (85.7%)	n/a	Small sample size (n=7 patients)	Study GS-US-2016-0128
PDVF	protocol-defined virologic failure	n/N (%)	0/7 (0%)	n/a		
Unfavourable Effects						
Treatment-emergent study drug related AE	Hyperlipidaemia	n/N (%)	2/7 (28.6%)	n/a	Small sample size. Hyperlipidemia is a known AR with DRV.	Study GS-US-2016-0128

Abbreviations: n= number of observations; N= number of subjects in the study (intention – to treat), n/a=not applicable, PDVF= protocol-defined virologic failure, AE=adverse event, AR=adverse reaction.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For extension of the indication to adolescents, it is important to show that exposure in adolescents is similar to adults. Further, the development of resistance mutations is important, which in turn may also have an impact on 2nd line ARV treatment options. As the target population are adolescents, potential effects on pubertal development or growth are also of importance.

3.7.2. Balance of benefits and risks

PK analyses show comparable drug exposure in adolescents and adults, which is further supported by the submitted efficacy data. Therefore, combining DRV and COBI at doses of 800 mg and 150 mg given once daily may be appropriate for use in adolescents aged ≥12 years and weighing at least40 kg. This should be balanced against the risk for development of resistance, which in the limited dataset available, seems to be acceptable.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Prezista remains positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends <, by a majority of {number} out of {number} votes,> the variation to the terms of the Marketing Authorisation, concerning the following change:

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

Extension of indication for Prezista (darunavir) in combination with cobicistat for the treatment of HIV-1 infection in adolescents aged 12 years and older with body weight at least 40 kg. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC and section 3 of the Package Leaflet are being updated accordingly. The updated RMP version 27.2 has been submitted.

In addition, in order to align the SmPC with recommendations for other HIV products, the MAH has also taken the opportunity to update section 4.2 throughout with regards to the administration of Prezista in case of vomiting. The MAH has also implemented some editorial changes in Annex II and IIIA. The package leaflet is updated accordingly.

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.