30 January 2020
EMA/74699/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rezolsta

International non-proprietary name: darunavir / cobicistat

Procedure No. EMEA/H/C/002819/II/0033

Note

Variation 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
$eGFR_{cr}$	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 7 June 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

To extend the approved therapeutic indication of Rezolsta to include the adolescent population (aged 12 years old and older with body weight at least 40 kg). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and sections 1, 2 and 3 of the PL are updated accordingly. The updated RMP version 6.0 has also been submitted.

The RMP of the product has been updated to meet the requirements and updated definitions in the European Medicines Agency (EMA) Guideline on good pharmacovigilance practices (GVP) Module V Revision 2 (EMA/838713/2011; Rev 2) and Guidance on the format of the RMP in the European Union (EMA/164014/2018 Rev 2.0.1) including proposed removal of safety concerns.

In addition, in order to align the PI 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 Rezolsta in case of vomiting.

The variation requested 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/0006/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the EMA Decision P/0006/2019 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 MAH 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: Johann Lodewijk Hillege Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	7 June 2019
Start of procedure:	20 July 2019
CHMP Rapporteur Assessment Report	12 September 2019
PRAC Rapporteur Assessment Report	20 September 2019
PRAC members comments	26 September 2019
Updated PRAC Rapporteur Assessment Report	27 September 2019
PRAC Outcome	3 October 2019
CHMP members comments	2 October 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	11 October 2019
Request for supplementary information (RSI)	17 October 2019
PRAC Rapporteur Assessment Report	7 January 2020
PRAC members comments	8 January 2020
Updated PRAC Rapporteur Assessment Report	9 January 2020
CHMP Rapporteur Assessment Report	16 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	20 January 2020
Updated CHMP Rapporteur Assessment Report	24 January 2020
Opinion	30 January 2020

2. Scientific discussion

2.1. Introduction

Rezolsta is a fixed-dose combination (FDC) tablet containing 800 mg darunavir and 150 mg cobicistat (DRV/COBI). It is a once-daily treatment currently indicated in the European Union (EU) for use in combination with other antiretroviral (ARV) medicinal products for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years or older, who are either:

- antiretroviral treatment (ART) naïve or

- ART experienced without DRV resistance associated mutations (RAMs) and have plasma HIV 1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells x 10^6/L.

The aim of the current procedure is to extent the approved indication of Rezolsta to include treatment of adolescents aged 12 years and older, weighing at least 40 kg. Both components of the FDC tablet have been approved for use in adolescents at the same doses as used in adults, either as part of a FDC tablets (E/C/F/TAF (Genvoya), D/C/F/TAF (Symtuza)), or as single entity (DRV (Prezista).

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.

Table 1: Tabulated Overview of Studies Supporting the Use of DRV and COBI in HIV-1 Infected Adolescent Subjects (Aged ⩾12 to <18 Years)

Study (Phase, Status)	Treatment	Number of Subjects[a]	Main Endpoints
DRV in HIV-1 Infected, ART-naïve, Adolescent Subjects (Aged ≥12 to <18 Years)			
TMC114-C230 (Phase 2, completed)	DRV (800 mg) and rtv (100 mg) once daily + ARV background regimen[b]	N=12	PK of DRV and rtv; Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per TLOVR
DRV and COBI in HIV-1 Infected, ART-experienced, Virologically Suppressed, Adolescent Subjects (Aged ≥12 to <18 Years)			
GS-US-216-0128 (Phase 2/3, ongoing)	DRV (800 or 675 mg)[d] and COBI (150 mg) once daily + ARV background regimen[e]	N=8[c]	PK of DRV and COBI at Day 10; Incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities
COBI (as part of E/C/F/TAF) in HIV-1 Infected, ART-naïve, Adolescent Subjects (Aged ≥12 to <18 Years)			
GS-US-292-0106[f] (Phase 2/3, ongoing)	E/C/F/TAF FDC (150/150/200/10 mg) once daily	N=50 (PK substudy: N=24)	PK of EVG, TAF, COBI, and FTC; Virologic response defined as HIV-1 RNA <50 copies/mL at Week 24 per FDA Snapshot Approach
Phase 1 Studies Providing Additional Supportive Data			
DRV/COBI and D/C/F/TAF FDC-matching Placebo (Acceptability/Swallowability Study) in HIV-1 Infected, Adolescent Subjects			
TMC114FD2HTX1003 (Phase 1, completed)	Placebo[h] single dose	N=27	Ease and acceptability of swallowing the DRV/COBI and D/C/F/TAF FDC-matching placebo tablets
DRV/COBI (as part of D/C/F/TAF) Relative Bioavailability Study in Healthy Adult Subjects[i]			
TMC114FD2HTX1004 (Phase 1, completed)	D/C/F/TAF FDC (800/150/200/10 mg) single dose[j]	N=30	Relative bioavailability of a whole, crushed, or split D/C/F/TAF FDC tablet

AE = adverse event; ART = antiretroviral treatment; ARV = antiretroviral; COBI = cobicistat; CSR = clinical study report; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; EVG = elvitegravir; FDA = Food and Drug Administration; FDC = fixed-dose combination; FTC = emtricitabine; HIV-1 = human immunodeficiency virus type 1; N° = number of subjects; PK = pharmacokinetics; rtv = low-dose ritonavir; TAF° = tenofovir alafenamide; TLOVR = time to loss of virologic response; W24 / 48 = Week 24 / 48.

[a] Subjects included in the intent-to-treat (ITT) or Safety Analysis Set. For the definitions of analysis sets, refer to Mod2.7.3/Sec1.2.

[b] The ARV background regimen consisted of zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC), dosed as indicated in the local Prescribing Information.

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

[d] DRV doses were administered according to applicable Prescribing Information: 675 mg once daily (body weight ≥30 kg–<40 kg, 1 subject) or 800 mg once daily (≥40 kg, 7 subjects).

[e] For all subjects, the ARV background regimen had to include 2 nucleoside reverse transcriptase inhibitors (NRTIs) and might contain additional antiretroviral agents except for the following disallowed agents: saquinavir, indinavir, nelfinavir, double protease inhibitor (PI) regimens, raltegravir, elvitegravir, efavirenz, nevirapine, delavirdine, maraviroc, etravirine, rilpivirine, dolutegravir, and investigational antiretroviral agents.

[f] In Study GS-US-292-0106, a subject population of virologically suppressed children (aged 6 to <12 years) was also included. However, these data are not described in this summary document.

[g] Safety and tolerability were evaluated in this placebo study through adverse event reporting throughout the study from signing of the Informed Consent Form/Assent Form onwards until the last study-related visit.

[h] Placebo tablet sized 23 mm x 11.5 mm matching the DRV/COBI 800/150 mg FDC tablet and placebo tablet sized 22 mm x 10 mm matching the D/C/F/TAF 800/150/200/10 mg FDC tablet. No active study drug was administered.

[i] Study subjects were healthy adults between 18 and 55 years of age.

[j] All subjects were to receive a single dose of D/C/F/TAF 800/150/200/10 mg FDC tablet swallowed as a whole tablet (Treatment A, reference), a split tablet (Treatment B, test), and a crushed tablet mixed in applesauce (Treatment C, test) in 3 separate treatment sessions, with a washout period of at least 7 days between D/C/F/TAF administrations.

The darunavir/cobicistat (DRV/COBI) 800/150 mg fixed-dose combination (FDC) tablet (REZOLSTA) is a once-daily treatment currently indicated in the European Union (EU) for use in combination with other antiretroviral (ARV) medicinal products for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years or older, who are either:

- antiretroviral treatment (ART) naïve or
- ART experienced without DRV resistance associated mutations (RAMs) and have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 cells x 10^6/L.

In HIV-1 infected adolescents (aged ≥12 to <18 years), pharmacokinetic (PK), efficacy, and safety data of DRV (800 mg) and COBI (150 mg) as single components are available from 3 paediatric studies:

- TMC114-C230 (DRV 800 mg in combination with ritonavir [rtv] 100 mg in ART-naïve subjects)

- GS US 216 0128 (DRV 800 or 675 mg in combination with COBI 150 mg [as single agents] in ART-experienced, virologically suppressed subjects)
- GS US 292-0106 (COBI, as part of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF] 150/150/200/10 mg FDC in ART-naïve subjects).

In addition, the acceptability/swallowability of the DRV/COBI FDC tablet was evaluated in study TMC114FD2HTX1003 in HIV-1 infected adolescents. Further supportive data are available from a relative bioavailability study (TMC114FD2HTX1004) with another authorised DRV/COBI containing FDC, darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF, 800/150/200/10 mg), which is physically similar to the DRV/COBI FDC, and which showed that there was no relevant effect on DRV and COBI PK after splitting the D/C/F/TAF FDC.

2.3.2. Biopharmaceutics

The proposed formulation for adolescents is the same as the marketed formulation for adults. This is supported by the results from the acceptability/swallowability study TMC114FD2HTX1003 (refer to Section 2.4.1 Main study). Some adolescents, however, might encounter difficulty to swallow the DRV/COBI FDC tablet as a whole. For those, the FDC tablet may be split in half based on results from stability data and in vivo data. Results from a loss of mass study in which DRV/COBI FDC tablets were split into 2 pieces using 2 different tablet cutters showed no significant loss of mass after splitting.

The Phase 1 study TMC114FD2HTX1004 assessed the relative bioavailability of the components in the D/C/F/TAF FDC tablet when split or crushed (and mixed with applesauce) compared to swallowed as a whole tablet, to facilitate intake for subjects who have difficulty swallowing larger tablets. This study showed that splitting the FDC tablet immediately prior to use has no clinically relevant effects on the PK of DRV and COBI. As the DRV/COBI FDC tablet is physically similar to the D/C/F/TAF tablet, and the amount of DRV/COBI is the same in both tablets, it can be reasonably assumed that the bioavailability of DRV and COBI would also be preserved after splitting the DRV/COBI FDC tablet.

2.3.3. Pharmacokinetics

In adolescents, the metabolic factors that determine the PK have matured to adult values well before adolescence and, generally, ARV doses are the same for adults and adolescents. The application for the use of the DRV/COBI FDC tablet in HIV-1 infected adolescents, aged 12 years and older and weighing at least 40 kg, is based on the combination of results summarized in this report.

A DRV 800 mg once daily dose is indicated for use in adolescents aged ≥12 years and weighing at least 40 kg. DRV PK data in adolescents are available from the Phase 2 Study TMC114-C230 with DRV (800 mg) and rtv (100 mg) once daily in combination with zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC) for 48 weeks in 12 HIV-1 infected, ART-naïve adolescents.

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).

Use of the adult doses for COBI for adolescents (≥12 to <18 years of age) is further confirmed from the clinical development of E/C/F/TAF FDC, containing COBI at a dose of 150 mg.

2.3.3.1. 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 coadministered 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 coadministered 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 predose and up to 12 hours postdose on Day -1 (for DRV) and on Day 10 (for DRV and COBI). 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 predose (0 hours) concentration was also used as 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 pediatrics 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.

DRV was analyzed using analytical method QPS 42-0902. 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. 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

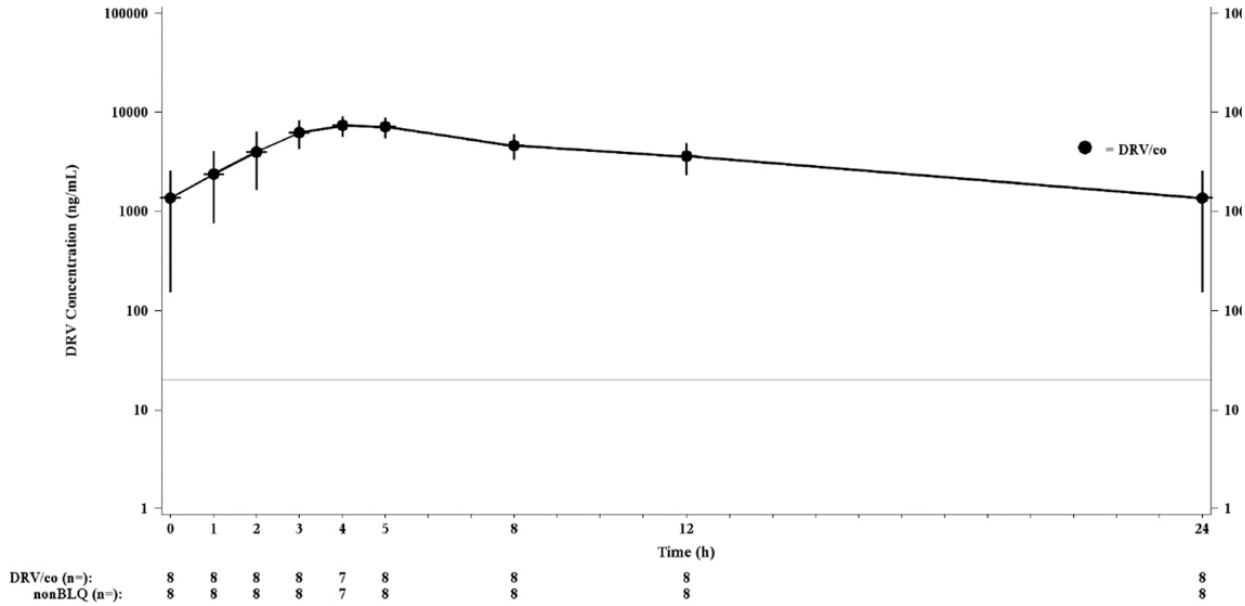
Demographics of the 8 subjects included in the PK dataset are given in Table 14 which shows that mean body weight at baseline was 55 kg (min 37 kg; max 78 kg). One subject of the eight subjects included was weighing 37 kg (< 40 kg. male, 12-yr old) and received a DRV dose of 600 mg (instead of the planned 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).

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)



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).

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)

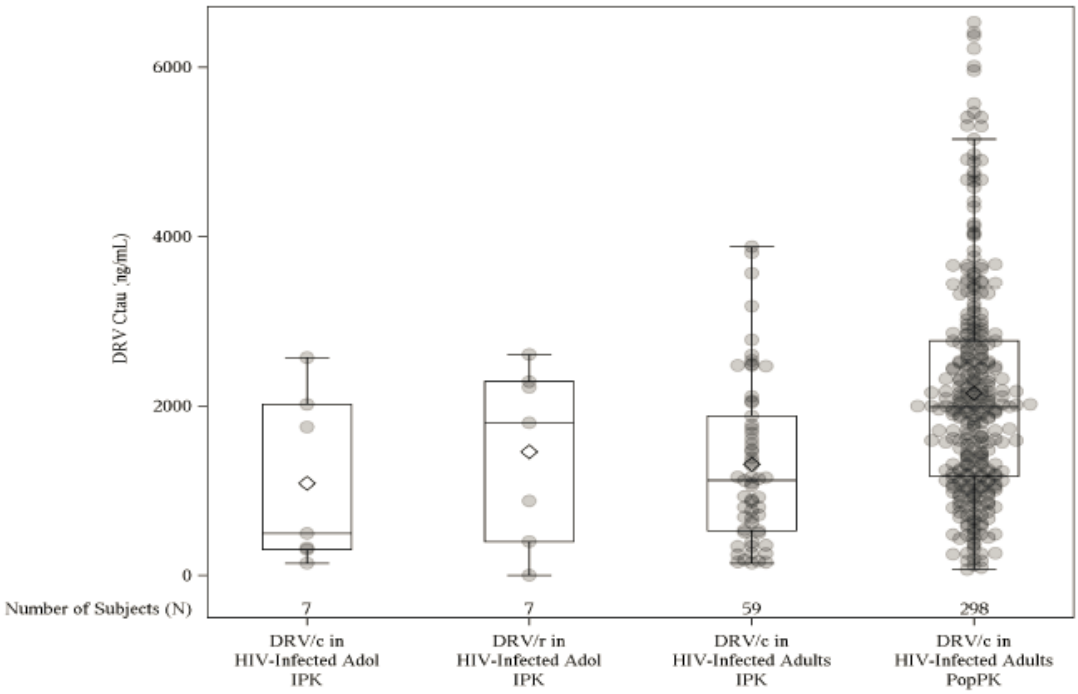
DRV PK Parameter	Mean (%CV) GLSM: Adults in Study GS-US-216-0130, Week 24 (Reference)	Mean (%CV) GLSM: Adolescents in Study GS-US-216-0128, Day 10 (Test)[a]	%GLSM Ratio (Test/Reference)	90% CI
N	60[b]	7		
AUC_{tau} (h.ng/mL)[c]	81,645.9 (32.2) 77,534.4	80,876.8 (29.5) 77,216.5	99.59	79.03 - 125.50
C_{max} (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 pediatric 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).

2.3.3.2. Supportive study TMC114-C230

Study TMC114-C230 was an open-label, Phase 2 study to evaluate the PK, safety, tolerability, and antiviral activity of DRV/rtv in treatment-naïve, HIV-1 infected, adolescent subjects. The primary objective of this study was to evaluate the PK, safety, tolerability, and efficacy of DRV/rtv 800/100 mg once daily, in combination with an investigator-selected background regimen, over a 24-week treatment period. Secondary objectives were to evaluate long-term safety, tolerability, efficacy, immunology, resistance characteristics, PK, and PK/PD relationships over 48 weeks of treatment in this population.

Subjects and Methods

A total of 12 treatment-naïve, HIV-1 infected, adolescent subjects (aged ≥12 to <18 years and weighing ≥40 kg) were included in the study. Subjects received the recommended dose of DRV/rtv for treatment-naïve, HIV-1 infected adults, 800/100 mg once daily, in combination with an investigator-selected background regimen, for 48 weeks. The investigator-selected background regimen was either AZT/3TC or ABC/3TC, whichever was approved and marketed or considered the local standard of care for subjects between ≥12 and <18 years of age in their particular country.

After 14 days of treatment with DRV/rtv 800/100 mg once daily, PK profiles for DRV and rtv in plasma were determined up to 24 hours after dosing for non-compartmental PK analysis. These samples were also used for population PK analysis of DRV, together with sparse samples obtained at Weeks 4, 24, and 48.

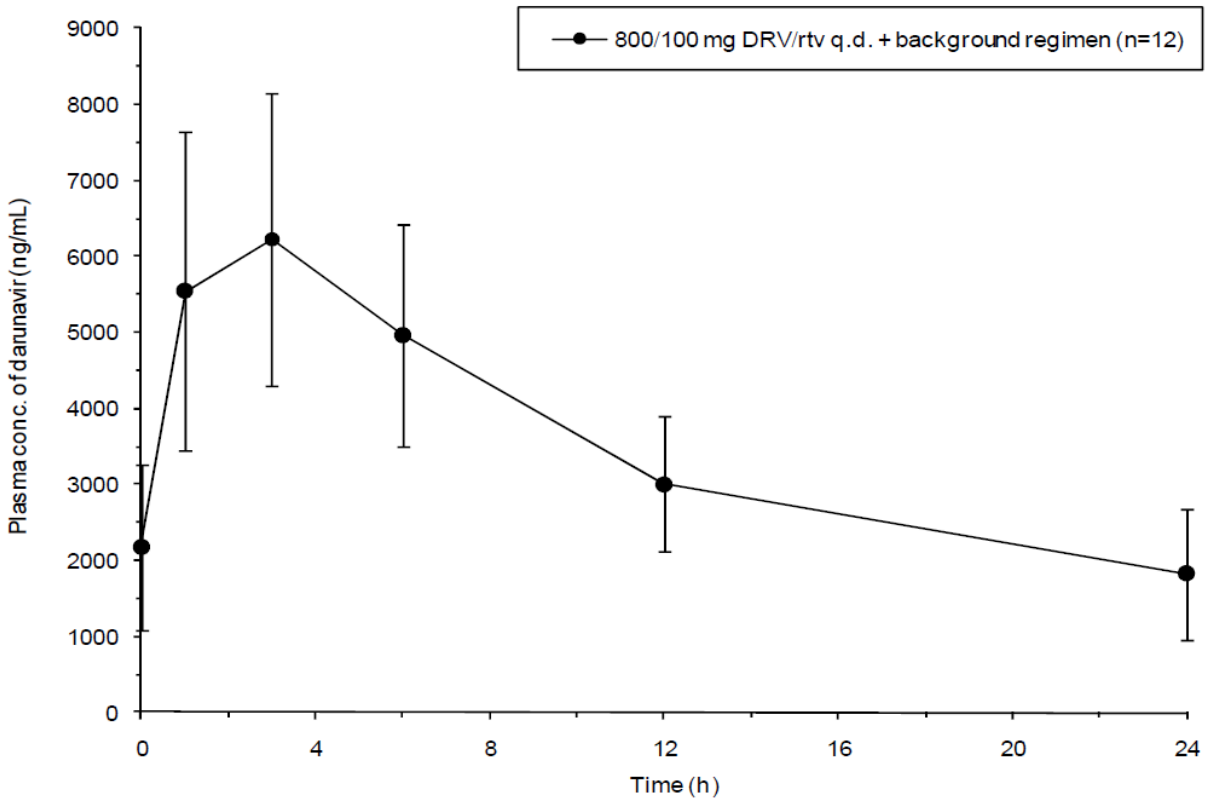
The primary statistical analysis (safety, efficacy, resistance, PK, and PK/PD) was performed at Week 24, and the final analysis was performed at Week 48.

The PK data from adolescents who received DRV/rtv in this study were compared to available PK data from HIV-1 infected adult subjects (adult comparator).

Results: Pharmacokinetics of DRV (Week 2)

The mean plasma concentration-time curve for DRV is shown in Figure 3. The maximum mean plasma concentrations were reached at 3 hours after intake of DRV/rtv.

Figure 3: Mean (SD) Plasma Concentration-time Profile of DRV at Week 2 After Administration of DRV/rtv 800/100 mg Once Daily in Treatment-naïve, HIV-1 Infected Subjects From ⩾12 to <18 Years of Age (Study TMC114-C230)



The PK parameters for DRV are summarized in Table 2. The interindividual variabilities (%CV) for minimum plasma concentration (Cmin), maximum plasma concentration (Cmax), and area under the plasma concentration-time curve (AUC) over 24 hours (AUC24h) were 48.3%, 25.3%, and 32.1%, respectively.

When compared with historical data for DRV administered as DRV/rtv 800/100 once daily in treatment-naïve, HIV-1 infected adults (substudy of Study TMC114-C211), the geometric mean Cmin, Cmax, and AUC24h values for DRV in treatment-naïve, HIV-1 infected adolescent subjects from ⩾12 to <18 years of age were 1.13-, 1.15-, and 1.16-fold higher, respectively, than in adults (

Table 9).

Table 9: Pharmacokinetics of DRV at Week 2 After Administration of DRV/rtv 800/100 mg Once Daily in Treatment-naïve, HIV-1 Infected Adolescents From ⩾12 to <18 Years of Age (Study TMC114-C230) and After Administration of DRV/rtv 800/100 mg Once Daily in HIV-1 Infected Adults (Study TMC114-C211 Substudy)

	Mean ± SD; t_{max}: Median (Range)			
Parameter	TMC114-C211 Substudy: DRV/rtv 800/100 mg Once Daily in Treatment-naïve, HIV-1 Infected Adults, Week 4 (Reference)	TMC114-C230: DRV/rtv 800/100 mg Once Daily in Treatment-naïve, HIV-1 Infected Adolescents, Week 2 (Test)	GLSM Ratio (Test/Reference)	90% CI
N	9	10[a]		
t_{max}, hours	3.0 (1.0 - 4.1)	3.00 (1.00 - 6.00)	-	-
C_{0h}, ng/mL	1,826 ± 1,003	2,172 ± 1,096	-	-
C_{min}, ng/mL	1,189 ± 410	1,589 ± 768	1.13	0.72 - 1.76
C_{max}, ng/mL	5,471 ± 1,320	6,721 ± 1,700	1.15	0.94 - 1.42
AUC_{24h}, ng.h/mL	64,230 ± 18,210	81,880 ± 26,300	1.16	0.86 - 1.57
CL/F, L/h	-	11.3 ± 5.8	-	-

AUC_{24h} = area under the plasma concentration-time curve over 24 hours; C_{0h} = predose plasma concentration; CI = confidence interval; CL/F = apparent clearance; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; DRV = darunavir; GLSM = geometric least-squares mean; HIV-1 = human immunodeficiency virus type 1; N = maximum number of subjects with data; rtv = low-dose ritonavir; SD = standard deviation; t_{max} = time to reach maximum plasma concentration.

[a] n=12 for C_{0h}, C_{max}, and t_{max}.

Results: Population Pharmacokinetic Analyses of DRV (Week 24 and Week 48 Analyses)

Empirical Bayesian estimates for DRV PK parameters in HIV-1 infected adolescents were obtained using a pediatric population PK model, which included the intensive and sparse PK sampling data from study TMC114-C230. These empirical Bayesian estimates for DRV PK parameters were obtained for each subject at each visit with PK sampling, and from these, the median estimate was determined for each subject. Summary statistics for the individual median values for PK parameters of DRV in the Week 24 and 48 analyses of Study TMC114-C230 are provided in

Table 10.

The geometric mean AUC24h for DRV exposure was 77.8 µg.h/mL at Week 24 and 80.7 µg.h/mL at Week 48, which represented 86.7% and 90.0%, respectively, of the geometric mean of the target DRV exposure in treatment-naïve, HIV-1 infected adults in the sub-study of Study TMC114-C211 (89.7 µg.h/mL; pre-planned comparison at the time of the study).

Table 10: Summary Statistics for Population Pharmacokinetic Estimates for DRV After Administration of DRV/rtv at 800/100 mg Once Daily in Treatment-naïve, HIV-1 Infected Subjects From ⩾12 to <18 Years of Age – Week 24 and Week 48 Analyses (Study TMC114-C230)

Parameter	N	Geometric Mean	Mean	SD	Median	Min	Max
AUC_{24h} (µg.h/mL)							
Week 24	12	77.8	81.9	25.1	87.9	34.6	128
Week 48	12	80.7	84.4	23.6	86.7	35.5	123
C_{0h} (ng/mL)							
Week 24	12	1,819	2,041	910	2,196	510	3,975
Week 48	12	1,930	2,141	865	2,234	542	3,776
$C_{ss,av}$ (ng/mL)							
Week 24	12	3,241	3,412	1,045	3,661	1,440	5,328
Week 48	12	3,364	3,516	983	3,614	1,480	5,139
CL/F (L/h)							
Week 24	12	10.3	11.0	4.6	9.1	6.3	23.2
Week 48	12	9.9	10.5	4.3	9.2	6.5	22.5

AUC_{24h} = area under the plasma concentration-time curve over 24 hours; C_{0h} = predose plasma concentration; CL/F = apparent clearance; $C_{ss,av}$ = average plasma concentration at steady-state; DRV = darunavir; HIV-1 = human immunodeficiency virus type 1; N = maximum number of subjects with data; rtv = low-dose ritonavir; SD = standard deviation.

2.3.3.3. Supportive study GS-US-292-0106

Study GS-US-292-0106 is an ongoing Phase 2/3, open-label study to evaluate the PK, safety, and antiviral activity of the E/C/F/TAF FDC in HIV-1 infected, ART-naïve adolescents. In this study, also a patient population of virologically suppressed children (aged 6 to <12 years) was included. However, these data are not described in this submission, which focuses on adolescent HIV-1 infected subjects.

The primary objectives of this study (adolescent group) are to evaluate the steady-state PK for EVG and TAF and confirm the dose of the E/C/F/TAF FDC in HIV-1 infected, ART-naïve adolescents (Part A of the study) and to evaluate the safety and tolerability of the E/C/F/TAF FDC through Week 24 in HIV-1 infected, ART-naïve adolescents (Part B of the study). The secondary objectives are to evaluate the safety, tolerability, and antiviral activity of the E/C/F/TAF FDC through Week 48 in HIV-1 infected, ART-naïve adolescents.

Subjects and Methods

All adolescents received the adult dose of E/C/F/TAF (150/150/200/10 mg). The steady-state PK (intensive PK visit at Week 4) of EVG, TAF, TFV, COBI, and FTC were evaluated in 24 adolescent subjects (aged ≥12 to <18 years and weighing ≥35 kg) enrolled in Part A of the study. The primary PK endpoint in Part A was AUCtau for EVG and the AUC from 0 hours up to the time of the last measurable (non-below quantification limit) concentration after dosing (AUClast) for TAF. The secondary PK endpoints included plasma concentration at the end of the dosing interval (Ctrough), Cmax, CL/F, and Vz/F for EVG; Cmax, CL/F, and Vz/F for TAF; and AUCtau, Cmax, and Ctrough for TFV, FTC, and COBI.

The PK data from adolescents who received E/C/F/TAF in this study were compared to combined available PK data from healthy adult subjects and HIV-1 infected adult subjects (adult comparator; total N=52).

For the purpose of this submission, the focus is on the COBI PK data. Data for EVG, FTC, TAF, and TFV can be found in the CSR.

Results: Pharmacokinetics of COBI

Pharmacokinetic parameters for COBI are presented in Table 11. For COBI, the AUCtau, Cmax, and Ctrough were 21.05%, 21.40%, and 39.59% lower, respectively, in adolescents in this study compared with the adult comparator, and the lower bound of the 90% CI of the GLSM ratio for each parameter extended below the 70% to 143% boundaries (Table 12). However, the COBI exposures were consistent with the totality of historical data for COBI and in the range of exposure associated with a robust PD effect (boosting) (Table 8), which is the function of COBI in E/C/F/TAF.

Table 11: Pharmacokinetic Parameters of COBI in HIV-1 Infected, ART-naïve Adolescents (Study GS-US-292-0106, Part A)

	Mean (%CV); t_{max}: Median (Range) (N=24)
Parameter	COBI (as Part of E/C/F/TAF FDC)
C_{max}, ng/mL	1,202.4 (35.0)
C_{trough}, ng/mL	25.0 (180.0)
t_{max}, h	4.00 (2.01, 5.00)
AUC_{tau}, ng.h/mL	8,240.8 (36.1)

ART = antiretroviral treatment; 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_{trough} = plasma concentration at the end of the dosing interval; CV = coefficient of variation; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDC = fixed-dose combination; HIV-1 = human immunodeficiency virus type 1; N = number of subjects; t_{max} = time to reach maximum plasma concentration.

Table 12: Statistical Comparisons of COBI PK Parameter Estimates Between Adolescents and Adults (All Substudy PK Analysis Set) (Studies GS-US-292-0106, GS-US-292-0102, and GS-US-292-0103)

	GLSM			
Parameter	Adults in Studies GS-US-292-0102 and GS-US-292-0103 (Reference)	Adolescents in Study GS-US-292-0106 (Test)	%GLSM Ratio (Test/Reference)	90% CI
N	52	24		
COBI				
AUC_{tau}, ng.h/mL	9,832.0	7,762.6	78.95	68.68 - 90.75
C_{trough}, ng/mL	22.2	13.4	60.41	39.13 - 93.26
C_{max}, ng/mL	1,456.3	1,144.6	78.60	69.71 - 88.62

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_{trough} = plasma concentration at the end of the dosing interval; GLSM = geometric least-squares mean; N = number of subjects; PK = pharmacokinetic(s).

2.3.4. 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 has been assessed in the adolescent cohort of the ongoing Phase 2/3 Study GS-US-216-0128, evaluating COBI coadministered with DRV in HIV-1 infected, ART-experienced, virologically

suppressed children. Adolescents in this cohort received DRV plus COBI (150 mg once daily) as separate tablets in combination with 2 NRTIs. The results of this cohort are relevant for the DRV/COBI FDC tablet, as the DRV/COBI FDC tablet is bioequivalent to combined administration of the separate tablets of DRV and COBI.

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.

The data from study GS-US-216-0128 are used as the main study for the extension of indication to adolescents. The data of other two studies are used as supportive evidence and are only be described and assessed shortly; these studies TMC114-C230 and GS-US-292-0106 have been part of previously approved marketing authorizations (Prezista, Genvoya and Symtuza)

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.

In general, the precision of the PK parameter estimates AUC and Cmax were sufficient both for DRV and COBI.

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). The MAH concluded that no clinically relevant differences in DRV exposures with COBI 150 mg once daily were observed in HIV-1 infected, virologically suppressed adolescents compared with adults. The PK data support the use of COBI 150 mg boosted DRV in adolescents weighing at least 40 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 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 was excluded from the primary statistical comparisons, hence the final number of subjects analysed was 7.

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.

The composition of the tablets is suitable for use in adolescent population. The size of the tablets is common for products used for this indication.

Rezolsta tablets do not contain a break mark; the MAH used tablet cutters to split the tablets. This principle could be acceptable as the intention is to swallow the complete dose. The MAH provided a PK study TMC114FD2HTX1004 of a similar FDC product containing D/C/F/TAF. In this study it was shown that the D/C/F/TAF tablet can be split prior to intake without impact on the bioavailability of the components. The CHMP considered that the results for clinical study TMC114FD2HTX1004 are relevant to support the proposed splitting instructions of the unscored tablets provided that that the entire dose is consumed immediately after splitting (as mentioned in the product information).

2.3.5. Conclusion on clinical pharmacology

Overall, the PK profile of the E/C/F/TAF components in adolescents was largely comparable to that in adults and was within clinically efficacious ranges for all components, supporting that the adult dose of COBI (150 mg) is appropriate for use in adolescents.

The composition of the tablets is suitable for use in the intended age group. The size of the tablets is common for products used for this indication.

Overall, the MAH has provided acceptable responses to all pharmacokinetic issues. There are no objections to an approval of the Paediatric indication from a pharmacokinetic point of view.

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:

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

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

Blinding (masking)

Study GS-US-216-0128 is an open-label study.

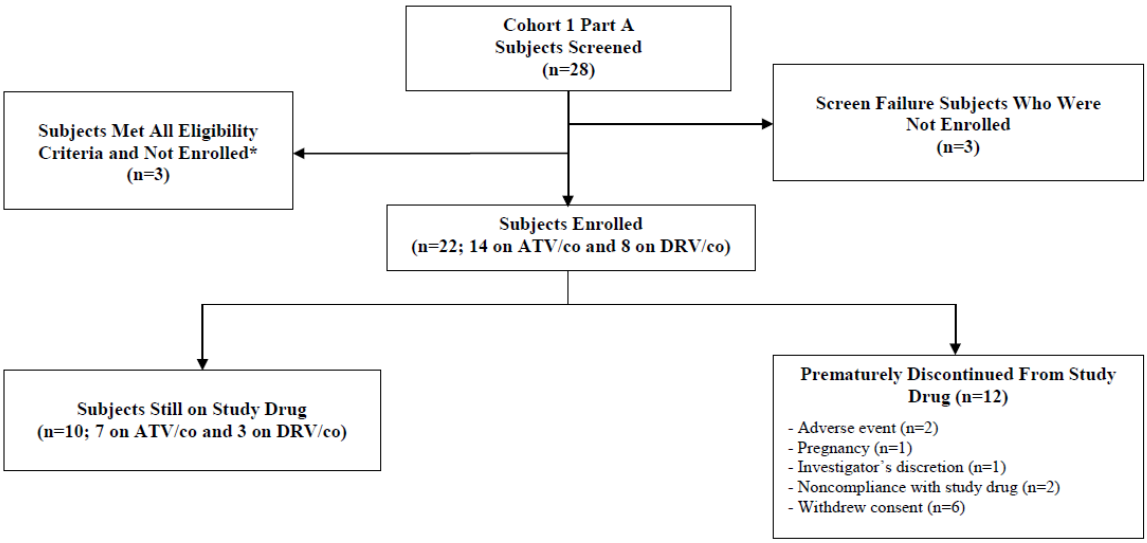
Statistical methods

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 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).

Adverse event and clinical laboratory data were summarized 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 summarized.

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 4. 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 finalization 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 predose 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 13 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 13. 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 14). 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 14. GS-US-216-0128: Demographic and Baseline Characteristics, Cohort 1 Part A (Safety Analysis Set)

Characteristic	Cohort 1 Part A: Age 12 to < 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
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 15).

Table 15. 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 16).

Table 16. 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.

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).

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 finalization)		
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

Analysis performed across trials (pooled analyses and meta-analysis)

Table 17 provides the FDA Snapshot outcome from Study GS-US-216-0128 and the two supportive studies TMC114-C230 and GS-US-292-0106 (see Supportive studies below).

Table 17. Virologic Outcomes at Week 48 in Studies TMC114-C230, GS-US-216-0128, and GS-US-292-0106; ITT

	TMC114-C230[b]	GS-US-216-0128[a,b,c]	GS-US-292-0106[a,b]
Efficacy Endpoint (Analysis Set)	**DRV/rtv + AZT/3TC or ABC/3TC (N=12)**	**DRV and COBI + 2 NRTIs (N=8)**	**E/C/F/TAF (N=50)**
FDA Snapshot Approach			
(ITT/FAS) N	12	8	50
Virologic Success at Week 48, n (%)			
HIV-1 RNA <50 copies/mL	11 (91.7)	6 (75.0)	46 (92.0)
Virologic Failure at Week 48, n (%)	1 (8.3)		3 (6.0)
HIV-1 RNA ≥50 copies/mL	1 (8.3)	0	2 (4.0)
Discontinued study drug due to lack of efficacy	0	0	0
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥50 copies/mL[d]	0	0	1 (2.0)
No Virologic Data in Week-48 Window, n (%)	0	2 (25.0)	1 (2.0)
Discontinued study drug due to AE/Death	0	1 (12.5)	0
Discontinued study drug due to other reasons and last available HIV-1 RNA <50 copies/mL (or missing)[d]	0	1 (12.5)	1 (2.0)

ABC/3TC = abacavir/lamivudine; AE = adverse event; AZT/3TC = zidovudine/lamivudine; COBI = cobicistat; DRV = darunavir; E/C/F/TAF = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FAS = Full Analysis Set; HIV-1 = human immunodeficiency virus type 1; FDA = Food and Drug Administration; ITT = intent-to-treat; N = number of subjects; NRTI = nucleoside reverse transcriptase inhibitor; rtv = low-dose ritonavir; SAS = Safety Analysis Set.

a. For Studies GS-US-216-0128 and GS-US-292-0106, analyses were done on the SAS, which corresponds to the ITT population.

b. The study population in Studies TMC114-C230 and GS-US-292-0106 consisted of ART-naïve adolescents (aged ≥12 to <18 years). The study population in Study GS-US-216-0128 consisted of ART-experienced, virologically suppressed adolescents (aged ≥12 to <18 years).

c. The numbers in the table refer to the subjects from the DRV and COBI arm.

d. 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.

Source: Mod5.3.5.2/TMC114-C230-W48-CSR/Sec5.3, Mod5.3.5.2/GS-US-216-0128-W48-Cohort1-CSR/Sec9.1, and Mod5.3.5.2/GS-US-292-0106-W48-CSR/Sec9.1.

Additionally, the MAH provided a comparison of the efficacy results in adolescents and adults, for Study TMC114-C230 (**ART-naïve subjects**) vs the historical pivotal Phase 3 Study TMC114-C211, which included adult, ART-naïve, HIV-1 infected subjects, who were treated with DRV/rtv 800/100 mg once daily in combination with FTC/tenofovir disoproxil fumarate (TDF), and Study TMC114FD2HTX3001, including adult, ART-naïve, HIV-1 infected subjects, who were treated with D/C/F/TAF once daily FDC or DRV and COBI 800/150 mg FDC with FTC/TDF 200/10 mg FDC once

daily. Virologic response and the change from baseline in CD4+ cell count/percentage was in general similar for these 3 studies.

The results of Study GS-US-216-0128, including **ART-experienced**, virologically suppressed, HIV-1 infected subjects from ≥12 to <18 years of age who were treated with DRV (800 or 675 mg) and COBI (150 mg), were presented next to the results of the Phase 3 Study TMC114IFD3013, which included ART-experienced, virologically suppressed HIV-1 infected adult subjects, who were treated with D/C/F/TAF FDC (800/150/200/10 mg). The efficacy results at Week 48 of Studies GS-US-216-0128 and TMC114IFD3013 are summarized and presented side by side in Table 18. Very low virologic failure rates were observed in both these studies. No clinically meaningful changes from baseline in CD4+ cell count and CD4+ percentage are noted in Studies GS-US-216-0128 and TMC114IFD3013.

Table 18. Virologic Outcomes (FAS - FDA Snaphot Analysis and Change From Baseline in CD4+ Percentage and Cell Count - Week-48 Analyses of Studies GS-US-216-0128 and TMC114IFD3013

Study Age at Screening Treatment Group	GS-US-216-0128 ≥12 to <18 years DRV (800 or 675 mg) and COBI (150 mg) + 2 NRTIs	TMC114IFD3013 Adults D/C/F/TAF (800/150/200/10 mg)
	(N=8)	(N=763)
Virologic Outcomes at Week 48		
FDA Snapshot Approach		
Virologic Failure at Week 48, n (%)	0	6 (0.8)
HIV-1 RNA ≥50 copies/mL	0	4 (0.5)
Discontinued due to other reason and last available HIV-1 RNA ≥50 copies/mL	0	2 (0.3)[c]
Virologic Success at Week 48, n (%)		
HIV-1 RNA <50 copies/mL at Week 48	6 (75.0)	724 (94.9)
No Virologic Data in Week-48 Window, n (%)	2 (25.0)	33 (4.3)
Discontinued due to AE/death	1 (12.5)	11 (1.4)
Discontinued due to other reason and last available HIV-1 RNA ≥50 copies/mL (or missing)	1 (12.5)	19 (2.5)[d]
Missing data during window but on study	0	3 (0.4)
Immunologic Parameters at Week 48		
Change from baseline in CD4+ cell count (x 10^6 cells/L), mean (SD)[e]	-411 (558.8)[a]	20 (5.7)[b]
median (range)	-342 (-1,389; 219)[a]	8 (-830; 899)[b]
Change from baseline in CD4+ percentage, median (range)	-6.1 (-12.1; 4.6)	0.7 (-17.9; 15.7)

AE = adverse event; COBI = cobicistat; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV= darunavir; FAS = Full Analysis Set; FDA = Food and Drug Administration; HIV-1 = human immunodeficiency virus type 1; ITT = intent-to treat; M=E = missing is excluded; N = number of subjects with data; n = number of subjects with that observation; NC=F = not completed is failure; NRTI = nucleoside reverse transcriptase inhibitor; SD = standard deviation; TLOVR = time to loss of virologic response.

a. The M=E imputation method was used for this calculation.
b. The NC=F imputation method was used for this calculation.
c. Reasons for discontinuation included lost to follow-up (1 subject) and withdrawal by subject (1 subject).
d. Reasons for discontinuation included lost to follow-up (4 subjects), noncompliance with study drug (2 subjects), withdrawal by subject (8 subjects), and other (5 subjects).
e. For Study TMC114IFD3013 the mean (SE) change from baseline in CD4+ cell count is presented.

Source: Mod5.3.5.2/GS-US-216-0128-W48-Cohort1-CSR/Sec9.1, Orkin C et al.[9], and data on file.

Supportive studies

Two studies have been submitted in support of efficacy of DRV/COBI in adolescents, Study TMC114-C230 (DRV/r, n=12 subjects enrolled) and Study GS-US-292-0106 (Genvoya, n=50 subjects enrolled). Both studies have also been assessed in support of the use of Symtuza (DRV/COBI/F/TAF) in adolescents.

At Week 48, the virologic success rate (HIV-1 RNA <50 copies/mL) in Study **TMC114-C230** was 83.3% (10/12 subjects) using the time to loss of virologic response (TLOVR) algorithm (primary efficacy endpoint) and 91.7% (11/12 subjects) using the FDA Snapshot Approach. The median (range) change from baseline in CD4+ cell count at Week 48 was +221 (64 to 370) cells/mm3, and the median (range) change from baseline in CD4+ percentage at Week 48 was +14 (-4 to 19) %.

In **Study GS-US-292-0106**, the virologic success rate (HIV-1 RNA <50 copies/mL) at Week 48 was 92.0%, (46/50 subjects) using the FDA Snapshot Approach. The median (range) change from baseline in CD4+ cell count of +220 (-87 to 661) cells/mm³, and the median (range) change from baseline in CD4+ percentage at Week 48 was +8.5 (-1.6 to 22.0) %.

In both studies, emergence of RAMs and phenotypic resistance against ARVs in the subjects' regimens were rare up to Week 96 and 192, with no DRV resistance observed in any study.

The MAH has included the acceptability study **TMC114FD2HTX1003** in support of the extension of indication to adolescents. In short, this was a Phase 1, open-label, randomized, single-dose, crossover study to evaluate the acceptability/swallowability of DRV/COBI and D/C/F/TAF FDC tablets (each administered as matching placebo tablets) in HIV-1 infected adolescent subjects, aged from ≥12 to <18 years and weighing at least 40 kg. The study consisted of a screening period and an open-label administration phase of 1 day. At screening, a reference placebo tablet (of similar size as approved products for adolescents) needed to be swallowed to assess willingness and ability to swallow. On Day 1, the 2 FDC placebo tablets (1x DRV/COBI and 1x D/C/F/TAF) were tested. After each intake of a placebo tablet, an acceptability/swallowability questionnaire had to be completed.

Intake of the DRV/COBI-matching placebo tablet, sized 23 mm x 11.5 mm, was considered easy for single administration and acceptable for long-term daily use by all 27 enrolled subjects. The complete CSR does not change this opinion.

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 stressed out 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/co) was provided, as this is the data submitted in support of the extension of indication for Rezolsta to include adolescents 12 to <18 years of age.

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 reason (subject's guardian did not want to

expose the subject to a non-FDA approved drug) and their last available HIV-1 RNA was < 50 copies/mL. Similar results were achieved at week 48 (75%) (response rate).

Body weight was 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. The MAH 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.

After excluding the subject with body weight below the 40 kg cut-off, 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). None of the subjects experienced protocol-defined virologic failure.

In relation to Virology Resistance Analyses, 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. Emergence of phenotypic resistance against DRV and NRTI background were rare in all studies up to 192 weeks.

Two studies have also been submitted in support of efficacy of DRV/COBI in adolescents, **Study TMC114-C230** (DRV/r, n=12 subjects enrolled) and **Study GS-US-292-0106** (Genvoya, n=50 subjects enrolled). Both studies have been previously assessed by the CHMP in support of the use of Symtuza (DRV/COBI/F/TAF) in adolescents.

At Week 48, the virologic success rate (HIV-1 RNA <50 copies/mL) using the FDA Snapshot Approach was 91.7% (11/12 subjects) in Study **TMC114-C230** and 92.0% (46/50 subjects) in **Study GS-US-292-0106**.

Acceptability was evaluated in study TMC114FD2HTX1003, which has already been assessed as part of the MAA assessment of Symtuza (approved in 2017), during which it was agreed with the MAH that the swallowability of the FDC was acceptable in the subjects who were enrolled in the study.

The requested extension of indication to adolescents for Rezolsta applies to both treatment-naïve and treatment-experienced patients, and hence the subjects enrolled in Study TMC114FD2HTX1003 are not fully representative for the envisioned population. This was agreed by CHMP considering that the tablet may also be split using a tablet-cutter in case of swallowability issues.

During the procedure the MAH clarified that protocol amendment 4, describing DRV suspension as alternative options for subjects who were unable to swallow tablets, was put in place 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. 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.

2.4.3. Conclusions on the clinical efficacy

Overall, the data to support the use of Rezolsta in adolescents, the efficacy of DRV, whether boosted with cobicistat or ritonavir, was overall acceptable (response rate ≥ 75%). Importantly, emergence of RAMs and phenotypic resistance against DRV and NRTI background were rare in all studies up to 192 weeks.

The overall efficacy was considered acceptable by the CHMP in the adolescent population.

2.5. Clinical safety

Introduction

To characterise the safety of Rezolsta in adolescents, studies TMC114-C230, GS-US-216-0128, and GS-US-292-0106 were submitted.

Patient exposure

At the data-cut date, the median (Q1, Q3) exposure to study drug in the DRV/co arm was 98.2 (28.6, 143.4) weeks.

Adverse events

An overall summary of AEs for Cohort 1 Part A is shown in Table 19. Two subjects experienced a treatment-emergent study drug related AE (Hyperlipidaemia in both cases). The 2 listed treatment-emergent SAEs were Chest pain (n=1) and Bipolar disorder (n=1). Two subjects prematurely discontinued the study due to treatment-emergent AEs: 1 subject due to hyperlipidemia and acanthosis nigricans, and the other subject due to chest pain and Becker's naevus.

Table 19. GS-US-216-0128: Overall Summary of Adverse Events, Cohort 1 Part A (Safety Analysis Set)

	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
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: Table 15.11.2.1.1

Adverse events considered related to study drug by the investigator were reported for 25.0% (2 of 8) of subjects (Table 20).

Table 20. 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		
	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%)
Jaundice	1 (7.1%)	0	1 (4.5%)
Proteinuria	1 (7.1%)	0	1 (4.5%)
Vomiting	1 (7.1%)	0	1 (4.5%)

Adverse events were coded using MedDRA version 21.1.
Preferred terms are presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject per preferred term.
Relatedness to study drug was assessed by the investigator.
Source: Table 15.11.2.3.1.2

Serious adverse event/deaths/other significant events

No treatment-emergent death was reported. Serious AEs, considered unrelated to study drug by the investigator, were reported for 25.0%(2 of 8) of subjects. These included bipolar disorder in 1 subject and chest pain in 1 subject No SAE was reported for > 1 subject. The SAE of chest pain led to premature study drug discontinuation.

Laboratory findings

There were no clinically relevant changes from baseline in median values for haematology or clinical chemistry parameters through the data-cut date, excluding some liver-related parameters as discussed below.

Most subjects (90.9%; 20 of 22) had at least 1 laboratory abnormality. The maximum toxicity was Grade 1 or 2 for 36.4% (8 of 22) of subjects and Grade 3 for 50.0% (11 of 22) of subjects; a transient Grade 4 laboratory abnormality (creatine kinase increased) was reported for 1 subject.

Most laboratory abnormalities were isolated and transient occurrences. 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 hyperlipidemia considered related to study drug by the investigator.

Renal Safety

There were no clinically relevant changes from baseline in blood urea nitrogen, uric acid, total protein, serum creatinine, serum cystatin C, or albumin through the data-cut date. The median values for each renal laboratory parameter remained within normal ranges.

Most graded renal laboratory abnormalities were Grade 1 or Grade 2; Grade 3 or 4 abnormalities included haematuria by quantitative assessment (4 subjects; all female). Clinical laboratory abnormalities related to renal laboratory parameters that were reported as AEs included proteinuria in 2 subjects and haematuria in 1 subject. All of the AEs were Grade 1 and only proteinuria in 1 subject was considered related to study drug.

Creatinine increases and modest decreases in eGFRSchwartz were observed as early as Day 10 (median increase in creatinine: 0.05 mg/dL; median decrease in eGFRSchwartz: -9.19 mL/min/1.73 m2) and at all other timepoints. The median changes from baseline at Weeks 24 and 48 were 0.08 mg/dL at both timepoints for serum creatinine, and -15.77 and -12.03 mL/min/1.73 m2, respectively, for eGFRSchwartz. These changes stabilized and remained relatively constant from Week 48 to Week 96 (median increase in creatinine: 0.04 mg/dL; median decrease in eGFRSchwartz: -8.78 mL/min/1.73 m2), after which an upward trend in serum creatinine and a downward trend in eGFRSchwartz was noted. No graded laboratory abnormalities in serum creatinine were observed. In general, renal laboratory assessments showed changes consistent with the inhibitory effects of COBI on renal tubular creatinine secretion.

Fasting Glucose and Lipids

There were no clinically relevant changes from baseline in median fasting values for total cholesterol, direct LDL cholesterol, HDL cholesterol, total cholesterol: HDL cholesterol ratio, triglycerides, or glucose through the data-cut date. The median values for each fasting metabolic laboratory analyte remained within normal ranges.

Most graded fasting lipid and glucose abnormalities were Grade 1 or Grade 2; 1 Grade 3 abnormality included fasting LDL increased (1 subject). Clinical laboratory abnormalities related to fasting lipid and glucose abnormalities that were reported as AEs included hyperlipidemia in 2 subjects (both Grade 2 and considered related to study drug).

Hepatic Safety

Median values for total bilirubin and indirect bilirubin were higher than normal range at various timepoints through the data-cut date, including Day 10 and Weeks 32, 48, 120, 156, 168, and 180 (median range, 1.3 – 2.6 mg/dL). These values in the total group were attributed to higher than normal values in the ATV/co group which occurred at most timepoints during the study. Hyperbilirubinemia is a known abnormality associated with ATV, which is reversible upon discontinuation {REYATAZ® 2018}. Median values for total and indirect bilirubin in the DRV/co group remained within normal ranges at all timepoints. Median values for other liver-related parameters remained within normal ranges.

Discontinuation due to adverse events

Adverse events that led to premature study drug discontinuation were reported for 2 subjects (25.0%).

- 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.

- One subject had 2 AEs that led to premature study drug discontinuation: Grade 2 chest pain that started on Day 73 and was reported as an SAE, and Grade 1 Becker's naevus that started on Day 56; both events were considered unrelated to study drug. This subject was prematurely discontinued from the study at the investigator's discretion. The last dose day was Day 56 and last study day was Day 212.

Post marketing experience

Based on the total of 87,045,630 tablets of DRV/COBI FDC distributed (from launch to 30 November 2018), the estimated exposure is 2,863,342 person-months and 238,612 person-years.

At the time of finalization of the Summary of Clinical Safefy addendum, which is included in the submission, 6 Periodic Benefit Risk Evaluation Reports/Periodic Safety Update Reports (PBRERs/PSURs) have been generated for DRV/COBI covering the period from 19 November 2014 to 18 May 2018 and summarizing the post marketing safety data obtained by the MAH. These concluded that based on review of nonclinical, clinical, epidemiologic information, scientific literature, and post marketing data, the DRV/COBI FDC continues to demonstrate a favourable benefit risk profile for its authorized indications.

2.5.1. Discussion on clinical safety

The safety of both single compounds of Rezolsta, DRV and COBI, in adolescents has been assessed before and is described in the Prezista (DRV) product information, as well as in the one of the fixed-dose combination tablets including COBI that are indicated for use in adolescents (Genvoya, Symtuza, Stribild). 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 for these 4 products that DRV or COBI affects pubertal development or growth in adolescents.

The only new information in the current submission comes from Study GS-US-216-0128, which included 7 patients on DRV/co which is considered too small to draw meaningful conclusions regarding the Rezolsta safety profile. However, the available safety data from this study did not reveal safety concerns that would preclude it's use in adolescents. Two of the eight (25%) subjects discontinued the study early due to adverse events. In one subject, this was due to Grade 2 hyperlipidemia (considered related to study drug by the investigator) and Grade 1 acanthosis nigricans (considered unrelated to study drug). The other subject discontinued with Grade 2 chest pain and Grade 1 Becker's naevus; both events were considered unrelated to study drug. Hyperlipidemia is a known AR with DRV/Cobi and is already listed as 'common' in section 4.8 of the Rezolsta SmPC, the other AEs mentioned above were considered unrelated to study drug which can be agreed with.

2.5.2. Conclusions on clinical safety

Overall, the available safety data showed that DRV and COBI is well tolerated in HIV-1 infected adolescents (12 years and older and weighing at least 40 kg) and that the safety profile of DRV and COBI is similar to that observed in adults. The safety profile of DRV and COBI FDC is largely based on the well-established safety profile of the individual components and it has been previously assessed in

other procedures (i.e. Prezista, Symtuza). The observed safety profile is in line with expectations and did not raise additional concerns.

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 requested to submit an updated RMP version with this application.

The PRAC considered that the risk management plan version 6.0 is acceptable.

Safety concerns

Table 21: Summary of the Safety Concerns (table from MAH RMP module SVIII)

Summary of safety concerns	
Important identified risks	none
Important potential risks	none
Missing information	none

Pharmacovigilance plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that:

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures

Risk minimisation measures

The PRAC Rapporteur having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. For further details, refer to the to the full SmPC in attachment

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:

- The patient information leaflet (PIL) for REZOLSTA (adult indication) has been created, starting

from the approved PREZISTA PIL (the "parent") and additional information, mainly triggered by the presence of COBI in the FDC, has been added (text from the approved COBI leaflet was used where possible). A justification for not performing user testing for REZOLSTA was included in the initial Marketing Authorisation Application, that has been approved on 19 November 2014. For PREZISTA, full user testing in compliance with the above-mentioned legislative requirements was performed (n=37 participants) on the initial patient leaflet for PREZISTA 300 mg film-coated tablets (EMEA/H/C/000707, approved on 12 February 2007).

- The proposed updated indication for REZOLSTA is an extension of the target group of users (i.e. antiretroviral treatment naïve or experienced HIV-1 infected adults and paediatric subjects [⩾12 to < 18 years of age] and weighing at least 40 kg, without DRV resistance associated mutations (RAMs) and who have plasma HIV-1 RNA < 100,000 HIV-1 RNA copies/mL and CD4+ cell count ⩾ 100 cells x 106/ L). No new tablet strength or formulation, or new route of administration is proposed.
- Safety analyses of the studies in adolescent subjects did not identify new safety concerns compared to the known safety profile of DRV and COBI in ARV treatment-naïve and treatment-experienced HIV-1 infected adults. The DRV/COBI safety profile, as established in ARV treatment-naïve and treatment experienced HIV-1 infected adults, was confirmed in ARV treatment-naïve and treatment experienced HIV-1 infected adolescents.
- Full user testing in compliance with the above-mentioned legislative requirements was performed (n=20 participants) on the patient leaflet for PREZISTA 75 mg for use in adolescents (ages 14 through 18 years of age were tested), and the patient leaflet for REZOLSTA has a similar format as the patient leaflet for PREZISTA 75 mg tablets.

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 minimizing 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). 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 MAH submitted the following studies in support of the proposed use in HIV-1 infected adolescents (aged ≥12 to <18 years):

- TMC114-C230 (DRV 800 mg in combination with ritonavir [rtv] 100 mg in n=12 ART-naïve subjects).
- 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).
- GS-US-292-0106 (COBI, as part of the elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF] 150/150/200/10 mg FDC in n=50 ART-naïve subjects).

Study GS-US-216-0218 is the main study for this extension of indication to adolescents.

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.

Additional analyses comparing adolescent and adult DRV PK data from subjects treated with DRV administered as DRV/rtv 800/100 once daily in combination with other ARV drugs (study TMC114-C211) and COBI PK data from subjects treated with an E/C/F/TAF combination (study vGS-US-292-0106) supported the conclusion from the main study GS-US-216-0128.

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. In addition, the emergence of RAMs and phenotypic resistance against DRV and NRTI background were rare in all studies up to 192 weeks although the available dataset is limited.

3.4. Unfavourable effects

Two subjects (25%) experienced a treatment-emergent study drug related AE (Hyperlipidaemia in both cases). Two subjects (25%) prematurely discontinued the study due to treatment-emergent AEs: 1 subject due to hyperlipidemia and acanthosis nigricans, and the other subject due to chest pain and Becker's naevus.

3.5. Uncertainties and limitations about unfavourable effects

The only new information comes from Study GS-US-216-0128, which 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 Rezolsta safety profile. However, as for both components of the FDC it was already concluded that the safety profile in adolescents is comparable to that in adults, there is no reason to assume that this will be any different for the Rezolsta FDC.

3.6. Effects Table

Table 22. Effects Table for Rezolsta 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 (%)	0/8 (0%)	n/a		
Unfavourable Effects						
Treatment-emergent study drug related AE	Hyperlipidaemia	n/N (%)	2/8 (25.0%)	n/a	Small sample size. Hyperlipidemia is a known AR with DRV/Cobi.	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.

*After excluding the subject with body weight below the 40 kg cut-off, 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).

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 are 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, the DRV/COBI FDC 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 least 40 kg. This should be balanced against the risk for development of resistance, which in the limited dataset available, seems to be acceptable given that emergence of RAMs and phenotypic resistance against DRV and NRTI background were rare in all studies up to 192 weeks.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Rezolsta remains positive.

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 extend the approved therapeutic indication of Rezolsta to include the adolescent population (aged 12 years old and older with body weight at least 40 kg). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and sections 1, 2 and 3 of the PL are updated accordingly. The updated RMP version 6.0 has also been submitted.

The RMP of the product has been updated to meet the requirements and updated definitions in the European Medicines Agency (EMA) Guideline on good pharmacovigilance practices (GVP) Module V

Revision 2 (EMA/838713/2011; Rev 2) and Guidance on the format of the RMP in the European Union (EMA/164014/2018 Rev 2.0.1) including proposed removal of safety concerns.

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

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

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/0006/2019 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

To extend the approved therapeutic indication of Rezolsta to include the adolescent population (aged 12 years old and older with body weight at least 40 kg). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and sections 1, 2 and 3 of the PL are updated accordingly. The updated RMP version 6.0 has also been submitted.

The RMP of the product has been updated to meet the requirements and updated definitions in the European Medicines Agency (EMA) Guideline on good pharmacovigilance practices (GVP) Module V Revision 2 (EMA/838713/2011; Rev 2) and Guidance on the format of the RMP in the European Union (EMA/164014/2018 Rev 2.0.1) including proposed removal of safety concerns.

In addition, in order to align the PI 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 Rezolsta in case of vomiting.

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

Summary

Please refer to Scientific Discussion: Rezolsta-H-C-002819-II-33.

Attachments

1. SmPC and Package Leaflet (changes highlighted) of REZOLSTA 800 mg, 150 mg, tablets as adopted by the CHMP on 30th January 2020.

Reminders to the MAH

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

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. The MAH is reminded that, at the same time as the submission on the eCTD closing sequence mentioned above, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

4. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.