22 May 2025
EMA/196660/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rezolsta

International non-proprietary name: Darunavir / Cobicistat

Procedure No. EMEA/H/C/002819/X/0054/G

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

abbreviation	description of abbreviated term
3TC	lamivudine
ABC	abacavir
ADR	Adverse Drug Reaction
AE	adverse event
AIDS	acquired immune deficiency syndrome
ART	antiretroviral treatment
ARV	antiretroviral
ATV	atazanavir
AZT	zidovudine
COBI	cobicistat
CSR	clinical study report
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DRV	darunavir
EACS	European AIDS Clinical Society
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
ECG	electrocardiogram
$eGFR_{cr}$	estimated glomerular filtration rate based on serum creatinine
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
GVP	Guideline on good pharmacovigilance practices
HBV	hepatitis B virus
HDL	high-density lipoprotein
HIV(-1)	human immunodeficiency virus (type 1)
MAH	Marketing Authorisation Holder
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
PI	protease inhibitor
PK	pharmacokinetic(s)
PL	Package Leaflet
PRT	proximal renal tubulopathy
PV	pharmacovigilance
RAM	resistance-associated mutation
RMP	Risk Management Plan
rtv	low-dose ritonavir
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
TAF	tenofovir alafenamide
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TLOVR	time to loss of virologic response

1. Background information on the procedure

1.1. Submission of the dossier

Janssen-Cilag International N.V. submitted on 30 May 2024 a group of variation(s) consisting of an extension of the marketing authorisation.

The MAH applied for an extension application to introduce a new strength (675 mg/150 mg film-coated tablets) grouped with an extension of indication to include: treatment of HIV-1 infected paediatric patients (aged 6 years and older with body weight at least 25 kg).

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0257/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0257/2023 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Patrick Vrijlandt

The application was received by the EMA on	30 May 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	3 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to	17 October 2024

the MAH during the meeting on	
The MAH submitted the responses to the CHMP consolidated List of Questions on	23 January 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 February 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	27 March 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	17 April 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	07 May 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rezolsta on	22 May 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The current application is intended to support registration of a scored DRV/COBI 675/150-mg FDC film-coated oral tablet for once-daily use for use in HIV 1 infected children aged ≥6 years and weighing ≥25 to <40 kg, who are either ART naïve or ART-experienced.

The following wording is proposed by the MAH:

4.1 Therapeutic indications

Rezolsta is indicated, in combination with other antiretroviral medicinal products, for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and paediatric patients (aged 6 years and older, weighing at least 25 kg).

Genotypic testing should guide the use of Rezolsta (see sections 4.2, 4.4 and 5.1).

2.1.2. Epidemiology

HIV continues to be a major global public health issue, having claimed more than 40 million lives so far. In 2022, 630 000 people died from HIV-related causes globally. There were approximately 39 million people living with HIV at the end of 2022, of whom 1.5 million were children 0-14 years old. Since 2010, the number of people acquiring HIV has been reduced, but there were still 1.3 million people becoming newly infected in 2022 globally, 130.000 being children 0-14 years old. (WHO FACT sheet).

There is no cure for HIV infection. However, with access to effective HIV prevention, diagnosis, treatment and care, including for opportunistic infections, HIV infection has become a manageable chronic health condition, enabling people living with HIV to lead long and healthy lives.

2.1.3. Biologic features

HIV-1 infection results in chronic activation of the immune system and a subsequent gradual loss of CD4+ T cells, eventually leading to a state of acquired immunodeficiency (AIDS). One of the predictors for HIV-1 disease progression is the level of HIV-1 RNA in the blood (i.e. viral load). The aim of treatment of HIV-1 infection is therefore to suppress, and subsequently maintain, the HIV-1 viral load to levels that are at least below the limit of detection of most commonly used assays (50 copies/mL of blood).

HIV-1 is a rapidly replicating virus, with an error-prone Reverse Transcriptase (RT). Mutations in the viral genome occur randomly when the virus replicates, with an estimated mutation rate of approximately one nucleotide mutation per replicative cycle. Many HIV variants are simultaneously present in each infected individual, which is also described as “quasispecies”. Resistance-associated mutations (RAMs) can rapidly be selected when there is selection pressure due to e.g. too low concentrations of antiviral drugs. Often, resistance to drugs in a certain ARV class results in cross-resistance to other drugs in that same class.

2.1.4. Clinical presentation, diagnosis

The symptoms of HIV vary depending on the stage of infection. Though people living with HIV tend to be most infectious in the first few months after being infected, many are unaware of their status until the later stages. In the first few weeks after initial infection people may experience no symptoms or an influenza-like illness including fever, headache, rash, or sore throat. As the infection progressively weakens the immune system, they can develop other signs and symptoms, such as swollen lymph nodes, weight loss, fever, diarrhoea, and cough. Without treatment, they could also develop severe illnesses such as tuberculosis, cryptococcal meningitis, severe bacterial infections, and cancers such as lymphomas and Kaposi's sarcoma.

Children may have more rapid disease progression and accelerated damage of the developing immune system compared to adults, with higher viral loads and less effective immunological responses to HIV infection than adults.

2.1.5. Management

Standard of care for the treatment of HIV-1 requires use of combination ART to suppress viral replication to below detectable limits, increase CD4 cell counts, and stop disease progression. The choice of the combination regimen depends on the status of the patient, particularly in terms of plasma HIV viral load, CD4 cell counts, any previous treatments and prior treatment failure/intolerance.

Commonly used guidelines are those developed by the WHO, the European AIDS Clinical Society (EACS), the Department of Health and Human Services (DHHS) in the USA and the Paediatric European Network for Treatment of AIDS (PENTA), for use in children and adolescents.

Treatment options in children are more limited compared to adults. The recommended (collaborative Penta/EACS HIV treatment guideline, 2022) initial treatment of HIV-1 infection for paediatric patients is therapy with two NRTIs in combination with a drug from a different class (third agent). DTG is the preferred third agent in all children over 4 weeks of age and 3 kg. Whilst “preferred options” are

recommended, "alternative options" are acceptable and remain important choices in settings where ART availability is limited or in individuals at particular risk of specific toxicity or DDIs.

2.2. About the product

The DRV/COBI 800/150-mg FDC film-coated tablet (EU: Rezolsta/US: PREZCOBIX) once daily is currently indicated in the EU and US, in combination with other ARV medicinal products, for the treatment of HIV-1 infection in adults and adolescents aged ≥12 years and weighing ≥40 kg, who are either ART-naïve or ART-experienced (Rezolsta SmPC 2022; PREZCOBIX USPI 2023). The DRV/COBI 800/150-mg FDC film-coated tablet was developed by Janssen in collaboration with Gilead Sciences, Inc. (Gilead).

In addition, a scored DRV/COBI 675/150-mg FDC film-coated oral tablet for once-daily use was developed, for use in HIV-1 infected children aged ≥6 years and weighing ≥25 to <40 kg, who are either ART naïve or ART-experienced.

The proposed indication is:

Rezolsta is indicated, in combination with other antiretroviral medicinal products, for the treatment of human immunodeficiency virus 1 (HIV 1) infection in adults and paediatric patients (aged 6 years and older, weighing at least 25 kg).

Genotypic testing should guide the use of Rezolsta (see sections 4.2, 4.4 and 5.1).

The proposed posology for paediatric patients aged 6 years and older weighing at least 25 kg to less than 40 kg is:

ART naïve paediatric patients

The recommended dose regimen in paediatric patients aged 6 years and older weighing at least 25 kg to less than 40 kg is one 675 mg darunavir/150 mg cobicistat film-coated tablet of Rezolsta once daily taken with food.

ART experienced paediatric patients

*One 675 mg darunavir/150 mg cobicistat film coated tablet of Rezolsta once daily taken with food may be used in paediatric patients aged 6 years and older weighing at least 25 kg to less than 40 kg with prior exposure to antiretroviral medicinal products, but without darunavir resistance associated mutations (DRV-RAMs) * and who have plasma HIV 1 RNA < 100,000 copies/mL and CD4+ cell count ≥ 100 cells x 106/L (see section 4.1).*

** DRV RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V, L89V.*

2.3. Type of Application and aspects on development

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC– relating to applications for new fixed combination products.

2.4. Quality aspects

This line extension relates to an addition of a new strength (675 mg/ 150 mg) of the already authorised film coated tablets.

2.4.1. Introduction

The finished product is presented as a film coated tablet containing 675 mg of darunavir (as ethanolate) and 150 mg of cobicistat as active substances.

Other ingredients are:

Tablet core: colloidal silicon dioxide, cellulose, microcrystalline, croscarmellose sodium, and magnesium stearate

Tablet film-coat: iron oxide yellow (E 172), iron oxide black (E 172), macrogol/polyethylene glycol, polyvinyl alcohol– partially hydrolysed, talc, and titanium dioxide (E 171).

The product is available in white, high density polyethylene (HDPE) bottle, fitted with polypropylene (PP) child resistant closure with induction seal as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The active substances darunavir as ethanolate and cobicistat are not described in the Ph. Eur. They are both already approved for commercial use in Rezolsta 800mg/150mg, film coated tablets.

No new documentation has been submitted about the active substances. This is acceptable as the proposed strength (i.e. 675mg/150mg) contains the same active substances form the same source as the commercially available strength (800 mg/150mg) and no additional controls on functionality related characteristics are proposed for the new strength.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as an immediate release, film-coated tablet containing 675 mg of darunavir and 150 mg cobicistat as active substances. The finished product is presented as a green to dark green oval-shaped scored tablet of 21 mm x 10 mm, debossed with "675" on one side and "TG" on the other side.

A fixed-dose combination (FDC) immediate release film-coated tablet for oral administration has been developed for the paediatric population (i.e. ≥6 years of age and weighing ≥25 kg and <40 kg). It is bioequivalent to the coadministration of single agent commercially approved tablet formulations darunavir 600 mg and darunavir 75 mg film-coated tablets in the presence of cobicistat 150 mg film-coated tablet.

No changes in the active substances are proposed for the new strength besides the ratios. The provided information regarding the active substances is therefore sufficient.

Compatibility of the active substances with the excipients in the new ratios is proved through stability studies together with the data already presented in the original dossier (i.e. approved 800/125 mg strength), this was considered sufficient.

All excipients are well characterised and widely used in pharmaceutical preparations. The excipients used in the tablet core of the proposed commercial formulation have detailed monographs in relevant pharmacopoeias (USP/NF and Ph. Eur.) and are recognized as safe. The components of the commercially available coating powder are also widely used in pharmaceutical preparations for the same route of administration. There are no novel excipients used in the finished product formulation.

The list of excipients is included in section 6.1 of the SmPC. The provided discussion of the safety profile of the selected excipients, shows that the excipients and their quantity are suitable for use in the target age group in scope of this line extension (i.e. paediatric patients aged 6 years and older weighing at least 25 kg to less than 40 kg).

Some changes compared to the formulation of the accepted strength are proposed for the new strength, i.e. the disintegrant crospovidone in the accepted formulation is replaced by croscarmellose sodium and the filler silicified microcrystalline cellulose is replaced by microcrystalline cellulose. The rest of the excipients are the same as those in the already authorised formulation.

The main development studies were based on previous manufacturing experience of the mono-products containing darunavir and cobicistat, and experience with the manufacturing of a fixed dose preparation containing darunavir, cobicistat, emtricitabine and tenofovir alafenamide. The composition of the batch used in the bioequivalence study was the same as the commercial formulation.

A clinical bioequivalence (BE) study compared the new strength (cobicistat 150 mg and darunavir 675 mg tablet) to co-administration of the approved single agents, cobicistat eq. 150 mg tablet with darunavir 600 mg and 75 mg darunavir film-coated tablets, under fed conditions. The new strength was found to be bioequivalent to the approved single agents.

The QC methods used are the same as those approved for the accepted darunavir/cobicistat strength. This is acceptable and no further justification is necessary. No comparative dissolution data complementary to the BE study was submitted. This was considered satisfactory as the BE study is leading, however the MAH provided comparative dissolution profiles of a different finished product batch than the original BE batch and commercial batches of the reference product were provided as the BE batch, and the batches of the reference product were past their shelf life. This was considered satisfactory.

To facilitate the administration to patients unable to swallow the tablet as whole, the proposed Rezolsta 675mg/150mg film-coated tablets includes a score line allowing the breaking of the tablet into two halves and not to divide into equal doses (see SmPC section 3). This is considered adequate taking into account the tablet dimensions and the target population.

One of the objectives of the development of the new strength was the generation of data on acceptability in the proposed paediatric population. However, no acceptability/swallowability study was performed using Rezolsta 675mg/150mg. These data were instead generated in a phase I study which was conducted with another product developed by the MAH, i.e., Symtuza (darunavir/ cobicistat/ emtricitabine/ tenofovir alafenamide) film coated tablet. Placebo tablets were used in the study. In addition to the swallowability of the tablet as whole or as a split tablet, the ease of splitting the scored film coated Symtuza placebo tablet was also tested. This quality related study was presented and extensively discussed by the PDCO on various occasions. Although it was highlighted that generating the data with the actual proposed product would have been preferable, the MAH's proposal to extrapolate the acceptability data for Symtuza to Rezolsta was ultimately accepted in view of the similarities of both products. This is agreed based on the tablet's dimensions (i.e. the Rezolsta tablet is slightly smaller than the Symtuza tablet) and the same oval shape of the two products; both tablets include a score line and a non-functional film coating, additionally the tablet hardness is similar. The acceptability data confirmed that the tablet size and form were found acceptable for the majority of the children when taken as a whole or as a split tablet. Breaking of the placebo-matched scored film-coated Symtuza tablets was assessed and found acceptable. Based on these results, administration of the Rezolsta new strength to the children in the new proposed target population is not expected to be a problem in the clinical practice.

The manufacturing process of the new strength consists of initial blending, blending, dry granulation, followed by final blending, compression, film-coating and packaging process steps. The MAH has developed a science-based criticality analysis approach to determine the critical controls for finished product manufacturing processes. This approach assigns criticality based on process parameter and material attribute impact on finished product Critical Quality Attributes (CQAs) within potential operating ranges. The CQAs are derived from the Quality Target Product Profile (QTPP) and patient impact (safety, efficacy, and therapy compliance). This impact assessment is based on process development and manufacturing data from the product, and/or on prior knowledge from process platform experience, scientific insight, or regulatory expectations. Potentially relevant quality attributes are first identified based on the QTPP and prior product and process knowledge. A criticality assessment of quality attributes is performed, during which the quality attributes are evaluated and ranked according to the severity of their impact on patient safety and finished product efficacy, and the degree of knowledge uncertainty in the severity ranking.

Table 1: Finished product QTTP and its links to CQAs

Quality Target Product Profile		Drug Product Critical Quality Attribute
Drug Product Attribute	Target	
Route of Administration	Oral	Appearance
Dosage Form	Film-coated tablet	Appearance
Dosage Strength	675 mg darunavir/ 150 mg cobicistat	Appearance, identification, assay, uniformity of dosage units
Purity	Sufficiently low level of impurities/degradation products, complying with the ICH requirements	Chromatographic Purity
Drug Release Profile	Immediate release	Dissolution
Microbial Purity	Sufficiently low level of microbial burden, complying with the ICH requirements	Microbiological purity
Container Closure System	120 mL high-density polyethylene (HDPE) bottle capped with a child-resistant (CR) polypropylene (PP) 38 mm closure, with an induction sealed liner	Appearance, chromatographic purity, dissolution, microbiological purity
Stability	Minimum 36 months shelf life	Appearance, assay, chromatographic purity, dissolution, microbiological purity

Any additional considerations were taken into account, for example regulatory expectations (e.g., compendial or ICH guidelines). As a result of this systematic evaluation, all quality attributes are assigned as CQA. A comprehensive criticality analysis was conducted to determine an appropriate control strategy for the finished product CQAs. Based on the development knowledge and using quality risk management tools as described in ICH Guideline Q9, the finished product manufacturing process was systematically evaluated to determine which process parameters and material attributes can potentially impact the CQAs of the finished product. No design space is claimed.

The identified critical process parameters (CPPs) and critical material attributes (CMAs) of the active substances and excipients were evaluated against the risk of CQA failure. Based on the outcome of this evaluation, a risk-based control strategy was proposed. CCPs are an essential element of this control strategy. A CPP is a control limit or range for a CPP, a CMA of an active substance or excipient or a critical in-process control (CIPC). Other elements of the control strategy include the manufacturing process design, final finished product release testing, and a compliant GMP quality system. Following the applicable guidelines, the elements of a compliant GMP quality system include standard operating procedures and batch records, trained operators, qualified equipment, engineering controls, deviation control, etc. In summary, the control strategy assures consistent quality of the final finished product.

The primary packaging is high density polyethylene (HDPE) bottle, fitted with polypropylene (PP) child resistant closure with induction seal. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The new proposed strength is manufactured in one manufacturing site. Satisfactory GMP documentation has been provided.

The manufacturing process consists of 7 main steps.: initial blending, blending, dry granulation, final blending, compression, tablet coating and packaging. The manufacturing process is considered as standard. The manufacturing process has been validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques, therefore process validation for full scaled batches will be performed post authorisation. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), tablet dimensions, identification (HPLC, UV), assay (HPLC), impurities related to darunavir (HPLC), impurities related to cobicistat (HPLC), uniformity of dosage (Ph. Eur.), dissolution (Ph. Eur.) and microbial purity (Ph. Eur.).

The MAH provided information on the impurities and degradation products in the approved active substance. This was acceptable. However, the CHMP raised a major objection and asked the MAH should provide rationale for product impurities. The MAH provided a toxicological justification for the limits of specified impurities based on qualification levels that have been determined for the intended paediatric population, and this justification was considered satisfactory.

During the evaluation the CHMP considered as MO2 that the dissolution limit could not be accepted as there were discrepancies in the dissolution data of the BE batch which need to be resolved before a limit can be set. The MAH clarified that the dissolution data originally provided was generated with the clinical dissolution method applicable at the time of clinical development. One clinical batch was re-tested with the proposed commercial QC method and the results from this testing were used to define the proposed limit and time point for both active substances. The data from other representative batches were also taken into account. The relevant section in the dossier has been revised to include the batch dissolution data generated with the proposed QC method. This was considered satisfactory.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/MAHs on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for six commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on the product has been provided on three commercial scaled batches. stored at 5 °C (up to 3 months), 25 °C/ 60% RH (up to 24 months), 30 °C/ 75% RH (up to 24 months) and 40 °C/ 75% RH (up to 6 months). The conditions used in the stability studies are not all according to the ICH stability guideline. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The shelf-life specifications are identical to the release specifications. The analytical procedures used are stability indicating.

Some changes are seen, but all results remain within specification.

Forced degradation studies were performed. To accommodate the target paediatric population, minor changes were introduced in the new strength formulation. Forced degradation studies of the accepted strength under stress conditions were performed to test the effects of acidic, alkaline, oxidative, thermal neutral and metal ions conditions on the finished product in solution, as well as the effect of light, dry heat and humid heat on the solid finished product.

The photostability study was conducted on the proposed finished product.

Additionally, use stability study was conducted on the finished product (to mimic daily use). Stability data has been provided demonstrating that no changes in the product quality occur during in-use shelf life. Based on the results an in-use shelf life of 8 weeks is claimed (SmPC section 6.3).

Based on available stability data, the proposed shelf-life of 3 years without storage conditions with no special storage conditions and the in-use shelf life of 8 weeks as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The present extension application concerns addition of one strength 675 mg/ 150 mg of the already authorised film coated tablets.

The development, characterisation, manufacture, and control of the active substances has already been assessed and approved. No changes are introduced for the additional strength.

Information on development, manufacture and control of the new strength of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure, two major objections were raised by the CHMP related to (1) impurities, and (2) the dissolution limit, which could not be accepted as there were discrepancies in the dissolution data of the BE batch which needed to be resolved before a limit can be set. In response to these major objections, the MAH provided a justificationfor the limits of specified impurities based on qualification levels that have been determined for the intended paediatric population, and also the batch dissolution data generated with the proposed QC method was provided. These responses were considered satisfactory.

The MAH has applied QbD principles in the development of the active substance and/or finished

product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Pharmacology

There are no new data for this section on primary or secondary pharmacodynamics, or safety pharmacology.

2.5.2. Pharmacokinetics

There are no new data for this section on methods of analysis, absorption, distribution, metabolism, excretion, or drug-drug interactions. However, exposure ratio in animals versus children (≥6 years to <12 years) were calculated and are discussed in the toxicology section.

2.5.3. Toxicology

The MAH has not performed new nonclinical studies to support the use of FDC DRV/COBI in children ≥6 to <12 years and weighing ≥25 kg to <40 kg.

In order to support the use of **DRV**/COBI FDC in this group, the MAH refers to the previously performed juvenile toxicity study with DRV in rat pups, where pups were dosed between Day 23 and Day 50. This corresponds to a human age range of ~2-12 years, therefore, dosing in the juvenile toxicity study is considered relevant regarding the proposed addition of children ≥6 to <12 years and weighing ≥25 kg to <40 kg to the current indication. In the juvenile toxicity study, animals aged 23-50 days revealed no toxicity higher than in adult animals. In addition, at the tested dose levels, plasma concentrations in juvenile rats were comparable to human levels observed in both paediatric (6-17 years) and adult patients in the DRV only program. Exposure multiples were calculated based on mean PK exposures from the clinical study GS-US-216-0128 (cohort 2 DRV/COBI), where the age range of ≥6 to <12 years was investigated. The newly calculated exposure multiples are similar (or even slightly increased in case of juvenile rats) compared to those calculated for the >12 years population studied previously. Therefore, the extension of the age range to children ≥6 to <12 years and weighing ≥25 kg to <40 kg is considered to be supported by the results from this study.

In order to support the use of DRV/**COBI** FDC in this group, the MAH refers to the already approved product GENVOYA, which is a combination of various antiretroviral compounds, including cobicistat. The dose of cobicistat of 150 mg in GENVOYA is recommended for children >25 kg (SmPC section 4.2

GENVOYA). Therefore, the use of 150 mg COBI in the current FDC DRV/COBI for patients ≥6 to <12 years and weighing ≥25 kg to <40 kg is considered to be supported.

2.5.4. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): darunavir			
CAS-number: 206361-99-1			
PBT/vPvB screening			
Study type	**Test protocol**	**Result**	**Conclusion**
Bioaccumulation potential - log K_{ow}	OECD 107	2.41 at pH 4 2.41 at pH 7 2.41 at pH 9	Potential PBT/vPvB: N
PBT/vPvB assessment			
PBT/vPvB statement	darunavir is considered to be not PBT, nor vPvB		
Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
$PEC_{SW,\ default}$	4	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Table 1.

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	192 mg/L at pH 4 and 20 °C 163 mg/L at pH 7 and 20 °C 179 mg/L at pH 9 and 20 °C	shake flask
Adsorption-Desorption Soil 1 = sandy loam	OECD 106	 $K_{OC,\ soil\ 1}$ = 993 L/kg_{oc}	
Soil 2 = loam		$K_{OC,\ soil\ 2}$ = 389 L/kg_{oc}	
Soil 3 = loamy sand		$K_{OC,\ soil\ 3}$ = 933 L/kg_{oc}	
Soil 4 = sandy clay loam		$K_{OC,\ soil\ 4}$ = 265 L/kg_{oc}	
Soil 5 = clay		$K_{OC,\ soil\ 5}$ = 732 L/kg_{oc}	
Sludge 1		$K_{OC,\ sludge\ 1}$ = 345 L/kg_{oc}	
Ready Biodegradability Test	OECD 301	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1	OECD 308	 $DT_{50,\ whole\ system\ 1}$ = 38.9 d	 20 °C
Sediment 2		$DT_{50,\ whole\ system\ 2}$ = 37.1 d	20 °C
Transformation products		>10% = N	

Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC	≥43	mg/L	growth rate
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	NOEC	19	mg/L	reproduction
Fish, *O. mykiss*	OECD 210	NOEC	≥9.4	mg/L	survival/ growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	163	mg/L	total respiration

Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD 218	NOEC	≥444	mg/kg_{dw}	emergence normalised to 10% o.c.

Risk characterisation				
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**
STP	40 µg/L	≥16,300 µg/L	≤ 0.003	No risk
Surface water	4 µg/L	≥940 µg/L	≤0.004	No risk
Groundwater	1 µg/L	≥94 µg/L	≤0.011	No risk
Sediment	249 µg/kg_{dw}	≥4,440 µg/kg_{dw}	≤0.056	No risk

Substance (INN/Invented Name): cobicistat			
CAS-number: 1004316-88-4			
PBT/vPvB screening			
Study type	**Test protocol**	**Result**	**Conclusion**
Bioaccumulation potential - log K_{ow}	OECD 117	3.05 at pH 5 4.00 at pH 7 4.10 at pH 9	Potential PBT/vPvB: N
PBT/vPvB assessment			
Property	**Parameter**	**Result**	**Conclusion**
Bioaccumulation	log K_{ow}	4.10 at pH 9	not B
	BCF_{KgL}	1.37/1.67 L/kg_{ww}	not B
Persistence	Ready biodegradability	N	potentially P
	$DT_{50,whole\ system}$ at 12°C	1076/866 d	vP
Toxicity	$NOEC_{aquatic}$ *	4.9 mg/L	not T
PBT/vPvB statement	cobicistat is considered to be not PBT, nor vPvB		
Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
$PEC_{SW,\ default}$	0.75	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Table 2.

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Adsorption-Desorption Soil 1 = clay loam	OECD 106	 $K_{OC,\ soil\ 1}$ = 3624 L/kg_{oc}	
Soil 2 = sandy loam		$K_{OC,\ soil\ 2}$ = 4903 L/kg_{oc}	
Soil 3 = sandy loam		$K_{OC,\ soil\ 3}$ = 9012 L/kg_{oc}	
Sludge 1 = municipal		$K_{OC,\ sludge\ 1}$ = 1654 L/kg_{oc}	
Sludge 2 = municipal		$K_{OC,\ sludge\ 2}$ = 2664 L/kg_{oc}	
Ready Biodegradability Test	OECD 301	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1	OECD 308	 $DT_{50,\ water\ 1}$ = 5.6 d $DT_{50,\ whole\ system\ 1}$ = 507 d	 20 °C
Sediment 2		$DT_{50,\ water\ 2}$ = 12 d	20 °C

		$DT_{50,\ whole\ system\ 2}$ = 408 d			
Transformation products		>10% = N			
Phase II Aquatic effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC	≥29.3	mg/L	growth rate
Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	NOEC	≥17.5	mg/L	immobilisation/ reproduction/survival
Fish, *P. promelas*	OECD 210	EC_{10}	4.9	mg/L	fry survival
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥60	mg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD 218	NOEC	1250	mg/kg_{dw}	emergence, normalised to 10% o.c.
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**	**Conclusion**	
STP	7.5 µg/L	≥6,000 µg/L	≤0.001	No risk	
Surface water	0.75 µg/L	490 µg/L	0.002	No risk	
Groundwater	0.19 µg/L	49 µg/L	0.004	No risk	
Sediment	0.68 mg/kg_{dw}	12.5 mg/kg_{dw}	0.054	No risk	

Conclusions on ERA

Considering the above data from Phase I and Phase II, darunavir and cobicistat are not expected to pose a risk to the environment: as regards to darunavir, a bioaccumulation potential is not indicated based on the log K_{OW} < 4.5. A definitive PBT/vPvB assessment is not required. In this light, whilst also considering the above data of the definitive hazard assessment, it can be concluded that Darunavir and cobicistat are not PBT or vPvB substances.

2.5.5. Discussion on non-clinical aspects

The MAH has not performed new nonclinical studies to support the use of FDC DRV/COBI in children ≥6 to <12 years and weighing ≥25 kg to <40 kg.

In order to support the use of **DRV**/COBI FDC in this group, the MAH refers to the previously performed juvenile toxicity study with DRV in rat pups, where pups were dosed between Day 23 and Day 50. In the juvenile toxicity study, animals aged 23-50 days revealed no toxicity higher than in adult animals and plasma concentrations in juvenile rats were comparable to human levels observed in both paediatric (6-17 years) and adult patients in the DRV only program. Exposure multiples were calculated based on mean PK exposures from the clinical study GS-US-216-0128 (cohort 2 DRV/COBI), where the age range of ≥6 to <12 years was investigated. The newly calculated exposure multiples are similar (or even slightly increased in case of juvenile rats) compared to those calculated for the >12 years population studied previously. Therefore, the extension of the age range to children ≥6 to <12 years and weighing ≥25 kg to <40 kg is considered to be supported by the results from this study.

In order to support the use of DRV/**COBI** FDC in this group, the MAH refers to the already approved product GENVOYA, which is a combination of various antiretroviral compounds, including cobicistat. The dose of cobicistat of 150 mg in GENVOYA is recommended for children >25 kg (SmPC section 4.2 GENVOYA). Therefore, the use of 150 mg COBI in the current FDC DRV/COBI for patients ≥6 to <12 years and weighing ≥25 kg to <40 kg is supported by the CHMP.

Environmental risk assessment:

The MAH provided a detailed ERA in line with the latest guideline. The conclusions of the ERA were agreed and the ERA was considered complete. However, the MAH was requested to implement minor changes to the ERA:

- The 12ºC DT_{50} values for whole system for cobicistat derived by the MAH are 512 and 363 days, and respectively 1076 and 886 days by the assessor. In the original marketing authorisation procedure DT_{50} values were recalculated by the assessor and based on total amount of parent in both water and sediment, and corrected for formation of NER, which is not seen as degradation. Although these results do not change the outcome of the ERA, the MAH was requested to adjust the values. The MAH revised the DT50 values in the ERA as required.
- A discrepancy between the ERA of the MAH and assessor is found for the toxicity value derived in the OECD 209 study for cobicistat. The MAH notes a NOEC of ≥ 1000 mg L^{-1} and the assessor notes an NOEC ≥ 60 mg L^{-1}, which is the concentration equal to water solubility. Although the difference in outcome does not influence the outcome of the ERA, the MAH was requested to adjust the value. The MAH revised the NOEC-value for the activated sludge respiration test in the ERA. The CHMP noted, however, that the MAH had forgotten to include the equal to and greater than symbol (≥) in the calculations and EPAR table in the ERA. To correctly show that the NOEC is equal to or higher than the water solubility, the MAH was requested by the CHMP to include the symbol ≥ in the ERA. The MAH included this symbol accordingly.
- For cobicistat the MAH gives different values for $K_{oc,}$ sludge in Table 3 in the ERA compared to the EPAR in the appendices of the ERA. Based on the original study report the values in table 3 are correct. Although the difference in outcome does not influence the outcome of the ERA, the MAH was requested to adjust the values in the EPAR. The CHMP is of the view that the values were correctly adjusted by the MAH.
- The MAH notes for cobicistat: 'For substances with 1000 ≤ K_{OC} (sludge) < 5000 L/kg, a Phase II risk assessment for soil compartment is required if the $PEC_{surfacewater}$ > 2 µg L^{-1} '. However, the trigger value for PEC_{SW} of ≥ 2 applies to substances with K_{OC} 2,500 ≤ $K_{FOC,SLUDGE}$< 5,000. As K_{FOC} are not available and the highest, worst-case, K_{OC} value is within this range, this does not influence the outcomes of the ERA. However, the MAH was requested to change the sentence. The CHMP is of the view that the MAH changed the sentence on triggering the soil assessment in the ERA correctly.
- The DT_{50} values for whole system for darunavir derived by the MAH are 26 and 46 days, and 38.9 and 37.1 days by the assessor. The values of the assessor are given in the original study report and were approved in an earlier procedure. Although these results do not change the outcome of the ERA, the MAH was requested to adjust the values. The values were correctly adjusted by the MAH.

2.5.6. Conclusion on the non-clinical aspects

The MAH has not performed new non-clinical studies to support the use of FDC DRV/COBI in children ≥6 to <12 years and weighing ≥25 kg to <40 kg. In order to support the use of DRV/COBI FDC in this group, the MAH refers to the previously performed juvenile toxicity study with DRV in rat pups. The dose of cobicistat of 150 mg in GENVOYA is recommended for children >25 kg (SmPC section 4.2 GENVOYA). Together, the CHMP considers that the extension of the age range to children ≥6 to <12 years and weighing ≥25 kg to <40 kg is considered to be supported by the results from this study.

As regards to the environmental risk assessment, darunavir and cobicistat are considered by the CHMP to be not PBT nor vPvB. Considering the above data, the CHMP is therefore of the opinion that darunavir and cobicistat are not expected to pose a risk to the STP, surface water, groundwater, soil and sediment compartment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

Not applicable

2.6.2. Clinical pharmacology

Table 6: Overview of new clinical PK studies

Study (Phase, Status)	Description	Treatment	Number of Participants	Main Endpoints
GS-US-216-0128 (Phase 2/3, ongoing) Cohort 2[a]	DRV and COBI in HIV-1 infected, ART-experienced, virologically suppressed[b] children (≥6 to <12 years and ≥25 kg[c])[d]	DRV (dose based on body weight)[e] and COBI (150 mg) qd[d] +ARV background regimen[f]	N=8[g]	• (1^{st}) PK DRV (AUC_{tau}) • (1^{st}) Safety over 24 weeks • (2^{nd}) PK DRV (C_{tau}, C_{max}, CL/F) and COBI (AUC_{tau}, C_{tau}, C_{max}, CL/F, V_z/F) • (2^{nd}) Virologic response at Weeks 24 and 48 • (2^{nd}) Change in CD4+ cell count at Weeks 24 and 48 • (2^{nd}) Safety over 48 weeks
TMC114IFD1004 (Phase 1, completed)	DRV and COBI administered as scored FDC tablet compared to administration of the separate tablet formulations under fed conditions in healthy adults (≥18 to <55 years and ≥50 kg)	DRV/COBI 675/150-mg FDC single dose and DRV (675 mg)[k] and COBI (150 mg) single dose	N=22[l]	Bioequivalence of DRV in presence of COBI when administered as scored DRV/COBI FDC tablet compared to coadministration as separate tablet formulations

[a] Data from Cohort 2 described in this summary document are based on Interim Analysis 2 (data cutoff date: 19 September 2023) of Study GS-US-216-0128, including 8 participants in Cohort 2 who received DRV and COBI and who had completed at least Week 48 on the study at the data cutoff date for Interim Analysis 2. Data from participants who received the combination ATV and COBI in Cohort 2 are not included in Interim Analysis 2 and are not relevant for this submission.

[b] Although Protocol Amendment 8 allowed enrollment of viremic participants (HIV-1 RNA ≥50 copies/mL) in Cohort 2, all 8 participants enrolled in Cohort 2 for which data are described in this summary document were virologically suppressed.

[c] The 8 participants enrolled in Cohort 2 for which data are described in this summary document enrolled under different protocol amendments with different weight criteria (ie, Protocol Amendments 4 [n=4] and 6 [n=1]: ≥25 kg [Group 1] and ≥15 to <25 kg [Group 2]; Protocol Amendments 7 [n=2] and 8 [n=1]: ≥25 to <35 kg). Therefore, ≥25 kg was used for the purpose of Interim Analysis 2.

[d] Participants (n=3) enrolled in Cohort 2 after implementation of Protocol Amendment 7 received F/TAF 200/25 mg qd as third agent. Participants (n=5) enrolled in Cohort 2 prior to implementation of Protocol Amendment 7 received COBI-boosted DRV with a background regimen of 2 NRTIs.

[e] The recommended daily dosage of DRV based on body weight according to the local Prescribing Information was to be given and was not to exceed the recommended adult dosage. Refer to Mod2.7.2/Tab2 for details on the DRV doses that were received by participants in Cohort 2 for which data are described in this summary document.

[f] For participants enrolled prior to the implementation of Protocol Amendment 7 (n=5), participants had to be on a stable ARV regimen at screening consisting of 2 NRTIs and ATV/rtv qd or DRV/rtv qd or bid. For participants enrolled after the implementation of Protocol Amendment 7 (n=3), participants had to be on a stable ARV regimen at screening consisting of 2 NRTIs and a third agent per local prescribing guidelines. Participants enrolled after the implementation of Protocol Amendment 7 taking DRV had to be on qd dosing or had to switch to qd at or prior to Day 1.

[g] Participants included in the SAS. For the definitions of analysis sets, refer to Mod2.7.3/Sec1.2.

[k] DRV 675 mg was administered as the commercially available tablet formulations (1x600-mg and 1x75-mg tablet).

[l] Participants included in the SAS, defined as all participants who were randomized and received at least 1 dose of treatment (any, DRV or COBI, whether alone or together).

Pharmacokinetics

Introduction

This assessment focusses only on the new paediatric data received from study GS-US-216-0128 for patients aged between 6 and 12 years and weighing more than 25 kg and on the new bioequivalence study comparing the FDC of DRV/COBI 675/150 mg and the separate agents.

Darunavir in combination with the booster cobicistat (only 150 mg COBI) has been approved only for adolescents weighing more than 40 kg and adults with a daily dose of DRV of 800 mg.

This is described not only in the Rezolsta SmPC, but likewise in the Prezista (DRV only) and Tybost (COBI) SmPCs. Tybost (COBI) is only available at a 150 mg dose (film-coated tablets) and has not yet been approved under the age of 12 years and weighing less than 40 kg. However, the 150 mg qd dose of COBI, as a component of GENVOYA (150 mg elvitegravir, 150 mg cobicistat, 200 mg emtricitabine , and 10 mg tenofovir alafenamide) has been evaluated in 23 virologically suppressed participants ages ≥6 to <12 years old and weighing ≥25 kg in study GS-US-292-0106 and is approved for this population.

Prezista (DRV) is available at doses of 75, 150, 400, 600 and 800 mg as film-coated tablets and as a 200 mg/mL suspension for oral use. Prezista in combination with the booster ritonavir has been approved previously in paediatric patients above 3 years weighing at least 15 kg, and the posology uses weight cut-offs of 15-30 kg, 30-40 kg and ≥ 40 kg.

Bioanalytical methods

In 2015, an assay was developed and validated at PRA (ICON) for DRV and COBI in EDTA plasma There was additional validation done for selectivity, matrix effect, comedications, haemolysis and lipemic plasma testing. For both DRV and COBI, a stable isotope labelled internal standard was used for quantification of plasma concentrations using LC-MS/MS with a LLOQ of 5.00 ng/mL for both DRV (ULOQ of 5000 or 10000 ng/mL) and COBI (ULOQ of 5000 ng/mL). This method developed at PRA allowed simultaneous measurement of DRV and COBI.

This method at PRA was also used for analysis of plasma samples originating from clinical study IFD1004. The bioanalytical method for study IFD1004 has been sufficiently validated.

For measurement of samples from study 216-0128 separate validated LC-MS/MS assays developed at QPS were used, with a LLOQ of 20 ng/mL for DRV and of 5 ng/mL for COBI. Thus, all samples from paediatrics were measured with a method validated at QPS versus a method developed at PRA for all other studies used in the paediatric vs adult comparison and popPK modelling. It is noted that the LLOQ is 4-fold different for the methods at PRA and QPS. However, comparison of PK exposure between paediatrics and adults is the primary objective of this paediatric extension.

The MAH compared the bioanalytical methods used for DRV and COBI for Study 216-0128 and the other clinical studies used in the population PK modelling (and thus in the exposure comparison between paediatrics and adults) and showed that similar bioanalytical assays were used which are both properly validated.

No cross-validation between the QPS methods for the Gilead sponsored studies and the bioanalytical methods for the Janssen sponsored studies, which were validated at ICON (formerly PRA), were performed. There are no future studies or bioanalytical validations of DRV/COBI planned by either Janssen or Gilead at this time.

The MAH could still consider doing such cross-validation for future submissions. For now it remains unclear whether potential differences in the bioanalytical assays may have contributed to the observed differences between studies, although this is considered to be not very likely.

Population PK modelling for DRV

The objectives of the population PK (PopPK) analysis for darunavir were:

To compare DRV $AUC_{0\text{-}24h,ss}$ and $C_{0h,ss}$ for paediatric participants enrolled in Cohorts 2 and 3 of Study 216-0128 with reference exposures from (i) adult Studies 216-0130 (DRV/COBI), TMC114FD2HTX3001 (DRV/COBI/emtricitabine/tenofovir), and TMC114IFD3013 (DRV/COBI/ emtricitabine/tenofovir), (ii) Cohort 1 Part A of Study 216-0128, and (iii) paediatric Studies TMC114-C228 (DRV/RTV, 3-6 yrs old) and TMC-114C230 (DRV/RTV, 12-18 yrs old).

To assess whether a unique DRV dose of 675 mg qd (in combination with COBI 150 mg qd) for paediatric patients weighing ≥25 to <40 kg and a DRV dose of 600 mg qd (in combination with 90 mg qd COBI) for paediatric patients weighing ≥15 to <25 kg result in comparable DRV $AUC_{0\text{-}24h,ss}$ and $C_{0h,ss}$ with respect to adults, using model-based PopPK simulations.

For the purpose of this submission, only results concerning paediatric patients weighing ≥25 to <40 kg (Cohort 2) will be discussed/assessed.

Compared to the adult data, the paediatric data were comparable in Cohorts 1 and 2. Mean profiles versus time since last dose suggested that PK in Cohort 2 was comparable to the PK in Cohort 1 (Part A) and in adults. Both Cohorts 1 and 2 had slightly higher and delayed peak concentrations and lower trough concentrations compared to adults.

An external evaluation of the previous DRV PopPK model developed in adults was initially performed based on the PK data from Study 216-0128 Cohorts 1 to 3, however, this model was not suitable to describe the data as suggested by GoF plots and pcVPCs. In particular, trough plasma concentrations appeared to be slightly overpredicted in Cohorts 1 and 2. These findings were expected, as the adult model accounted for allometric scaling only on CL/F with an estimated coefficient, and the exposure in Cohort 1 Part A was observed to be approximately 20% lower at Interim Analysis 1 of Study 216-0128 compared to adults from Study 216-0130. In addition, peak concentrations in Study 216-0128 appeared to be reached slightly later compared to adults (Studies FD2HTX3001 and IFD3013).

The model was then updated to include the effect of body weight on CL/F and Q/F (with fixed coefficient of 0.75) and on V_c/F and V_p/F (with fixed coefficient of 1), and CL/F and D_1 were re-estimated. The other parameters were fixed to the adult values. This model (run 213) described the data from Study 216-0128 well, both at population and individual level, as attested by GoF plots and pcVPCs, and was therefore considered the final PopPK model for Study 216-0128. The parameter estimates of run 213 are reported in Table 7.

Table 7: Parameter Estimates for final PopPK model (Run 213)

Parameter (unit)	**Estimate (RSE%)**
CL/F (L/h, typical value[b])	69.2 (6.43%)
V_c/F (L, typical value[c])	88.3 (fixed[i])
Q/F (L/h, typical value[d])	24.0 (fixed[i])
V_p/F (L, typical value[e])	90.0 (fixed[i])
k_a (h^{-1})	0.393 (fixed[i])
F1[a]	1.18 (fixed[i])
D_1 (h)	2.02 (10.9%)
Effect of body weight on CL/F[b] and Q/F[d]	0.75 (fixed[j])
Effect of body weight on V_c/F[c] and V_p/F[e]	1 (fixed[j])
Effect of TDD on CL/F[b]	0.388 (fixed[i])
Effect of AAG on CL/F[b]	0.0304 (fixed[i])
IIV on CL/F[f]	0.0517 (fixed[i]) (CV=23.0%) (shr=3.92%)
IIV on V_c/F[f]	0.0244 (fixed[i]) (CV=15.7%) (shr=79.4%)
IIV on Q/F[f]	0.260 (fixed[i]) (CV=54.5%) (shr=85.5%)
IIV on V_p/F[f]	0.310 (fixed[i]) (CV=60.3%) (shr=28.6%)
IIV on D_1[g]	0.782 (fixed[i]) (CV=108%) (shr=38.0%)
RUV[h]	0.387 (16.9%) (CV=68.7%)
OFV	105.172

AAG=α1 acid glycoprotein; CL/F=clearance; D_1=zero-order duration; DRV=darunavir; F1=apparent bioavailability; IIV=interindividual variability; k_a=first-order absorption rate constant; OFV=objective function value; PopPK=population pharmacokinetics; Q/F=apparent intercompartmental clearance; RSE=relative standard error; RUV=residual unexplained variability; shr=shrinkage; TDD=total daily dose; V_c/F=apparent volume of distribution central compartment; V_p/F=apparent volume of distribution of peripheral compartment.

[a] For DRV single agent commercial formulation relative to tablet used in previous clinical trials (F_{rel}).

[b] Implemented as $CL/F=69.2\times(1/(1+0.0304\times AAG))\times(TDD/1{,}200)^{0.388}\times(WT/70)^{0.75}$; where TDD=800 mg and AAG=94.2 mg/dL.

[c] Implemented as $V_c/F=88.3\times(WT/70)^{1}$.

[d] Implemented as $Q/F=24.0\times(WT/70)^{0.75}$.

[e] Implemented as $V_p/F=90.0\times(WT/70)^{1}$.

[f] Estimate (RSE%) represents the OMEGA point estimate and its associated RSE. CV represents the coefficient of variation for a lognormal distribution, calculated as sqrt(exp(OMEGA)-1)×100. Shrinkage calculated as (1-sd(ETA)/sqrt(OMEGA))×100, where sd(ETA) is the sample standard deviation of the random effects.

[g] Implemented on the logit scale, CV% not evaluable.

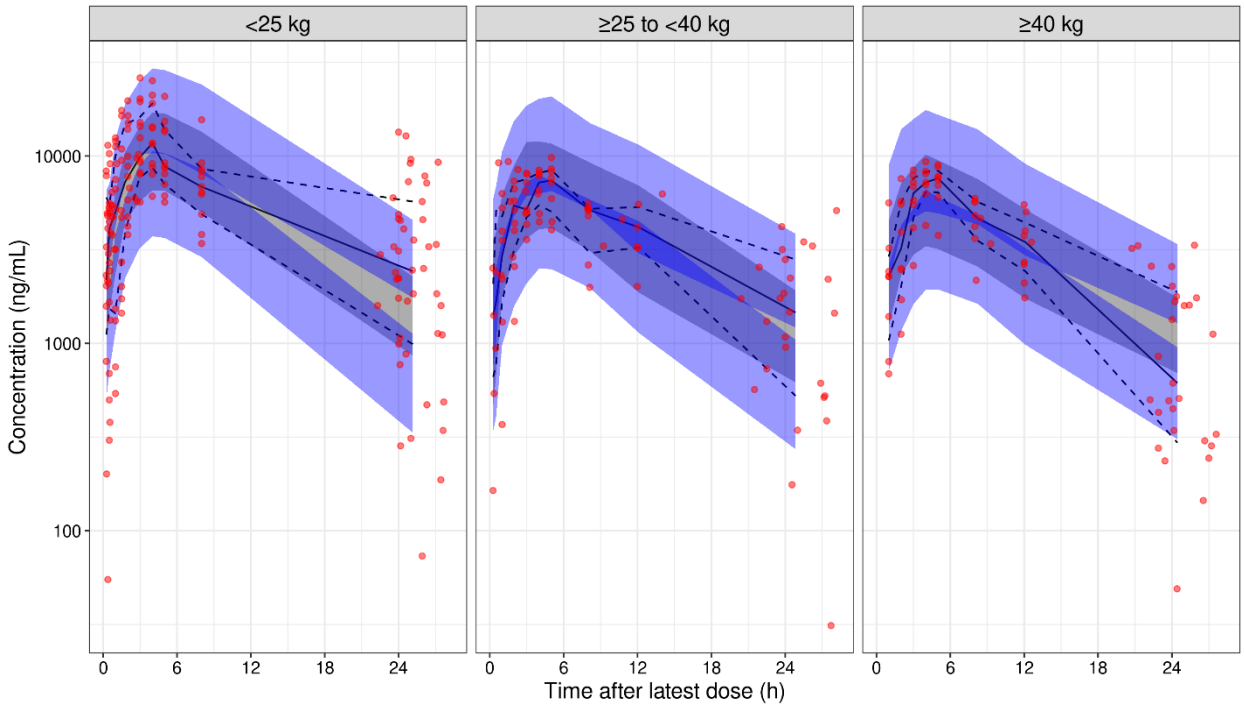
[h] Estimate (RSE%) represents the SIGMA point estimate and its associated RSE. CV represents the coefficient of variation for a lognormal distribution, calculated as sqrt(exp(SIGMA)-1)×100.

[i] Fixed to value from previous PopPK model developed in adults.

[j] Fixed to standard allometric coefficient.

The prediction corrected (pc) VPCs show that the model adequately captured the central tendency and variability of the data, as attested by the agreement between the observed 20th, 50th, and 80th percentiles of the data and the respective 95% CIs obtained from the simulations (stratified by weight band: see Figure 1).

Figure 1: pcVPC Stratified by Cohort for the (Final) PopPK Model



The re-estimated parameter estimates had RSEs <20%. Shrinkage of the random effects was <30% for CL/F and Vp/F, and over 30% for the other parameters. These shrinkage values were expected because the IIVs were kept fixed to the estimates from the previously developed PopPK model.

The updated PopPK model is considered fit-for-purpose.

Bioequivalence (study TMC114IFD1004)

Single dose PK data of the new DRV/COBI 675/150 mg FDC tablet were additionally assessed for BE with DRV and COBI tablets taken separately in Study IFD1004. The DRV/COBI 675/150 mg FDC tablet is administered according to the same once daily dose regimen as the separate available tablet formulation. The development program for the DRV/COBI 675/150 mg FDC tablet is based on the clinical development programs of the DRV and COBI single agents and the PK bridging of the separate available tablets with the FDC tablet.

The primary objective was to evaluate the single-dose PK and bioequivalence of **DRV** 675 mg in the presence of COBI 150 mg when administered as a scored FDC tablet (proposed commercial drug product G011) compared with the coadministration as the separate available tablet formulations (DRV 1×600 mg and 1×75-mg tablet and COBI 1×150-mg tablet), under fed conditions in healthy adult participants. The secondary objective was to evaluate the single-dose PK and relative bioavailability of **COBI** 150 mg in the presence of DRV 675 mg.

This was a Phase 1, randomized, open-label, 2-way crossover, single-center study. The study consisted of a screening phase of approximately 4 weeks (Days -28 to -1) followed by an open-label treatment phase consisting of 2 single-dose treatment periods (Period 1 and Period 2) of 4 days each (Days 1 to 4), separated by a washout period of ≥7 days between doses (starting on Day 1).

Twenty-two participants were randomly assigned to 1 of 2 possible treatment sequences (AB or BA) and received the following treatments, 1 in each period:

- Treatment A (test): a single oral dose of DRV 675 mg and COBI 150 mg as 1×scored FDC tablet under fed conditions.
- Treatment B (reference): a single oral dose of DRV as 1×600-mg and 1×75-mg tablet and COBI as 1×150-mg tablet under fed conditions.

The results of the statistical analysis for DRV PK parameters (C_{max}, AUC_{last}, and AUC_{∞}) evaluating the bioequivalence of Treatment A compared with Treatment B, are summarized in Table 8 and Table 9.

Table 8: Summary of the Bioequivalence Analysis of the PK Parameters of DRV

	Geometric Means		Geometric Mean Ratio (Test/Reference)		
PK Parameter	**Treatment A (Test)**	**Treatment B (Reference)**	**Ratio (%)**	**90% CI**	**Intraindividual %CV**
N	22	22	-	-	-
C_{max} (ng/mL)	6,976	7,416	94.07	88.29-100.22	12.2
AUC_{last} (ng.h/mL)	78,134	81,189	96.24	90.46-102.39	12.0
AUC_{∞} (ng.h/mL)	78,335	81,403	96.23	90.47-102.36	11.9

Test (Treatment A): a single oral dose of DRV 675 mg and COBI 150 mg as 1×scored FDC tablet under fed conditions.
Reference (Treatment B): a single oral dose of DRV as 1×600 mg and 1×75-mg tablet and COBI as 1×150-mg tablet under fed conditions.

Table 9: Summary of the Statistical Analysis of the PK Parameters of COBI

	Geometric Means		Geometric Mean Ratio (Test/Reference)		
PK Parameter	**Treatment A (Test)**	**Treatment B (Reference)**	**Ratio (%)**	**90% CI**	**Intraindividual %CV**
N	22	22	-	-	-
C_{max} (ng/mL)	774	839	92.27	85.33-99.78	15.1
AUC_{last} (ng.h/mL)	6,013	6,486	92.70	87.41-98.32	11.3
AUC_{∞} (ng.h/mL)	6,113	6,578	92.93	87.55-98.66	11.5

Test (Treatment A): a single oral dose of DRV 675 mg and COBI 150 mg as 1×scored FDC tablet under fed conditions.
Reference (Treatment B): a single oral dose of DRV as 1×600 mg and 1×75-mg tablet and COBI as 1×150-mg tablet under fed conditions.

The bioequivalence study (IFD1003) in healthy adults demonstrating bioequivalence between the FDC of DRV/COBI 800/150 mg compared to coadministration of the approved single agents (DRV 800 mg film-coated tablets with COBI 150 mg tablet), under fasted and fed (standardized breakfast) conditions, has been assessed and approved previously.

Likewise, the PK results of the new study (IFD1004) showed that DRV and COBI administration as a scored FDC tablet (DRV/COBI 675/150 mg) was bioequivalent to the coadministration as the separate available tablet formulations (DRV 1×600 mg and 1×75-mg tablet and COBI 1×150-mg tablet), under fed conditions. For both analytes, the 90% CIs of the GMRs for the primary PK parameters (C_{max}, AUC_{last}, and AUC_{∞}) were contained within the acceptance range of 80 to 125%.

Pharmacokinetics in the target population (study GS-US-216-0128)

Study 216-018 evaluates PK, safety, and efficacy of COBI-boosted ATV, COBI-boosted DRV, and 2 NRTIs in HIV-1 infected children and adolescents aged ≥4 weeks to <18 years under 5 cohorts, which are defined as follows (per most recent Protocol Amendment 9 dated 07 September 2022):

Cohort 1: adolescents aged ≥12 to <18 years and weighing ≥25 kg.

Cohort 2: children aged ≥6 years and weighing ≥25 kg[1] (scope of this EoI).

Cohort 3: children aged ≥2 years and weighing ≥14 to <25 kg.

Cohort 4: children aged ≥4 weeks and weighing ≥3 to <25 kg.

Cohort 5: children aged ≥4 weeks and weighing ≥3 to <14 kg.

In Cohort 2, 8 participants on DRV/COBI received DRV (dosed based on body weight per local prescribing information in combination with COBI 150 mg tablets qd. An intensive PK evaluation (predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 8, and 24 hours postdose) occurred during either the Week 2 or the Week 4 visit or within 7 days after the completion of Week 2 or the Week 4 visit. Trough plasma PK sample was collected predose at Weeks 8, 24, and 36. Timed PK samples (15 minutes to 3 hours postdose) were taken at Weeks 12, 16, and 48.

Administered doses

The recommended daily dosage of DRV was based on body weight according to the local prescribing information for each drug provided in the product monograph, and was not to exceed the recommended adult dosage:

Body weight ≥15 to <30 kg: 600 mg.

Body weight ≥30 to <40 kg: 675 mg.

Body weight ≥40 kg: 800 mg.

The 150 mg qd dose of COBI, as a component of GENVOYA, has been evaluated in 23 virologically suppressed participants ages ≥6 to <12 years old and weighing ≥25 kg in study GS-US-292-0106 and is approved for this population. The PK exposures of all analytes were within the safe and efficacious ranges of the adult PK exposures. These data support the dose of COBI 150 mg as a pharmaco-enhancer of DRV in this population.

In Cohort 1 and 2 the 150 mg COBI tablet was administered qd and in Cohort 3 the 90 mg COBI tablet was administered qd (the 90 mg tablet has not been registered yet).

Pharmacokinetics of Darunavir

The individual DRV exposure parameters $AUC_{0\text{-}24h}$ and C_{0h} for paediatric participants in Study 216-0128, based on the final PopPK model (run 213), using baseline covariates and starting dose in each participant, are summarized in Table 10.

[1] The 8 participants enrolled in Cohort 2 for which data are described were enrolled under different protocol amendments with different weight criteria (i.e. Amendments 4 [n=4] and 6 [n=1]: ≥25 kg [Group 1] and ≥15 to <25 kg [Group 2]; Amendments 7 [n=2] and 8 [n=1]: ≥25 to <35 kg), therefore ≥25 kg was used for the purpose of Interim Analysis 2.

Table 10: Summary of Individual $AUC_{0\text{-}24h}$ and C_{0h} in Study 216-0128

Parameter	Cohort	N	Mean (SD)	Median (Min-Max)	Geometric mean
$AUC_{0\text{-}24h}$ (ng.h/mL)	1	8	68,971 (10,258)	70,258 (47,261-79,710)	68,208
	2	8	84,453 (13,024)	81,629 (72,310-106,617)	83,619
	3	11	146,477 (40,055)	149,358 (94,046-199,639)	141,269
	All	27	105,135 (44,138)	87,434 (47,261-199,639)	97,471
C_{0h} (ng/mL)	1	8	919 (439)	909 (421-1,559)	825
	2	8	1,237 (484)	1,157 (463-2,044)	1,143
	3	11	2,265 (1,293)	2,519 (379-4,194)	1,797
	All	27	1,562 (1,062)	1,195 (379-4,194)	1,248

$AUC_{0\text{-}24h}$=area under the concentration-time curve over a 24-hour dosing interval at steady-state; C_{0h}=plasma concentration at the end of a 24-hour dosing interval at steady-state; Max=maximum; Min=minimum; N=number of participants; SD=standard deviation.

Individual DRV $AUC_{0\text{-}24h}$ and C_{0h} for paediatric participants in Study 216-0128 assuming the proposed DRV/COBI dosing regimen in paediatric patients (i.e. DRV/COBI 800/150 mg qd for ≥40 kg, 675/150 mg qd for ≥25 to <40 kg, and 600/90 mg qd for ≥14 to <25 kg) are summarized and compared versus the reference studies in Table 11. DRV $AUC_{0\text{-}24h,ss}$ in the ≥25 to <40 kg group was comparable to DRV $AUC_{0\text{-}24h,ss}$ from the reference studies. DRV $C_{0h,ss}$ was 25% to 40% lower in the ≥25 to <40 kg group compared to adults and approximately 60% lower compared to the C228 substudy, but 50% higher compared to the adolescents in the BW ≥40 kg group.

Table 11: Comparison of $AUC_{0\text{-}24h,ss}$ and $C_{0h,ss}$ for Participants in Study 216-0128 ***Assuming the Proposed DRV/COBI Dosing Regimen*** *in Paediatric Participants (DRV/COBI 800/150 mg qd for ≥40 kg, 675/150 mg qd for ≥25 to <40 kg) Versus Paediatric and Adult DRV Studies*

Parameter (dose)	GS-US-216-0128 BW ≥40 kg: DRV 800 mg/COBI 150 mg (N=8)	GS-US-216-0128 BW ≥25 to <40 kg: DRV 675 mg/COBI 150 mg (N=8)	GS-US-216-0130 Week 48 in Adults (DRV 800 mg/COBI 150 mg) (N=298)	TMC114FD2HTX3001 in Adults (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg) (N=355) (Ackaert 2021)	TMC114IFD3013 in Adults (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg) (N=750) (Ackaert 2021)	TMC114-C228 Week 24 (qd substudy) in children aged ≥3 to <6 years (DRV 40 mg/kg+rtv 7 mg/kg [BW <15 kg] or DRV 600 mg/rtv 100 mg [BW ≥15 kg]) (N=10)	TMC114-C230 Week 48 in participants aged ≥12 to <18 years (DRV 800 mg/rtv 100 mg) (N=12)
Mean (SD) $AUC_{0\text{-}24h,ss}$ (ng.h/mL)	69,474 (10,359)	92,052 (17,254)	101,711 (33,066)	87,909 (20,232)	85,972 (22,413)	120,000 (40,600)	84,400 (23,600)
Mean (SD) $C_{0h,ss}$ (ng/mL)	938 (445)	1,345 (569)	2,151 (1,322.5)	1,899 (759)	1,813 (859)	3,371 (1,715)	2,141 (865)

$AUC_{0\text{-}24hss}$=area under the concentration-time curve over 24 hours at steady-state; BW=body weight; $MC_{0h,ss}$=plasma concentration at the end of a 24-hour dosing interval at steady-state; COBI=cobicistat; DRV=darunavir; FTC=emtricitabine; N=number of participants; rtv=ritonavir; SD=standard deviation; TAF=tenofovir alafenamide; qd=once daily.

DRV exposure parameters were simulated in 1,000 paediatric participants with body weight ranging from 14 to 80 kg, with 1-kg increments, using the final DRV PopPK model. AAG was randomly sampled from the historical database of AAG observations from paediatric participants enrolled in 3 randomized studies with DRV/rtv conducted in children and adolescents. The simulations were summarized for each body weight value as median and 90% PI (i.e. 5^{th} and 95^{th} percentile) of the simulated exposure parameters. Study FD2HTX3001 was considered as reference study for adult exposures as this was one of the larger adult Phase 3 studies available to the Sponsor. Furthermore, the DRV exposure parameters were comparable across studies FD2HTX3001 (D/C/F/TAF arm), IFD3013 (D/C/F/TAF arm), and 216-0130 (DRV/COBI arm) and thus the conclusions on comparability should not be impacted by the choice of the adult reference study (see Table 12).

Table 12: Adult Reference Values for AUC and C_{0h} Across Adult DRV/COBI and D/C/F/TAF Studies

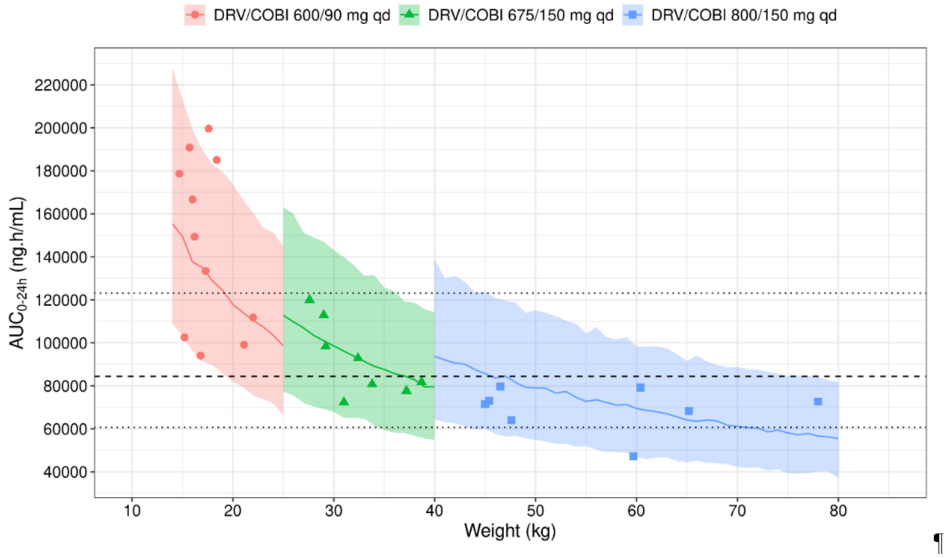
Parameter	Study	Treatment	N	5th percentile	Median	95th percentile
$AUC_{0\text{-}24h,ss}$ (ng.h/mL)	TMC114FD2HTX3001	D/C/F/TAF	356	60,667	84,380	123,130
	TMC114IFD3013	D/C/F/TAF	750	55,170	82,528	126,256
	GS-US-216-0130	DRV/COBI	298	57,640	99,100	171,000
$C_{0h,ss}$ (ng/mL)	TMC114FD2HTX3001	D/C/F/TAF	356	960	1,784	3,288
	TMC114IFD3013	D/C/F/TAF	750	708	1,679	3,417
	GS-US-216-0130	DRV/COBI	298	444	1,985	4,902

N=number of participants with available exposure parameters.

DRV $AUC_{0\text{-}24h,ss}$ and $C_{0h,ss}$ in paediatric participants, simulated using the parameter estimates from the final PopPK model, are presented in Figure 2 and Figure 3 (respectively) for the proposed DRV/COBI dosing regimen in paediatric participants, i.e. specifically a unique DRV/COBI dosing regimen of 675/150 mg qd for the entire weight band ≥25 to <40 kg.

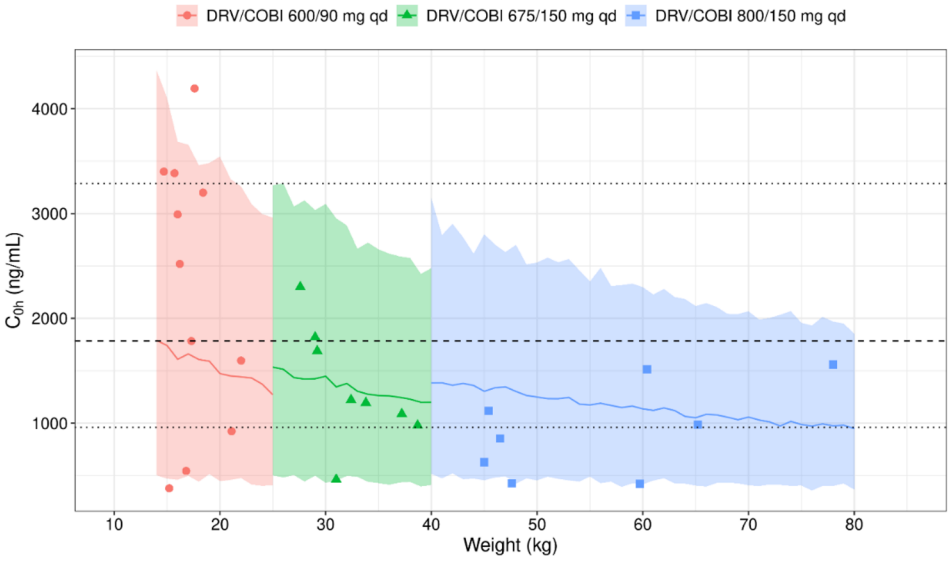
The simulations show that for paediatric patients in the weight band ≥25 to <40 kg a DRV/COBI dosing regimen of 675/150 mg qd results in comparable or slightly higher (up to 34% higher at 25 kg) DRV $AUC_{0\text{-}24h,ss}$ and comparable or slightly lower (up to 33% lower at 39 kg) DRV $C_{0h,ss}$ with respect to adults. At this dose, DRV C_{0h} below 55 ng/mL (protein-binding adjusted EC_{50} for wild-type virus [De Meyer 2005]) is estimated to occur in <1% of paediatric patients.

Figure 2: Distribution of DRV $AUC_{0\text{-}24h,ss}$ in Paediatric Patients ≥25 to <40 kg (DRV/COBI Dosing Regimen of 675/150 mg qd) Compared to Adults (Study FD2HTX3001)



$AUC_{0\text{-}24h}$ on the figure's axis refers to $AUC_{0\text{-}24h,ss}$. The colored lines and shaded areas represent the median and 90% PI for $AUC_{0\text{-}24h,ss}$ for each DRV/COBI dosage. Colored symbols represent individual exposure values for the pediatric patients in Study GS-US-216-0128. The black lines represent the adult median (dashed line), 5th and 95th percentiles of the 90% PI (dotted lines) of individual predicted $AUC_{0\text{-}24h,ss}$ in Study TMC114FD2HTX3001.

Figure 3: Distribution of DRV $C_{0h,ss}$ in Paediatric Patients ≥25 to <40 kg (DRV/COBI Dosing Regimen of 675/150 mg qd) Compared to Adults (Study FD2HTX3001)



¶

▪ C_{0h} on the figure's axis refers to $C_{0h,ss}$. The colored lines and shaded areas represent the median and 90% PI for $C_{0h,ss}$ for each DRV/COBI dosage. Colored symbols represent individual exposure values for the pediatric patients in Study GS-US-216-0128. The black lines represent the adult median (dashed line), 5th and 95th percentiles of the 90% PI (dotted lines) of individual predicted $C_{0h,ss}$ in Study TMC114FD2HTX3001.¶

Overall, the DRV exposure data for the proposed regimen indicate on average somewhat lower trough values and somewhat higher AUC values at steady state in 6-12 yr old children as compared to adults, indicating the proposed regimen could be acceptable.

The approximately 20% higher exposure for a DRV dose of 675 mg in the ≥25 to <30 kg weight band compared with the ≥30 to <40 kg weight band can be explained by the known relationship between body weight and exposure. The exposure parameters of all three participants weighing ≥25 to <30 kg were within the adult reference ranges.

As concluded during the approval of the adolescent data, 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 AUC_{tau} and C_{max} were similar and the DRV C_{tau} was 29% lower, respectively, in adolescents than in adults. When compared with the overall adult population PK data for DRV in Study GS-US-216-0130, DRV AUC_{tau} and C_{tau} were 20% and 61% lower, respectively, in adolescents. The lower DRV exposures in adolescents relative to adults were not considered clinically relevant, as the DRV C_{tau} values in adolescents were within the overall range of those observed previously with COBI-boosted DRV in adults. Also, the mean DRV C_{tau} 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.

Finally, it may be repeated that there was a large degree of variability in C_{tau} both for DRV and COBI, both in adolescents and adults. 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 changed the lower weight cut-off for use of DRV 675 mg from ≥30 kg (PREZISTA SmPC 2024) to ≥25 kg (proposed Rezolsta 675/150 mg SmPC) to facilitate treatment in this paediatric population with a DRV/COBI FDC. This weight change was supported by the PopPK model, as the estimated median DRV $C_{0h,ss}$ in children aged 6 to <12 years and weighing ≥25 to <40 kg is lower than the median adult value. DRV $C_{0h,ss}$ would be even lower when using 600 mg of DRV in combination with 150 mg COBI in the ≥25 to <30 kg weight band (if the dose were to match PREZISTA). As a compromise, median DRV $AUC_{0\text{-}24h,ss}$ is slightly higher in the ≥25 to <30 kg weight band compared with the median observed in adults, but it is still within the 95th percentile of the 90% PI of adults.

As the adult dose of COBI (150 mg) is approved for use in the paediatric population weighing ≥25 kg (GENVOYA SmPC, 2022), instead of using two different weight bands and doses for DRV/COBI (ie, 600/150 mg qd for 25 to <30 kg and 675/150 mg qd for 30 to <40 kg), the MAH proposed the development of one FDC, using the 675/150 mg qd dose for this weight band. This has been agreed by the EMA Paediatric Committee (EMEA-001280-PIP01-12-M06, PIP Decision P/0257/2023).

However, the extension of indication of Rezolsta will also influence the prescription of DRV in combination with COBI administered separately, thus for Prezista. Section 4.2 of the Prezista SmPC now includes the following tables (for treatment naïve and treatment experienced paediatric patients, respectively) regarding the posology:

Recommended dose for treatment-naïve paediatric patients (3 to 17 years) with PREZISTA and ritonavir[a] or cobicistat[b]	
Body weight (kg)	**Dose (once daily with food)**
≥ 15 kg to < 30 kg	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily
≥ 30 kg to < 40 kg	675 mg (6.8 ml)[c] PREZISTA/100 mg (1.2 ml) ritonavir once daily
≥ 40 kg	800 mg (8 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily or 800 mg (8 ml) PREZISTA/150 mg (tablet) cobicistat[b] once daily

[a] ritonavir oral solution: 80 mg/ml
[b] adolescents 12 years and older
[c] rounded up for suspension dosing convenience

Recommended dose for treatment-experienced paediatric patients (3 to 17 years) with PREZISTA and ritonavir[a] or cobicistat[b]		
Body weight (kg)	**Dose (once daily with food)**	**Dose (twice daily with food)**
≥ 15 kg to < 30 kg	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily	380 mg (3.8 ml) PREZISTA/50 mg (0.6 ml) ritonavir twice daily
≥ 30 kg to < 40 kg	675 mg (6.8 ml)[c] PREZISTA/100 mg (1.2 ml) ritonavir once daily	460 mg (4.6 ml) PREZISTA/60 mg (0.8 ml) ritonavir twice daily
≥ 40 kg	800 mg (8 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily or 800 mg (8 ml) PREZISTA/150 mg (tablet) cobicistat[b] once daily	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir twice daily

[a] ritonavir oral solution: 80 mg/ml
[b] adolescents 12 years and older
[c] rounded up for suspension dosing convenience

The recommended posology may become unclear if different weight cut-offs for DRV combined with ritonavir vs DRV combined with COBI are agreed. If for Rezolsta 25 kg will be accepted as the lower weight cut-off, the MAH is requested to harmonize the weight cut-offs also for use with ritonavir with the next Prezista SmPC update. Of note, ritonavir 100 mg is authorized also as a booster for children >15 kg in combination with other ARVs (e.g. Atazanavir) so there is no reason why 675 mg Prezista / 100 mg ritonavir could not be recommended for paediatric patients weighing 25 kg and more. The MAH agrees to update the Prezista SmPC at the next opportunity.

Pharmacokinetics of Cobicistat

For COBI no popPK model was used, only NCA PK parameters are available. Steady-state PK parameters for COBI in Cohort 2 in comparison to reference studies are presented in Table 13. Mean C_{0h} was 86.3 ng/mL (N=5, CV 95.9%).

Table 13: Summary of PK Parameters of DRV and COBI after Single Administration of DRV/COBI as Separate Agents, and as FDC in HIV-1 Infected Patients (GS-US-292-0106, GS-US-216-0130, and GS-US-216-0128)

Table 16: Summary of the Pharmacokinetic Parameters and Respective CV% of DRV and COBI after Single Administration of DRV/COBI as Separate Agents, and as FDC in HIV-1 Infected Patients (GS-US-292-0106, GS-US-216-0130, and GS-US-216-0128)

	GS-US-292-0106		GS-US-216-0130		GS-US-216-0128			
	Adolescents aged ≥12 to <18 years with HIV-1 E/C/F/TAF FDC (150/150/200/10 mg) qd		Adults with HIV-1 DRV/COBI single agents 800/150 mg qd		Cohort 1 Part A Patients aged ≥12 to <18 years with HIV-1 DRV/COBI single agents 675-800/ 150 mg qd		Cohort 2 Patients aged ≥6 to <12 years with HIV-1 DRV/COBI single agents variable/ 150 mg qd	
	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%	Mean (SD)	CV%
DRV								
n	NA		59[a]		8		7[b]	
C_{max} (ng/mL)			7,663 (1,920)	25.06	7,591 (1,528)	20.1	7,150 (1,745)	24.4
AUC_{0-24h} (ng.h/mL)			81,646 (26,322)	32.24	83,540 (23,347)	27.9	82,008 (27,630)	33.7
COBI								
n	24[c]		60[a]		8		7[b]	
C_{max} (ng/mL)	1,202 (421)	35.0	991 (331)	33.40	1,121 (207)	18.5	1,510 (330)	21.9
AUC_{0-24h} (ng.h/mL)	8,241 (2,973)	36.1	7,596 (3,657)	48.14	9,248 (3,168)	34.3	16,103 (5,642)	35.0

AUC_{∞}=area under the plasma concentration-time curve from time of intake until infinity; AUC_{0-24h}=area under the concentration-time curve over a 24 hours; AUC_{last}=area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration; 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; CV=coefficient of variation; DRV=darunavir; E/C/F/TAF=elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; FDC=fixed-dose combination; HIV-1=human immunodeficiency virus type 1; NA=not applicable; NC=not calculated; SD=standard deviation; $t_{1/2}$=elimination half-life; t_{max}=time to reach maximum plasma concentration; qd=once daily.

[a] n=59 for AUC_{0-24h}. Collected as AUC_{tau}: concentration at predose (0 hour) was used as surrogate for concentration at 24 hours for the purposes of estimating AUC_{tau}.

[b] n=5 for AUC_{0-24h}. Collected as AUC_{tau}: concentration at predose (0 hour) was used as surrogate for concentration at 24 hours for the purposes of estimating AUC_{tau}.

[c] n=23 for AUC_{0-24h}. Collected as AUC_{tau}: concentration at predose (0 hour) was used as surrogate for concentration at 24 hours for the purposes of estimating AUC_{tau}.

CV% calculated as SD/mean × 100.

The PK parameters from COBI presented in Table 13 show that the daily exposure to COBI (AUC_{0-24h}) for children 6-12 yr old in Cohort 2 in study 216-0128 were on average 1.7-fold, 2.0-fold and 1.7-fold higher than for 12-18 yr old adolescents in Cohort 1 study 216-0218, for 12-18 yr old adolescents in study 292-0106 and adults with HIV-1 infection in study 216-0130, respectively.

Although the COBI exposures in children aged 6 to <12 years in Cohort 2 of study 216-0128 (mean $AUC_{0-24h,ss}$ of 16103 ng.h/mL and $C_{max,ss}$ of 1510 ng/mL) were 1.7- to 2.0-fold higher compared with those in adolescents and adults, this increase was not considered clinically relevant, because a similar increase in COBI exposure was observed in children aged 6 to <12 years treated with GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide). GENVOYA has been approved in this age group, with a mean $AUC_{0-24h,ss}$ of 15891 ng.h/mL and $C_{max,ss}$ of 2079 ng/mL (GENVOYA SmPC 2022). Additionally, COBI was well tolerated in Cohort 2 of study 216-0128, with a similar safety profile compared with that in adults and adolescents. Therefore, the increased exposures of COBI in children aged 6 to <12 years compared with adolescents and adults with HIV-1 are considered acceptable.

Pharmacodynamics

Mechanism of action

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (K_D of 4.5×10^{-12}M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

Cobicistat is a mechanism based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates, such

as darunavir, where bioavailability is limited and half-life is shortened due to CYP3A dependent metabolism.

Primary and Secondary pharmacology

No new information has been provided.

2.6.3. Discussion on clinical pharmacology

The scored DRV/COBI 675/150-mg FDC film-coated tablet is administered according to the same once-daily dose regimen as the separate commercially available tablet formulations. The development program for the scored DRV/COBI 675/150-mg FDC film-coated tablet is based on the clinical development programs of the single agents of DRV and COBI and the PK bridging of the separate commercially available tablets with the FDC tablet.

The aim of the drug product development was to develop a scored DRV/COBI 675/150-mg FDC film-coated tablet that is bioequivalent to the single agents of DRV and COBI administered concomitantly as the commercially available tablet formulations (DRV 1x600-mg and 1x75-mg tablet; and COBI 1x150-mg tablet). Excipient selection and manufacturing process development of the drug product was executed based on prior knowledge gained during the development of the commercially approved SYMTUZA (D/C/F/TAF 800/150/200/10-mg) FDC film-coated tablet. An initial paediatric formulation was developed, which was only used for development purposes. The formulation was modified to improve the manufacturability of the tablets at a larger scale (see Section 3.1.3).

In Study IFD1004, the scored DRV/COBI 675/150-mg FDC film-coated tablet was shown to be bioequivalent to the single agents of DRV and COBI administered concomitantly as the commercially available tablet formulations (DRV 1x600-mg and 1x75-mg tablet; and COBI 1x150-mg tablet) under fed conditions in healthy adults, which confirms the suitability of the proposed formulation for use in children.

In vitro biopharmaceutic studies were conducted to assess the compatibility of several liquids and soft foods as vehicles for the administration of the scored DRV/COBI 675/150-mg FDC film coated tablet. The results demonstrate that there is no or negligible impact of the preparations with the tested vehicles on the performance of the scored DRV/COBI 675/150-mg FDC film coated tablet. In conclusion, apple sauce, strawberry jam, yogurt, drinking water, and orange juice are suitable vehicles to disperse the scored DRV/COBI 675/150-mg FDC film-coated tablet when administered immediately after preparation (see Section 3.1.3).

The MAH changed the lower weight cut-off for use of DRV 675 mg from ≥30 kg (PREZISTA SmPC 2024) to ≥25 kg (proposed Rezolsta 675/150 mg SmPC) to facilitate treatment in this paediatric population with a DRV/COBI FDC. This weight change was supported by the PopPK model, as the estimated median DRV $C_{0h,ss}$ in children aged 6 to <12 years and weighing ≥25 to <40 kg is lower than the median adult value. DRV $C_{0h,ss}$ would be even lower when using 600 mg of DRV in combination with 150 mg COBI in the ≥25 to <30 kg weight band (if the dose were to match PREZISTA). As a compromise, median DRV $AUC_{0\text{-}24h,ss}$ is slightly higher in the ≥25 to <30 kg weight band compared with the median observed in adults, but it is still within the 95th percentile of the 90% PI of adults.

As the adult dose of COBI (150 mg) is approved for use in the paediatric population weighing ≥25 kg (GENVOYA SmPC, 2022), instead of using two different weight bands and doses for DRV/COBI (ie, 600/150 mg qd for 25 to <30 kg and 675/150 mg qd for 30 to <40 kg), the MAH proposed the development of one FDC, using the 675/150 mg qd dose for this weight band. This has been agreed by the EMA Paediatric Committee (EMEA-001280-PIP01-12-M06, PIP Decision P/0257/2023).

However, the extension of indication of Rezolsta will also influence the prescription of DRV in combination with COBI administered separately, thus for Prezista. Section 4.2 of the Prezista SmPC now includes the following tables (for treatment naïve and treatment experienced paediatric patients, respectively) regarding the posology:

Recommended dose for treatment-naïve paediatric patients (3 to 17 years) with PREZISTA and ritonavir[a] or cobicistat[b]	
Body weight (kg)	**Dose (once daily with food)**
≥ 15 kg to < 30 kg	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily
≥ 30 kg to < 40 kg	675 mg (6.8 ml)[c] PREZISTA/100 mg (1.2 ml) ritonavir once daily
≥ 40 kg	800 mg (8 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily or 800 mg (8 ml) PREZISTA/150 mg (tablet) cobicistat[b] once daily

[a] ritonavir oral solution: 80 mg/ml
[b] adolescents 12 years and older
[c] rounded up for suspension dosing convenience

Recommended dose for treatment-experienced paediatric patients (3 to 17 years) with PREZISTA and ritonavir[a] or cobicistat[b]		
Body weight (kg)	**Dose (once daily with food)**	**Dose (twice daily with food)**
≥ 15 kg to < 30 kg	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily	380 mg (3.8 ml) PREZISTA/50 mg (0.6 ml) ritonavir twice daily
≥ 30 kg to < 40 kg	675 mg (6.8 ml)[c] PREZISTA/100 mg (1.2 ml) ritonavir once daily	460 mg (4.6 ml) PREZISTA/60 mg (0.8 ml) ritonavir twice daily
≥ 40 kg	800 mg (8 ml) PREZISTA/100 mg (1.2 ml) ritonavir once daily or 800 mg (8 ml) PREZISTA/150 mg (tablet) cobicistat[b] once daily	600 mg (6 ml) PREZISTA/100 mg (1.2 ml) ritonavir twice daily

[a] ritonavir oral solution: 80 mg/ml
[b] adolescents 12 years and older
[c] rounded up for suspension dosing convenience

The recommended posology may become unclear if different weight cut-offs for DRV combined with ritonavir vs DRV combined with COBI are agreed. If for Rezolsta 25 kg will be accepted as the lower weight cut-off, the MAH is requested to harmonize the weight cut-offs also for use with ritonavir with the next Prezista SmPC update. Of note, ritonavir 100 mg is authorized also as a booster for children >15 kg in combination with other ARVs (e.g. Atazanavir) so there is no reason why 675 mg Prezista / 100 mg ritonavir could not be recommended for paediatric patients weighing 25 kg and more. The MAH agrees to update the Prezista SmPC at the next opportunity.

2.6.4. Conclusions on clinical pharmacology

The proposed posology in paediatric patients with HIV-1 infection aged 6-12 years weighing between 25 and 40 kg is considered acceptable by the CHMP.

2.6.5. Clinical efficacy

Table 14: Overview of main clinical studies

Study (Phase, Status)	Description	Treatment	Number of Participants	Main Endpoints
GS-US-216-0128 (Phase 2/3, ongoing) Cohort 2[a]	DRV and COBI in HIV-1 infected, ART-experienced, virologically suppressed[b] children (≥6 to <12 years and ≥25 kg[c])[d]	DRV (dose based on body weight)[e] and COBI (150 mg) qd[d] +ARV background regimen[f]	N=8[g]	• (1st) PK DRV (AUC_{tau}) • (1st) Safety over 24 weeks • (2nd) PK DRV (C_{tau}, C_{max}, CL/F) and COBI (AUC_{tau}, C_{tau}, C_{max}, CL/F, V_z/F) • (2nd) Virologic response at Weeks 24 and 48 • (2nd) Change in CD4+ cell count at Weeks 24 and 48 • (2nd) Safety over 48 weeks
TMC114FD2HTX1006 (Phase 1, completed)	Scored film-coated D/C/F/TAF FDC tablet administered as a matching placebo tablet in HIV-1 infected children (≥6 to <12 years and ≥25 to <40 kg)	Placebo[h] single dose	N=24[i]	Ease and acceptability of swallowing the D/C/F/TAF FDC-matching placebo tablets[j]

[a] Data from Cohort 2 described in this summary document are based on Interim Analysis 2 (data cutoff date: 19 September 2023) of Study GS-US-216-0128, including 8 participants in Cohort 2 who received DRV and COBI and who had completed at least Week 48 on the study at the data cutoff date for Interim Analysis 2. Data from participants who received the combination ATV and COBI in Cohort 2 are not included in Interim Analysis 2 and are not relevant for this submission.

[b] Although Protocol Amendment 8 allowed enrollment of viremic participants (HIV-1 RNA ≥50 copies/mL) in Cohort 2, all 8 participants enrolled in Cohort 2 for which data are described in this summary document were virologically suppressed.

[c] The 8 participants enrolled in Cohort 2 for which data are described in this summary document enrolled under different protocol amendments with different weight criteria (ie, Protocol Amendments 4 [n=4] and 6 [n=1]: ≥25 kg [Group 1] and ≥15 to <25 kg [Group 2]; Protocol Amendments 7 [n=2] and 8 [n=1]: ≥25 to <35 kg). Therefore, ≥25 kg was used for the purpose of Interim Analysis 2.

[d] Participants (n=3) enrolled in Cohort 2 after implementation of Protocol Amendment 7 received F/TAF 200/25 mg qd as third agent. Participants (n=5) enrolled in Cohort 2 prior to implementation of Protocol Amendment 7 received COBI-boosted DRV with a background regimen of 2 NRTIs.

[e] The recommended daily dosage of DRV based on body weight according to the local Prescribing Information was to be given and was not to exceed the recommended adult dosage. Refer to Mod2.7.2/Tab2 for details on the DRV doses that were received by participants in Cohort 2 for which data are described in this summary document.

[f] For participants enrolled prior to the implementation of Protocol Amendment 7 (n=5), participants had to be on a stable ARV regimen at screening consisting of 2 NRTIs and ATV/rtv qd or DRV/rtv qd or bid. For participants enrolled after the implementation of Protocol Amendment 7 (n=3), participants had to be on a stable ARV regimen at screening consisting of 2 NRTIs and a third agent per local prescribing guidelines. Participants enrolled after the implementation of Protocol Amendment 7 taking DRV had to be on qd dosing or had to switch to qd at or prior to Day 1.

[g] Participants included in the SAS. For the definitions of analysis sets, refer to Mod2.7.3/Sec1.2.

[h] Placebo tablet identical in size (21 mm x 11 mm), shape, and appearance to the active scored film-coated D/C/F/TAF 675/150/200/10-mg FDC tablet. No active study drug was administered.

[i] Participants included in the ITT Analysis Set, defined as all participants who were randomized and received at least 1 dose of treatment subsequent to randomization in the study.

[j] Irrespective of the mode of intake (as a whole or as a split tablet).

Dose-response studies

No dose response studies were performed.

The proposed DRV dose of 675 mg is aligned with the approved DRV dose in combination with 100 mg ritonavir (rtv) for patients weighing ≥30 to <40 kg. COBI 150 mg qd showed to be generally safe and well tolerated throughout its development, and boosted DRV exposures to levels that were comparable to the boosting effect of coadministered rtv 100 mg. The proposed DRV dose of 675 mg was extended

down to a body weight of 25 kg supported by PopPK modelling for dosing weight-bands simplification and to align with the approved paediatric dose for COBI in, ie, for use in patients weighing ≥25 kg.

Based on the PopPK simulations, a DRV/COBI 675/150-mg qd dosing regimen for the weight-band ≥25 to <40 kg in paediatric patients would result in similar or slightly higher DRV AUC0-24h,ss and similar or slightly lower DRV C0h,ss compared to adults.

Main study(ies)

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 SubjectsTitle of Study

Methods

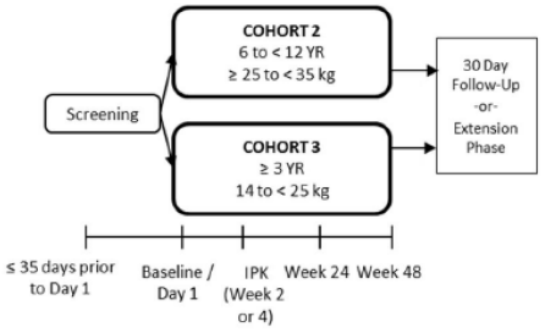
This is an ongoing open-label, multicenter, multicohort, two-part study (Part B only applicable to Cohort 1) evaluating the PK, safety, efficacy, and antiviral activity of ATV/co or DRV/co administered with a BR in HIV-1 infected treatment-experienced, virologically suppressed paediatric subjects.

The Study Schema for Cohort 2 is shown in Figure 4 below.

A total of approximately 100 paediatric subjects, ages 3 months to < 18 years, of either sex are being enrolled across the cohorts, of which 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

Figure 4. GS-US-216-0128: Study Schema Cohort 2



IPK = intensive PK; PK = pharmacokinetic(s); YR = years

For the current EoI, only Cohort 2 is of relevance.

Study Participants

Main inclusion criteria for participation in cohort 2 of the study were:

- HIV-1 infected, treatment-experienced, virologically suppressed, male and female subjects 6 years to < 12 years (according to requirements of enrolling cohort) at the Day 1 visit.
- Body weight ≥25 to <35 kg at screening.
- Stable antiretroviral for a minimum of 3 months prior to the Screening visit.
    - Participants enrolled prior to implementation of Protocol Amendment 7: 2 NRTIs and ATV/r once daily or DRV/r once daily or twice daily.
    - Participants enrolled after the implementation of Protocol Amendment 7: 2 NRTIs plus a third agent per local prescribing guidelines. Participants were to switch from their current third agent to ATV or DRV at Day 1. Participants taking DRV had to be on once daily dosing or should switch to once daily.
    - Participants must not have had documented or suspected resistance to applicable study drugs including ATV or DRV.
- Documented plasma HIV-1 RNA concentrations for ≥ 3 months preceding the screening visit:
    - Participants enrolled prior to implementation of Protocol Amendment 7: HIV-1 RNA (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.
    - Participants enrolled after the implementation of Protocol Amendment 7: HIV-1 RNA < 50 copies/mL on a stable regimen (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection was ≥ 50 copies/mL).
    - Participants enrolled after the implementation of Protocol Amendment 8:
        - Virologically suppressed ≥ 3 months preceding the Screening visit: HIV-1 RNA < 50 copies/mL on a stable regimen (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection was ≥ 50 copies/mL).
        - Viraemic: HIV-1 RNA ≥ 50 copies/mL and on a stable regimen.
        - For virologically suppressed participants, unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or "blip") prior to screening were acceptable. If the lower limit of detection of the local HIV-1 RNA assay was < 50 copies/mL (eg, < 20 copies/mL), the plasma HIV-1 RNA level could not exceed 50 copies/mL on 2 consecutive HIV-1 RNA tests.

Main exclusion criteria for participation in cohort 2 of the study were:

- Screening CD4 cell count < 200 cells/µl.
- An opportunistic illness indicative of Stage 3 HIV diagnosed within the 30 days prior to screening.
- Active hepatitis C virus (HCV) infection. Participants with positive HCV antibody, and without detectable HCV RNA were permitted to enrol.

- Hepatitis B virus (HBV) surface antigen (HBsAg) positive or other evidence of active HBV infection. Note: Participants with positive HBV surface antibody, and no evidence of active HBV infection were permitted to enrol.

Treatments

The treatment regimen for Cohort 2 is summarized below (Table 15).

Table 25: GS-US-216-0128: Summary of Study Treatments

Cohort	Description	Dose[a, b]
2	6 to < 12 years and weight ≥ 25 to < 35 kg[c]	COBI 150-mg tablets administered orally QD with food, in combination with DRV, and F/TAF as third agent 200/25 mg orally QD, as applicable. The recommended daily dosage of DRV based on body weight according to the local prescribing information was to be given.

ATV = atazanavir; COBI = cobicistat; DRV = darunavir; F/TAF = emtricitabine/tenofovir alafenamide; QD = once daily
a Although participants received ATV or DRV, for the purpose of this analysis only participants receiving DRV were
considered with the exception of screen failures.
b COBI 150-mg tablets QD with food, in combination with DRV with a background regimen for participants in Cohort 2
enrolled prior to implementation of Protocol Amendment 7.
c ≥ 25 kg for participants in Cohort 2 enrolled prior to implementation of Protocol Amendment 7.

Participants were treated for at least 48 weeks, plus an optional long-term extension phase.

Objectives

The primary objectives, related to DRV/co, of this ongoing study are as follows for Cohort 2:

- To evaluate the steady-state PK of DRV and confirm the dose of DRV/co in paediatric participants with HIV-1 weighing ≥ 25 to < 35 kg (6 to < 12 years of age).
- To evaluate the safety and tolerability of DRV/co through 24 weeks in paediatric participants with HIV-1 weighing ≥ 25 to < 35 kg (6 to < 12 years of age).

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

- To evaluate the efficacy of DRV/co through 24 weeks in paediatric participants with HIV-1 weighing ≥ 25 to < 35 kg (6 to < 12 years of age).
- To evaluate the safety, tolerability, and efficacy of DRV/co through 48 weeks in paediatric participants with HIV-1 weighing ≥ 25 to < 35 kg (6 to < 12 years of age).

Outcomes/endpoints

The primary endpoints, related to DRV/co, of this ongoing study are as follows for Cohort 2:

- PK parameters of AUCtau for DRV.

- The incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities through Week 24.

The secondary endpoints, related to DRV/co, of this ongoing study are as follows for Cohort 2:

- PK parameters of:
    - Ctau, Cmax, and CL/F for DRV.
    - AUCtau, Ctau, Cmax, CL/F, and Vz/F for COBI.
- The incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities through Week 48.
- The percentage of participants with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 and as defined by the US FDA–defined snapshot algorithm.
- The change from baseline in CD4 cell counts (cells/µL), and CD4 percentage at Weeks 24 and 48.

Sample size

The proposed sample size for Cohort 2 is based on historical recruitment experience and precision criteria for dose confirmation targeting a 95% CI of the geometric mean estimates of PK parameter (CL/F and Vz/F, as applicable) with at least 80% power for TAF and 77% power for DRV. The proposed sample size of 9 participants provided 77% power for DRV CL/F and ≥ 96% power for TAF CL/F and Vz/F used with DRV.

The sample size and power calculation for the DRV/co + F/TAF treatment group for Cohorts 2 and 3 are tabulated below (Table 16).

Table 16: GS-US-216-0128: Sample Size and Power for Analytes DRV and TAF (Used With DRV) for Cohorts 2 and 3

Analyte	PK Parameter	SD (natural log scale)	Assessment Boundary[a]	Power (Sample Size of 9)
DRV	CL/F[c]	0.38[b]	60% to 140%	77%
TAF	CL/F	0.31[d]	60% to 140%	96%
	Vz/F	0.24[d]	60% to 140%	> 99%

CI = confidence interval; COBI = cobicistat; DRV = darunavir; HIV = human immunodeficiency virus; IPK = intensive PK; PK = pharmacokinetics; SD = standard deviation; TAF = tenofovir alafenamide

a Assessment boundary for CL/F or Vz/F is for the lower and upper bounds of the 95% CIs of the geometric mean relative to the point estimate of the geometric mean.
b HIV-infected pediatric (adolescent) participants with IPK data from Study GS-US-216-0128 Cohort 1.
c Per Written Request issued on 27 March 2014 for COBI, study was required to be powered using CL/F only for DRV.
d HIV-infected adults with population PK data from Study GS-US-311-1089.

Randomisation and blinding (masking)

Not applicable.

Statistical methods

Analysis sets and their definitions are as follows:

All Enrolled Analysis Set included all participants who were enrolled into the study. This is the primary analysis set for by-participant listings.

The Full Analysis Set (FAS) included all participants who took at least 1 dose of study drug. This is the primary analysis set for efficacy analyses.

The Safety Analysis Set included all participants who took at least 1 dose of study drug. All the data collected up to 30 days after participants permanently discontinued their study drug was included in the safety summaries. This is the primary analysis set for safety analyses.

The Intensive PK (IPK) Analysis Set was defined for each analyte of interest and included all participants who received at least 1 dose of study drug and for whom steady-state PK profiles at IPK visits were evaluable for the analyte of interest. The IPK Analysis Set was used for IPK analyses.

The Pharmacokinetic (PK) Analysis Set included all participants who received at least 1 dose of study drug and for whom at least 1 observed concentration data of any analyte of interest was available. This is the primary analysis set for all PK analyses. The PK analysis was used for the trough blood concentration listing.

The Spine DXA Analysis Set included all participants who (1) were enrolled in the study, (2) had received at least 1 dose of study drug, and (3) had non-missing spine BMD value for the Day 1 visit.

The Total Body Less Head (TBLH) DXA Analysis Set included all participants who (1) were enrolled in the study, (2) had received at least 1 dose of study drug, and (3) had non-missing TBLH BMD value for the Day 1 visit.

The FAS is the primary analysis set for efficacy endpoints. No formal statistical testing was planned.

All **HIV-1 RNA data** collected on treatment (ie, data collected up to 1 day after the last dose date) was used in the US FDA–defined snapshot algorithm. For the snapshot algorithm, the numbers and percentages of participants with HIV-1 RNA < 50 copies/mL, HIV-1 RNA ≥ 50 copies/mL, and reasons for no virological data at Week 24/48 were summarized by cohort. The 95% CI for the percentage of participants with HIV-1 RNA < 50 copies/mL was constructed using the Clopper-Pearson exact method. The Week 24 virologic outcomes for the US FDA–defined snapshot algorithm were listed.

The proportion of participants with HIV-1 RNA < 50 copies/mL was also analysed by cohort and by visit using the following 2 methods for imputing missing HIV-1 RNA values:

- missing = failure (M = F)

  In this approach, all missing data were treated as HIV-1 RNA ≥ 50 copies/mL. The denominator for the percentage was the number of participants in the FAS, excluding ongoing participants who had both missing HIV-1 RNA at a visit and had not reached the upper limit of that analysis window for the corresponding visit.

- missing = excluded (M = E)

  In this approach, all missing data were excluded in the computation of the percentages (ie, missing data points were excluded from both the numerator and denominator in the computation). The denominator for percentages at a visit is the number of participants in the FAS with non-missing HIV-1 RNA value at that visit.

For both M = F and M = E analyses, the number and percentage of participants with HIV-1 RNA in the following categories were summarized: < 50 copies/mL (< 20 copies/mL [< 20 copies/mL not detectable, < 20 copies/mL detectable], 20 to < 50 copies/mL), 50 to < 200 copies/mL, 200 to < 400 copies/mL, 400 to < 1000 copies/mL, ≥ 1000 copies/mL, and missing (only applicable to M = F analysis).

The **CD4 cell count and CD4% data** 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

participants who were still on study drug). Absolute values and changes from baseline in CD4 cell count (cells/μL) and CD4% at each visit were summarized by cohort and by visit descriptively (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) and also included the 95% CI based on the t-distribution. The mean and 95% CI of change from baseline over time by cohort was plotted.

Adverse event and clinical laboratory data were summarized using descriptive statistics. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0. 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

The participant disposition in Study 216-0128 (Cohort 2) is summarized in table 17. A total of 8 participants were enrolled and received at least 1 dose of study drug. At the data cutoff date (19 September 2023), 5 (62.5%) participants had completed the main (48-week treatment) phase and had entered the extension phase. Three (37.5%) participants had discontinued the study drug in the main phase prior to the data cutoff date due to withdrawal of consent during the Week-48 window. At the data cutoff date, 4 (80.0%) participants who had completed the main phase were continuing to receive study drug in the extension phase. One (20.0%) participant had discontinued the study in the extension phase at the investigator's discretion. No participants had discontinued treatment due to efficacy-related reasons.

Table 17: Disposition of Participants in Study GS-US-216-0128 (Cohort 2); All Screened Participants

	Cohort 2
Participants enrolled, N	8
Main Phase (48-week Treatment Phase)	
Participants who completed study drug, n (%)	5 (62.5)
Participants who prematurely discontinued study drug, n (%)	3 (37.5)
Reasons for premature discontinuation of study drug, n (%)	
Withdrew consent	3 (37.5)
Extension Phase	
Participants who entered Extension Phase, n (%)	5 (62.5)
Participants still on study drug up to the data cutoff date	4 (80.0)
Participants who prematurely discontinued study drug, n (%)	1 (20.0)
Reasons for premature discontinuation of study drug, n (%)	
Investigator's discretion	1 (20.0)

Denominator for percentages in the Main Phase as well as the category of "Participants who entered Extension Phase" was the SAS. Denominator for percentages in the Extension Phase was the number of participants who entered the Extension Phase.
Modified from Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Tab6.
Source: Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Sec8.1.

Recruitment

First participant first visit: 11 May 2017, last participant last visit for the primary endpoint: 19 Sept 2023.

Database finalisation: 03 Nov 2023.

Conduct of the study

Cohort 2 started enrolment under Protocol Amendment 4 (dd 14 Nov 2016) and the protocol was amended 5 times during the conduct of Cohort 2. Main changes were related to updates of Section 5.4 Prior and Concomitant Medication and Section 4.3 Exclusion Criteria to include disallowed/discouraged use of Direct Oral Anticoagulants (DOACs) and Antipsychotics, include recommendations on Atorvastatin and Drospirenone usage, addition of emtricitabine/tenofovir alafenamide (F/TAF) with the goal of studying F/TAF and cobicistat (COBI) in paediatric patients in the most expedient manner, and update inclusion/exclusion criteria to add viraemic paediatric participants to enhance enrolment.

Baseline data

Main demographic, baseline, and baseline HIV disease characteristics in Study 216-0128 (Cohort 2) are summarized in table 18.

The median (range) age was 10 (7; 11) years and median (range) weight was 31.7 (27.6; 45.4) kg. The study included 75.0% female participants and 87.5% black participants.

All participants were virologically suppressed at baseline (HIV 1 RNA <50 copies/mL). The median (range) baseline CD4+ cell count was 998 (439; 1,113) cells/μL and all participants had a baseline CD4+ cell count ≥350 cells/μL. The median (range) baseline CD4+ percentage was 40.0 (29.1; 48.5) %. The median (range) time since HIV 1 diagnosis was 8.0 (1.0; 11.0) years. Note that all participants were receiving a regimen containing 2 NRTIs, in accordance with study eligibility criteria, and had received multiple ARVs prior to switch. Background ARVs given in combination with DRV/c were F/TAF (n=3), ABC/3TC (n=3), ABC/DDI (n=1) and AZT/3TC (n=1). The most common mode of HIV-1 infection was vertical transmission (7 [87.5%] participants). All participants were asymptomatic.

The median (Q1; Q3) baseline eGFRcr was 150.3 (144.7; 159.8) mL/min/1.73 m2.

Table 18: Main Demographic and Baseline Characteristics, and Baseline HIV Disease Characteristics in Study GS-US-216-0128 (Cohort 2); SAS

	Cohort 2 (N=8)
Main Demographic and Baseline Characteristics	
Age (years)	
Mean (SD)	10 (1.7)
Median	10
IQ range	(8; 11)
Range	(7; 11)
Sex at birth, n (%)	
Male	2 (25.0)
Female	6 (75.0)
Race, n (%)	
American Indian or Alaska Native	0
Asian	0
Black	7 (87.5)
Native Hawaiian or Pacific Islander	0
White	0
Other	1 (12.5)
Baseline Weight (kg)	
Mean (SD)	33.4 (5.97)
Median	31.7

Table 18: Main Demographic and Baseline Characteristics, and Baseline HIV Disease Characteristics in Study GS-US-216-0128 (Cohort 2); SAS

	Cohort 2 (N=8)
IQ range	(29.1; 36.3)
Range	(27.6; 45.4)
Main Baseline HIV Disease Characteristics	
HIV-1 RNA categories (copies/mL), n (%)	
<50	8 (100.0)
≥50	0
CD4+ cell count (/μL)	
Mean (SD)	894 (240.2)
Median	998
IQ range	(732; 1,071)
Range	(439; 1,113)
CD4+ percentage (%)	
Mean (SD)	39.5 (6.46)
Median	40.0
IQ range	(35.0; 44.3)
Range	(29.1; 48.5)
HIV disease status, n (%)	
Asymptomatic	8 (100.0)
Symptomatic HIV infection	0
AIDS	0
Years since participant diagnosed with HIV	
Mean (SD)	7.4 (3.20)
Median	8.0
IQ range	(6.0; 9.5)
Range	(1.0; 11.0)

Modified from Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Tab8 and Tab9.
Source: Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Sec8.3.1 and Sec8.3.2.

Table 19: DRV Doses Administered in Study GS-US-216-0128 (Cohort 2)

Participant ID	Weight at Baseline[a]	Weight at Dose Change	Actual DRV Dose[b]	DRV First Dose (Study Day[c])	DRV Last Dose (Study Day[c])
[redacted]	29.2 kg	-	600 mg qd	-377	340
	-	34.2 kg	675 mg qd	341	590
	-	43.4 kg	800 mg qd	591	Cont.[e]
	27.6 kg	-	600 mg qd[d]	1	59
	-	30.6 kg	675 mg qd[d]	60	675
	-	42.0 kg	800 mg qd[d]	676	Cont.[e]
	33.8 kg	-	675 mg qd	1	252
	-	40.0 kg	800 mg qd	253	337
	38.7 kg	-	600 mg qd	-1,160	Cont.[e]
	32.4 kg	-	600 mg qd	-448	Cont.[e]
	45.4 kg	-	800 mg qd	~ -10 months	330
	29.0 kg	-	600 mg	1	168
	-	31.1 kg	675 mg	169	Cont.[e]
	31.0 kg	-	675 mg	1	Cont.[e]

bid=twice daily; COBI=cobicistat; DRV=darunavir; ID=identification; qd=once daily.
All participants received COBI 150 mg qd from Study Day 1 onwards.

[a] Baseline weight on Study Day 1.
[b] DRV 675 mg qd was administered as the commercially available tablet formulations (1x600-mg and 1x75-mg tablet qd). DRV 800 mg qd was administered as the commercially available tablet formulation (1x400-mg tablet bid).
[c] Study Day was relative to the first dose date of study drug.
[d] For this participant, DRV 600 mg, 675 mg, and 800 mg correspond to DRV 6 mL, 6.8 mL, and 8 mL, respectively, using 100 mg/mL suspension. The 6.8 mL was rounded up for suspension dosing convenience.
[e] At the data cutoff date for Interim Analysis 2 (19 September 2023).

Source: Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/App16/Listing16.2.4.5 (DRV doses), App17/Listing16.2.5.1 (DRV doses), and App20/Listing16.2.8.2.2 (weight values).

.

Outcomes and estimation

Virologic Response

The virologic outcomes at Week 24 and Week 48, with HIV-1 RNA cutoff at 50 copies/mL and according to the US FDA-defined snapshot algorithm, are presented in table 20. At both Week 24 and Week 48, the percentage of participants with HIV-1 RNA <50 copies/mL in the FAS was 100% (8/8 participants).

Table 20: Virologic Outcomes at Week 24 and 48 (HIV-1 RNA Cutoff at 50 Copies/mL, US FDA Snapshot Algorithm) in Study GS-US-216-0128 (Cohort 2); FAS

	Cohort 2 (N=8)
FDA Snapshot Algorithm - Week 24	
Virologic Failure at Week 24, n (%)	0
Virologic Success at Week 24, n (%)	
HIV-1 RNA <50 copies/mL	8 (100.0)
No Virologic Data in Week-24 Window, n (%)	0
FDA Snapshot Algorithm - Week 48	
Virologic Failure at Week 48, n (%)	0
Virologic Success at Week 48, n (%)	
HIV-1 RNA <50 copies/mL	8 (100.0)
No Virologic Data in Week-48 Window, n (%)	0

Participants enrolled prior to implementation of Protocol Amendment 7 had a different visit schedule than those enrolled afterwards. Week 24 window was between: (1) Day 141 and 196 (inclusive) for participants enrolled prior to implementation of Protocol Amendment 7, (2) Day 141 and 210 (inclusive) for participants enrolled after implementation of Protocol Amendment 7. Week 48 window was between: (1) Day 309 and 378 (inclusive) for participants enrolled prior to implementation of Protocol Amendment 7, (2) Day 295 and 378 (inclusive) for participants enrolled after implementation of Protocol Amendment 7.

Modified from Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Tab12 and Tab13.
Source: Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Sec9.2.1.

CD4+ Cell Count (Absolute and Percentage)

The mean and median CD4+ cell count and CD4+ percentage at baseline, Week 24, and Week 48, and changes from baseline at Week 24 and Week 48 are presented in table 21.

Table 21: CD4+ Cell Count and CD4+ Percentages at Baseline, Week 24, and Week 48, and Changes from Baseline in Study GS-US-216-0128 (Cohort 2); FAS

	Cohort 2 (N=8)	
	Mean (SD)	**Median (Range)**
CD4+ Cell Count (cells/µL)		
Baseline	894 (240.2)	998 (439; 1,113)
Week 24	886 (257.1)	912 (457; 1,202)
Week 48	839 (204.8)	789 (643; 1,150)
Change From Baseline		
Change From Baseline at Week 24	-9 (179.7)	25 (-347; 186)
Change From Baseline at Week 48	-55 (198.7)	-20 (-318; 245)
CD4+ Percentage (%)		
Baseline	39.49 (6.457)	39.95 (29.10; 48.50)
Week 24	39.61 (6.414)	42.00 (28.80; 46.00)
Week 48	38.26 (7.281)	37.10 (30.00; 47.90)
Change From Baseline		
Change From Baseline at Week 24	0.13 (2.108)	-0.35 (-2.50; 3.30)
Change From Baseline at Week 48	-1.23 (4.828)	0.75 (-11.40; 3.20)

Modified from Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Tab15.9.3.1 and Tab15.9.3.2.
Source: Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Sec9.2.2.

Resistance Assessments

None of the participants experienced virologic failure and none met criteria for postbaseline resistance testing. No pre-treatment resistance data were available for any of the participants. Therefore, no genotypic/phenotypic data are available.

3.3.4.3. Summary of main efficacy results

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

Table 23: Summary of efficacy for trial GS-US-216-0128

Title: 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			
Study identifier	GS-US-216-0128 EU CT number: 2013-001402-28 NCT number: NCT02016924		
Design	open-label, multicenter, multicohort, two-part study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks (Cohort 2) not applicable 30 days
Hypothesis	No formal statistical testing was planned		
Treatments groups	DRV/co		DRV/co, 48 weeks, n=8
Endpoints and definitions	Virologic response (snapshot)	Virologic success at week 24	8 (100%)
		Virologic success at week 48	8 (100%)
	CD4+ cell count mean (SD)	Change From Baseline at Week 24	-9 (179.7)
		Change From Baseline at Week 48	-55 (198.7)
	Resistance assessment	None of the participants experienced virologic failure and none met criteria for postbaseline resistance testing	
Database lock	03 Nov 2023		

Clinical studies in special populations

Not applicable

In vitro biomarker test for patient selection for efficacy

Not applicable

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

Not applicable

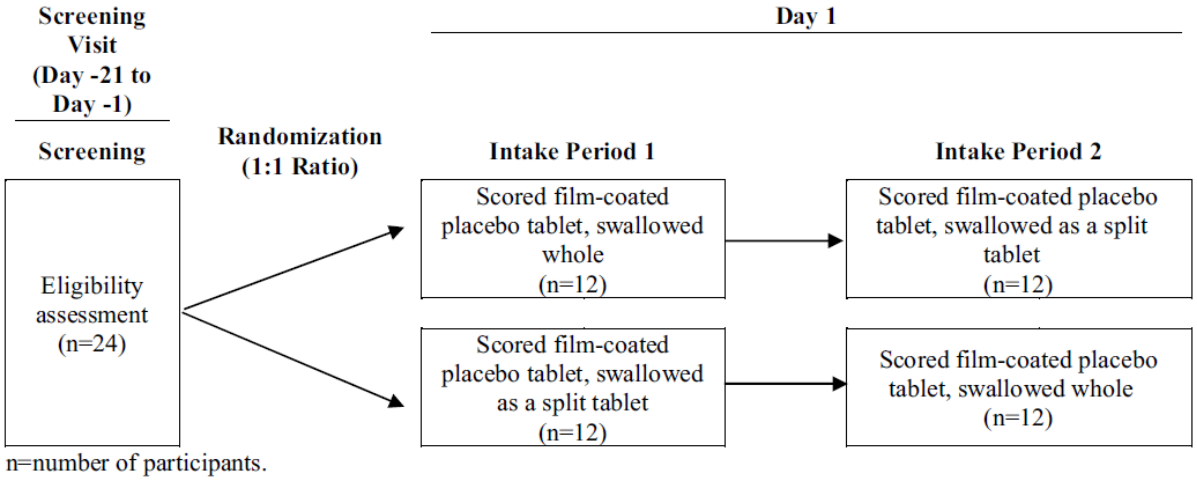
Supportive study(ies)

Study TMC114FD2HTX1006, A Study to Assess the Acceptability of Scored Film-coated darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) Fixed-dose Combination (FDC) Tablets in HIV-1 Infected Paediatric Participants Aged ≥6 to <12 years, Using Matching Placebo Tablets.

Methods

This was a Phase 1, open-label, randomised, single-dose, cross-over, international, multicenter study to evaluate the acceptability of a scored film-coated D/C/F/TAF FDC tablet administered as a matching placebo tablet, one taken as a whole and one as a split tablet. Refer to Figure 5 for a schematic overview of the study.

Figure 5: Schematic Overview of the Study (Study TMC114FD2HTX1006)



n=number of participants.

The primary objective was to assess the ability to swallow the placebo-matched scored film-coated D/C/F/TAF FDC (fixed-dose combination) tablet, irrespective of the mode of intake.

The main secondary objectives were:

- to assess the acceptability of swallowing the placebo-matched scored film-coated D/C/F/TAF FDC tablet, taken as a whole tablet and as a split tablet.
- to assess the ease of splitting the placebo-matched scored film-coated D/C/F/TAF FDC tablet.

The primary endpoint was the ability to swallow the tablet, irrespective of the mode of intake. The main secondary endpoints were:

- a 3-point questionnaire to assess the acceptability of the intake of the whole tablet and as a split tablet by the participant and by the caregiver.
- a 3-point questionnaire to assess the ease of splitting the tablet by the participant's caregiver.
- a questionnaire to assess the swallowing difficulties as reported by the observer.

The study population was planned to include 24 male or female participants ≥6 to <12 years of age, weighing at least 25 kg and less than 40 kg with documented chronic HIV-1 infection, who were on a stable ARV regimen for at least 3 months prior to screening and had documented plasma HIV-1 ribonucleic acid (RNA) <400 copies/mL within 6 months prior to screening, with the aim of including at least 7 participants in the age group from ≥6 to <9 years. Any active condition (eg, active oral infection [candidiasis], significant physical or psychological disease, or other findings during screening)

that could prevent the participant from swallowing, or limit or confound the protocol-specified assessments and outcomes or for which, in the opinion of the investigator, participation could have compromised the safety or well-being of the participant, was exclusionary.

The placebo tablets were 21 mm x 11 mm x 7 mm in size, and participants could indicate their preferred method for tablet swallowing (ie, taken with 1 tablespoon [~15 mL] of semi solid food [ie, apple sauce, yogurt, or pudding] followed by drinking up to 150 mL of liquid [ie, water, milk, apple juice, or cranberry juice], or taken only with up to 150 mL of liquid).

After each intake of a placebo tablet, the participant had to complete an acceptability questionnaire (one questionnaire for the whole tablet and one for the split tablet). Similarly, after each intake of a placebo tablet by the participant, an acceptability questionnaire (one questionnaire for the whole tablet and one for the split tablet) had to be completed by the caregiver and by the observer based on observation of the child. In addition, the observer had to record in the observer questionnaire whether the tablet was hard, OK, or easy to break by hand (based on observation of the caregiver).

Randomisation was used to minimise bias in the assignment of participants to intake period sequences, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) were evenly balanced across intake period sequences and was stratified by age category (≥6 to <9 years and ≥9 to <12 years).

Participants had to continue their antiretroviral (ARV) regimen without interruption or change in administration schedule.

Results

Out of 27 participants screened, 24 were randomized and treated, and 3 failed screening. The screening failures were not related to non-willingness or inability to swallow the tablets.

A total of 24 participants was enrolled and all participants completed the study. Two major protocol deviations were identified during the conduct of this study, both at screening, for 1 participant in the whole-split treatment group and 1 participant in the split-whole treatment group. Both protocol deviations were related to a violation of inclusion criterion 3 (participants weighed >40 kg instead of ≥25 to <40 kg at screening, ie, 1 participant weighed 56.4 kg and 1 participant weighed 71.3 kg). The major protocol deviations are not expected to have impacted the conclusions in this study, as both participants are part of the patient population for which the Symtuza D/C/F/TAF 675/150/200/10 mg scored FDC tablet is being developed (ie, children aged ≥6 years to <12 years, weighing ≥25 kg).

Demographic and baseline characteristics are presented below (Table 24).

Table 24: Demographic Data; Intent-to-treat (Study TMC114FD2HTX1006)

	D/C/F/TAF FDC Placebo		
	Whole – Split (N=12)	Split – Whole (N=12)	Overall (N=24)
Age (Years)			
n	12	12	24
Median (Min; Max)	9.0 (7; 11)	9.5 (7; 11)	9.0 (7; 11)
Age groups (n [%])			
≥6 - <9 years	4 (33.3%)	3 (25.0%)	7 (29.2%)
≥9 - <12 years	8 (66.7%)	9 (75.0%)	17 (70.8%)
Sex (n [%])			
Female	7 (58.3%)	8 (66.7%)	15 (62.5%)
Male	5 (41.7%)	4 (33.3%)	9 (37.5%)
Race (n [%])			
Black or African American	5 (41.7%)	8 (66.7%)	13 (54.2%)
White	3 (25.0%)	4 (33.3%)	7 (29.2%)
Not Reported	4 (33.3%)	0	4 (16.7%)
Ethnicity (n [%])			
Hispanic or Latino	7 (58.3%)	5 (41.7%)	12 (50.0%)
Not Hispanic or Latino	5 (41.7%)	7 (58.3%)	12 (50.0%)
Height (cm)			
n	12	12	24
Median (Min; Max)	136.00 (122.7; 160.0)	132.10 (121.0; 155.0)	132.75 (121.0; 160.0)
Weight (kg)			
n	12	12	24
Median (Min; Max)	28.45 (25.0; 71.3)	30.15 (25.4; 56.4)	29.65 (25.0; 71.3)
Body Mass Index (kg/m^2)			
n	12	12	24
Median (Min; Max)	16.00 (13.0; 28.0)	17.00 (15.0; 23.0)	16.50 (13.0; 28.0)

Note: Participant 100017 re-enrolled/re-randomized as participant 100024, thus participant 100017 data excluded from the analysis.

Adapted from: [TSIDEM01.RTF] [/SAS/4688/TMC114FD2HTX1006/FILES/RE/CSR/PROGRAMS/TSIDEM01.SAS] 29JAN2021, 17:30

Overall, 20 (83.3%) out of 24 participants took FDC ARV medication, and 17 (70.8%) participants took single-agent ARV medication. Eight (33.3%) out of 24 participants took 1 FDC as the only current ARV medication. Twenty-two (91.7%) out of 24 participants took their current ARV medication as pills, 1 (4.2%) participant in liquid form, and 1 (4.2%) participant partly in liquid form and partly as pills. Seventeen (70.8%) out of 24 participants indicated it was easy to take their current ARV medication.

Swallowability results are summarised in Table 25. Twenty-three (95.8%) of the 24 participants were able to swallow the placebo-matched tablet after 1 or 2 attempts, irrespective of the mode of intake.

Table 25: Swallowability (Observer) Primary Endpoint; Intent-to-treat (TMC114FD2HTX1006)

	Mode of Intake-Questionnaire Response							
	Was the participant successful in swallowing the tablet after 1 or 2 attempts?							
	D/C/F/TAF FDC Either Whole or Split Tablet		**D/C/F/TAF FDC Whole**		**D/C/F/TAF FDC Split 1**		**D/C/F/TAF FDC Split 2**	
	No	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
D/C/F/TAF FDC Placebo Overall (N=24)								
n (%)	1 (4.2%)	23 (95.8%)	1 (4.2%)	23 (95.8%)	1 (4.2%)	23 (95.8%)	1 (4.2%)	23 (95.8%)
95% CI[a]	(0.74-20.24)	(79.76-99.26)	(0.74-20.24)	(79.76-99.26)	(0.74-20.24)	(79.76-99.26)	(0.74-20.24)	(79.76-99.26)

D/C/F/TAF=darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDC=fixed-dose combination; N=number of participants.

[a] 95% Wilson confidence interval.

Source: Mod5.3.5.4/TMC114FD2HTX1006/Tab2

Results of the participant acceptability questionnaires are presented in Table 26. Twenty-one (87.5%) and 20 (83.3%) of the 24 participants rated the swallowability of the whole or split placebo-matched tablet, respectively, as 'easy' or 'neither hard nor easy'. Taking the tablet (as a whole or split tablet) for a longer period (qd) was rated as either 'acceptable' or 'good to take' by most participants (20 [83.3%] for the tablets swallowed as a whole and 17 [70.8%] of the 24 participants for the tablets swallowed as a split tablet).

Table 26: Swallowability/Acceptability Questionnaires (Participant); Intent-to-treat (TMC114FD2HTX1006)

	Current ARV Treatment (N=24) n (%)	**D/C/F/TAF FDC–Whole (N=24) n (%)**	**D/C/F/TAF FDC–Split (N=24) n (%)**
Questionnaire Response			
How are you taking your current medication			
All in liquid form	1 (4.2%)	NA	NA
Part in liquid, part as pills[a]	1 (4.2%)	NA	NA
All as pills	22 (91.7%)	NA	NA
How easy or hard was it to take your current medication or this tablet (whole or 2 split pieces)?			
Hard	1 (4.2%)	3 (12.5%)	4 (16.7%)
Neither hard nor easy	6 (25.0%)	1 (4.2%)	6 (25%)
Easy	17 (70.8%)	20 (83.3%)	14 (58.3%)
Acceptability to take this tablet (whole or 2 split pieces) for a longer period (qd)			
Not acceptable	NA	4 (16.7%)	6 (25.0%)
Acceptable	NA	2 (8.3%)	6 (25.0%)
Good to take	NA	18 (75.0%)	11 (45.8%)
Unable to assess this question	NA	-	1 (4.2%)

ARV=antiretroviral; D/C/F/TAF=darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDC=fixed-dose combination; N, n=number of participants; NA=not applicable; qd=once daily.

[a] Answer includes both current ARV medication taken as tablet formulation and other concomitant medication taken as liquid formulation.

Source: Mod5.3.5.4/TMC114FD2HTX1006/Tab4

Acceptability results from the caregiver questionnaires are presented in Table 27. Most caregivers assessed the intake by the child of the whole tablet, the first half of the split tablet, and the second half of the split tablet as 'easy' or 'neither hard nor easy' (21 [87.5%], 23 [95.8%], and 22 [91.7%] of the 24 caregivers, respectively).

Table 27. Swallowability/Acceptability Questionnaires (Caregiver); Intent-to-treat (TMC114FD2HTX1006)

	D/C/F/TAF FDC–Whole (N=24) n (%)	D/C/F/TAF FDC–Split 1 (N=24) n (%)	D/C/F/TAF FDC–Split 2 (N=24) n (%)
Questionnaire Response			
How easy or hard was it for the child to take this tablet?			
Hard	3 (12.5%)	1 (4.2%)	2 (8.3%)
Neither hard nor easy	2 (8.3%)	7 (29.2%)	5 (20.8%)
Easy	19 (79.2%)	16 (66.7%)	17 (70.8%)

D/C/F/TAF=darunavir/cobicistat/emtricitabine/tenofovir alafenamide; FDC=fixed-dose combination; N, n=number of participants.
Source: Mod5.3.5.4/TMC114FD2HTX1006/Tab5

2.6.6. Discussion on clinical efficacy

In support of the current variation, data from Interim Analysis 2 of **Study 216-0128 (Cohort 2)** was submitted. Study 216-0128 is an ongoing open-label, multicenter, multicohort, two-part study (Part A and B) evaluating the PK, safety, efficacy, and antiviral activity of ATV/co or DRV/co administered with a background regimen (BR) in HIV-1 infected treatment-experienced, virologically suppressed paediatric subjects. A total of 8 participants were enrolled and received at least 1 dose of study drug. Further, **study TMC114FD2HTX1006** was submitted to support the acceptability/swallowability of the scored DRV/COBI 675/150-mg FDC film-coated tablet for children aged ≥6 years and weighing ≥25 to <40 kg.

The proposed DRV dose of 675 mg is aligned with the approved DRV dose in combination with 100 mg rtv for patients weighing ≥30 to <40 kg. COBI 150 mg qd showed to be generally safe and well tolerated throughout its development, and boosted DRV exposures to levels that were comparable to the boosting effect of co-administered rtv 100 mg. The proposed DRV dose of 675 mg was extended down to a body weight of 25 kg supported by PopPK modelling for dosing weight-bands simplification and to align with the approved paediatric dose for COBI in Genvoya (E/C/F/TAF 150/150/200/10-mg FDC), ie, for use in patients weighing ≥25 kg. Based on the PopPK simulations, a DRV/COBI 675/150-mg qd dosing regimen for the weight-band ≥25 to <40 kg in paediatric patients would result in similar or slightly higher DRV AUC0-24h,ss and similar or slightly lower DRV C0h,ss compared to adults. There are however some PK OCs that need to be resolved before a decision on the proposed weight cut-off of 25 kg or 30 kg can be taken, see PK section. Further, no clinical data has been generated in patients <30kg as patients with a body weight between 25 and 30 kg received 600mg DRV in Study 216-0128 Cohort 2.

The design of Study 216-0128 Cohort 2, and the in- and exclusion criteria are fit for purpose. As specific demonstration of antiviral efficacy in paediatric patients is not required for an EoI (rather, efficacy and safety data from adults and adolescents can be extrapolated to children provided that comparable exposures are reached), a non-randomised, non-comparative study can be accepted. Information on the estimands for the primary and secondary objectives has been provided upon request. The study is part of the agreed PIP.

The efficacy outcomes that have been generated are supportive of the use of Cobicistat-boosted Darunavir (DRV/co) and Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 infected, virologically suppressed paediatric subjects. All 8 participants in Cohort 2 remained virologically suppressed and

non-experienced virologic failure. The changes in CD4+ cell count is not clinically relevant and may have been due to chance/small sample size of the enrolled population.

Data generated in Study HTX1006 suggest that acceptability and swallowability of the tablet is acceptable for the target population, though results have not been presented by age group. Although this study investigated the acceptability/swallowability of a proposed scored Symtuza (D/C/F/TAF 675/150/200/10-mg) FDC film-coated tablet, due to the similarity of the scored DRV/COBI 675/150-mg FDC film-coated tablet and the scored paediatric Symtuza FDC film-coated tablet (eg, minimal differences in shape and size), it is agreed that the results of Study FD2HTX1006 can also be used in the current EoI. The participants enrolled in this study were all HIV-1 infected, ART-experienced patients, and do not represent treatment-naïve paediatric patients who are also part of the proposed target population for the current EoI application. Also, one of the inclusion criterion was that participants were willing to swallow tablets. The CHMP considers that this is however not a blocking issue. The MAH no longer proposes to include instructions for crushing/dispersing of the tablets in food/drinks.

2.6.7. Conclusions on the clinical efficacy

As there are no clinically relevant differences in PK exposures of either component of the DRV/COBI 800/150 mg FDC film-coated tablet (in adults and in adolescents aged ≥12 to <18 years and weighing ≥40 kg) and both components of the scored DRV/COBI 675/150-mg FDC film-coated tablet (in children aged ≥6 to <12 years and weighing ≥25 kg), the CHMP is of the view that a similar safety and efficacy profile is expected.

The CHMP noted that no efficacy concerns have been raised by the data submitted in the current application.

2.6.8. Clinical safety

In support of the current variation, safety data from Interim Analysis 2 of Study 216-0128 (Cohort 2) was submitted. Safety was evaluated based on AEs, clinical laboratory tests (including haematology, serum chemistry, and urinalysis), vital sign measurements, ECG measurements, physical examinations, and Tanner stage assessments.

The following analysis set was used in the safety analyses:

SAS: All participants who received at least 1 dose of study drug. All data collected up to 30 days after participants permanently discontinued their study drug were included.

Patient exposure

The median (range) duration of exposure to DRV and COBI was 69.4 (45.0, 270.1) weeks in Study 216-0128 (Cohort 2).

Adverse events

An overall summary of AEs in Study 216-0128 (Cohort 2) through the data cutoff date is provided in Table 28.

No deaths, AEs leading to premature study drug discontinuation, SAEs, or Grade ≥3 AEs were reported. All participants reported at least 1 AE, all of which were Grade 1 or Grade 2 in severity.

Three (37.5%) participants experienced AEs considered related to study drug by the investigator: Grade 1 product size issue and Grade 1 product taste abnormal (both in the same participant), Grade 2 vomiting (1 participant), and Grade 1 vomiting (1 participant).

The most frequently (>1 [12.5%] participant) reported AEs by PT were (Table 29): vomiting and nasal congestion (each for 3 [37.5%] participants); and upper respiratory tract infection, abdominal pain, cough, headache, cerumen impaction, and influenza (each for 2 [25.0%] participants).

Table 28: Overall Summary of Adverse Events in Study GS-US-216-0128 (Cohort 2); SAS

	Cohort 2 (N=8)
Participants experiencing any AE, n (%)	8 (100.0)
Any Grade ≥2	5 (62.5)
Any Grade ≥3	0
Participants experiencing any AE related to study drug, n (%)	3 (37.5)
Any Grade ≥2	1 (12.5)
Any Grade ≥3	0
Participants experiencing any SAE, n (%)	0
Any SAE related to study drug	0
Participants experiencing any AE leading to premature study drug discontinuation, n (%)	0
Deaths, n (%)	0

Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Deaths included treatment-emergent deaths.
Modified from Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Tab20.
Source: Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Sec11.2.

Table 29: Adverse Events Reported For >1 (12.5%) Participant by Preferred Term in Study GS-US-216-0128 (Cohort 2); SAS

	Cohort 2 (N=8)
Participants with 1 or more AE, n (%):	8 (100.0)
Participants with 1 or more AE, by PT, n (%):	
Vomiting	3 (37.5)
Nasal congestion	3 (37.5)
Upper respiratory tract infection	2 (25.0)
Abdominal pain	2 (25.0)
Cough	2 (25.0)
Headache	2 (25.0)
Cerumen impaction	2 (25.0)
Influenza	2 (25.0)

AEs were coded according to MedDRA Version 26.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug or led to premature study drug discontinuation.
Multiple AEs were counted only once per participant per PT.
Modified from Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Tab21.
Source: Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Sec11.2.1.

AEs considered related to study drug were reported in 3 participants (Grade 1 product size issue and Grade 1 product taste abnormal [both in the same participant]; Grade 2 vomiting [1 participant]; and Grade 1 vomiting [1 participant]).

No new ADRs were identified.

Serious adverse events, deaths, and other significant events

No **deaths or SAEs** were reported in Study 216-0128 (Cohort 2).

No participant in Study 216-0128 (Cohort 2) experienced a **fracture** event through the interim analysis data cutoff date.

Overall, spine and TBLH **BMD** increased relative to baseline through Week 96. At Weeks 24 (n = 3), 48 (n = 2), and 72 (n = 2), respectively, mean (SD) percentage increases in spine BMD were 6.66% (5.997%), 6.96% (7.829%), and 16.79% (11.617%), and mean (SD) percentage increases in TBLH BMD were 3.70% (2.517%), 6.96% (3.415%), and 13.85% (0.301%). No participant had a ≥ 4% decrease from baseline in spine or TBLH BMD through Week 96. Median (Q1, Q3) spine BMD Z-Score (Standard) was −1.41 (−3.25, −0.19). The median (Q1, Q3) change from baseline at week 48 (n=2) was −0.31 (−0.79, 0.17). These figures for TBLH BMD Z-Score (Standard) were −2.15 (−2.48, −1.51) and −0.09 (−0.30, 0.12).

No **renal-related** AEs were reported during Study 216-0128 (Cohort 2).

A gradual increase from baseline in serum creatinine was observed at most time points after Week 4 (Table 30). A decrease from baseline in eGFRcr (Schwartz formula) was observed from Week 4 onwards. This decrease was not considered clinically relevant given the high median (Q1; Q3) eGFRcr (Schwartz formula) at both baseline and Week 96 (150.33 [144.68; 159.80] and 135.10 [124.25; 171.62] mL/min/1.73m², respectively) (Table 30).

No Grade 4 laboratory abnormalities were observed. A transient Grade 3 laboratory abnormality of urine RBC (haematuria) was observed in 2 (25.0%) participants at Week 144 and Week 216, respectively.

Table 30: Changes From Baseline in Serum Creatinine and $eGFR_{cr}$ in Study GS-US-216-0128 (Cohort 2); SAS

	N	Median (Q1; Q3)
Serum Creatinine (mg/dL)		
Baseline	8	0.52 (0.47; 0.55)
Change at Week 4	6	0.05 (-0.06; 0.11)
Change at Week 8	8	0.02 (-0.03; 0.07)
Change at Week 24	8	0.03 (-0.04; 0.08)
Change at Week 48	8	0.08 (0.03; 0.12)
Change at Week 96	3	0.13 (0.05; 0.14)
$eGFR_{cr}$ (Schwartz formula) (mL/min/1.73m²)		
Baseline	8	150.33 (144.68; 159.80)
Change at Week 4	6	-9.25 (-19.75; 20.06)
Change at Week 8	8	-3.65 (-20.05; 9.79)
Change at Week 24	8	-2.97 (-18.99; 16.58)
Change at Week 48	8	-8.06 (-19.62; 11.81)
Change at Week 96	3	-21.08 (-25.97; -0.38)

Source: Mod5.3.5.2/GS-US-216-0128-W48-Cohorts2&3-CSR/Tab15.11.6.2.8 (serum creatinine) and Tab15.11.6.2.22 ($eGFR_{cr}$ [Schwartz formula]).

No **lipid-related** AEs were reported during Study 216-0128 (Cohort 2).

There were no clinically relevant changes from baseline in median fasting values of total cholesterol, direct LDL cholesterol, HDL cholesterol, total cholesterol: HDL cholesterol ratio, or triglycerides through the data cutoff date in Study 216-0128 (Cohort 2). Median values remained within normal ranges. All graded fasting lipid laboratory abnormalities were Grade 1 or Grade 2.

No **glucose-related** AEs were reported during Study 216-0128 (Cohort 2).

There were no clinically relevant changes from baseline in median values of fasting glucose through the data cutoff date in Study 216-0128 (Cohort 2). Median values remained within normal ranges. There were no fasting glucose laboratory abnormalities.

No **liver-related** AEs were reported during Study 216-0128 (Cohort 2).

There were no clinically relevant changes from baseline in median values of total bilirubin, direct bilirubin, indirect bilirubin, ALP, ALT, AST, and lipase through the data cutoff date in Study 216 0128 (Cohort 2). Median values remained within normal ranges. Median amylase values were slightly higher than normal at baseline but did not increase from baseline up to Week 144. No participants had elevations in AST, ALT, or total bilirubin. One (12.5%) participant had ALP elevation >1.5xULN. No Hy's Law cases were identified. All graded liver-related laboratory abnormalities were Grade 1 or Grade 2.

No **cardiovascular-, vital signs-, or ECG-related** AEs were reported during Study 216 0128 (Cohort 2).

No AEs related to **severe skin reactions** were reported during Study 216-0128 (Cohort 2).

No **IRIS-related** AEs were reported during Study 216 0128 (Cohort 2).

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

No additional data are available.

Discontinuation due to adverse events

No AEs leading to study drug discontinuation were reported in Study 216-0128 (Cohort 2).

Post marketing experience

Based on the 217,156,710 DRV/COBI 800/150-mg FDC film-coated tablets that were distributed worldwide by the Company from launch to 30 April 2023, the estimated exposure to the DRV/COBI 800/150 mg FDC is 595,276 person-years.

PBRERs/PSURs have been generated for the DRV/COBI 800/150-mg FDC film-coated tablet covering the period from 19 November 2014 to 18 May 2023, summarising the post-marketing safety data obtained by the MAH. These reports concluded that, based on review of nonclinical, clinical, and epidemiologic information, as well as scientific literature and post-marketing adverse reaction cases, the DRV/COBI 800/150-mg FDC continues to demonstrate a favourable benefit-risk profile for its authorized indications.

2.6.9. Discussion on clinical safety

In support of the current variation, safety data from Interim Analysis 2 of Study 216-0128 (Cohort 2) was submitted. Study 216-0128 is an ongoing open-label, multicenter, multicohort, two-part study (Part A and B) evaluating the PK, safety, efficacy, and antiviral activity of ATV/co or DRV/co

administered with a background regimen (BR) in HIV-1 infected treatment-experienced, virologically suppressed paediatric subjects. A total of 8 participants were enrolled and received at least 1 dose of study drug. At the data cut-off date (19 September 2023), 5 (62.5%) participants had completed the main (48-week treatment) phase and had entered the extension phase. Three (37.5%) participants had discontinued the study drug in the main phase prior to the data cutoff date due to withdrawal of consent during the Week 48 window. At the data cutoff date, 4 (80.0%) participants who had completed the main phase were continuing to receive study drug in the extension phase. One (20.0%) participant had discontinued the study in the extension phase at the investigator's discretion. The median (Q1, Q3) duration of exposure to DRV and COBI in Cohort 2 was 69.4 (47.6, 165.2) weeks.

As such, exposure is too limited to reliably assess the safety profile in paediatric patients 6 to 12 years of age. Rather, exposure of DRV and cobicistat are shown to be comparable to either adults (DRV) or licensed products for this age group (cobicistat in Genvoya). Safety will therefore be extrapolated through a PK/PD-bridge which is in line with EMA guidance.

The submitted clinical data did not raise concerns. The observed AEs were consistent with those expected in the study population as well as with those observed in the already approved population. No deaths, AEs leading to premature study drug discontinuation, SAEs, or Grade ≥3 AEs were reported. AEs considered related to study drug were reported in 3 participants (Grade 1 product size issue and Grade 1 product taste abnormal [both in the same participant]; Grade 2 vomiting [1 participant]; and Grade 1 vomiting [1 participant]). Vomiting is already listed as a common adverse reaction in section 4.8 of the SmPC. Overall, no new ADRs were identified.

2.6.10. Conclusions on the clinical safety

Given that exposure of DRV and cobicistat are shown to be comparable to either adults (DRV) or licensed products for this age group (cobicistat in Genvoya), the CHMP is of the view that a similar safety and efficacy profile is expected for the scored DRV/COBI 675/150-mg FDC film-coated tablet (in children aged ≥6 to <12 years and weighing ≥25 kg).

The CHMP noted that no safety concerns have been raised by the data submitted in the current application.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns

The MAH proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety in patients with cardiac conduction disorders

Discussion on safety specification

Following review of the safety information, no update to the list of safety concerns in the EU-RMP was made by the MAH. This is agreed by the PRAC.

Conclusions on the safety specification

The PRAC is of the opinion that the safety concerns listed by the MAH are appropriate.

2.7.2. Pharmacovigilance plan

2.8. Summary of planned additional pharmacovigilance activities from RMP

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Safety Concerns Addressed	Milestones	Due Dates	
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

The PRAC noted that no amendments to the Pharmacovigilance Plan have been proposed by the MAH.

The PRAC, 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 also considers that routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.8.1. Risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information		
Safety in patients with cardiac conduction disorders	Routine risk minimization measures: Legal status: restricted medical prescription Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

The MAH has proposed routine RMMs only.

The PRAC having considered the data submitted is of the opinion that: the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

2.8.2. Conclusion

The CHMP considered that the risk management plan version 7.1 is acceptable.

2.9. Pharmacovigilance

2.9.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9.2. Periodic Safety Update Reports submission requirements

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.

2.10. Product information

2.10.1. 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 the Rezolsta 800/150 mg FDC tablet (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).
- For the extension of the indication of Rezolsta to adolescents, a justification for not performing user testing was included in the Type II variation application, that has been approved on 9 March 2020 (procedure EMEA/H/C/002819/II/0033). Reference was made to the full user testing that was performed, in compliance with the above-mentioned legislative requirements, on the patient leaflet for PREZISTA 75 mg tablets for use in adolescents and children ≥ 6 years (n=20 participants, ages 14 through 18 years of age were tested)(procedure EMEA/H/C/000707/X/20, approved on 23 June 2009), and the fact that the patient leaflet for Rezolsta has a similar format as the patient leaflet for PREZISTA 75 mg tablets.
- The proposed updated indication for Rezolsta is an extension of the target group of users (i.e. HIV-1 infected paediatric subjects aged ≥ 6 years and weighing at least 25 kg). No new route of administration is proposed for the 675/150 mg FDC tablet.

- Safety analyses from study GS-US-216-0128 in HIV-1 infected paediatric 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 and adolescents.
- In the justification for not performing user testing included in the Type II variation application submitted for the extension of the indication of Rezolsta to adolescents (procedure EMEA/H/C/002819/II/0033) reference was made to the full user testing that was performed, in compliance with the above-mentioned legislative requirements, on the patient leaflet for PREZISTA 75 mg tablets for use in adolescents and children ≥ 6 years (procedure EMEA/H/C/000707/X/20, approved on 23 June 2009). The extension of the indication of PREZISTA for children ≥ 6 years was approved in procedure EMEA/H/C/000707/X/20 based on the user testing in 20 participants, ages 14 through 18 years of age and EMA acknowledged that it was not relevant to collect data in children below the age of 14.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The most recent UNAIDS report estimates that of the 39.9 million people globally living with HIV in 2023, 1.4 million (4.4%) were children aged 0 to 14 years (UNAIDS 2023).

The current application is intended to support registration of a scored DRV/COBI 675/150-mg FDC film-coated oral tablet for once-daily use for use in HIV 1 infected children aged ≥6 years and weighing ≥25 to <40 kg, who are either ART naïve or ART-experienced.

The following wording is proposed by the MAH:

Rezolsta is indicated, in combination with other antiretroviral medicinal products, for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and paediatric patients (aged 6 years and older, weighing at least 25 kg).

Genotypic testing should guide the use of Rezolsta (see sections 4.2, 4.4 and 5.1).

3.1.2. Available therapies and unmet medical need

As for adults, HIV infection is a life-threatening condition in the paediatric population. Lifelong treatment is needed, and although treatment options have markedly improved the last decades, there remains a need to expand the available treatment options for children by a.o. additional age-appropriate formulations.

The recommended (collaborative Penta/EACS HIV treatment guideline, 2022) initial treatment of HIV-1 infection for paediatric patients is therapy with two NRTIs in combination with a drug from a different class (third agent). DTG is the preferred third agent in all children over 4 weeks of age and 3 kg. Whilst "preferred options" are recommended, "alternative options" are acceptable and remain important choices in settings where ART availability is limited or in individuals at particular risk of specific toxicity or DDIs.

The choice of HIV-1 therapy depends on various factors including the availability of age-appropriate formulation, ease of use, age/developmental stage of the patient, prior exposure (maternal or prevention), adherence, and in adolescent girls, the risk of pregnancy.

The goal of combination ART in paediatric patients is to achieve and sustain HIV-1 virologic suppression, preserve/restore immune function, minimise drug toxicity, prevent drug resistance, and ultimately lead to normal growth and neurocognitive development.

People living with HIV-1 who are aware of their status, take ART as prescribed, and get and keep an undetectable viral load can live healthy lives.

3.1.3. Main clinical studies

The proposed extension of indication is based on Study GS-US-216-0128 (hereafter referred to as 216-0128), which is an ongoing, Phase 2/3, multicenter, open-label, multicohort study evaluating PK, safety, and efficacy of COBI-boosted ATV, COBI-boosted DRV, and F/TAF in HIV-1 infected children and adolescents aged ≥4 weeks to <18 years.

For this application, the PK, efficacy, and safety of the scored DRV/COBI 675/150-mg FDC film coated tablet in HIV-1 infected children (aged ≥6 years and weighing ≥25 to <40 kg) are supported by data on COBI-boosted DRV from Cohort 2 (N=8) of Study 216-0128, combining DRV (dose based on body weight, once daily) and COBI (150 mg, once daily) in HIV-1 infected, ART-experienced, virologically suppressed children aged ≥6 to <12 years and weighing ≥25 kg.

Further, Study TMC114FD2HTX1006 (hereafter referred to as FD2HTX1006) investigated the acceptability/swallowability of a proposed scored SYMTUZA (D/C/F/TAF 675/150/200/10-mg) FDC film-coated tablet for use in children aged ≥6 to <12 years using matching placebo tablets, which - due to its similarities with the scored DRV/COBI 675/150-mg FDC film-coated tablet - support the acceptability/swallowability of the scored DRV/COBI 675/150 mg FDC film-coated tablet for children aged ≥6 years and weighing ≥25 to <40 kg.

3.2. Favourable effects

The efficacy of Rezolsta has been established in adult and adolescent patients 12 years of age and older. The efficacy demonstration in children is based on a PK bridge, inferred through similar exposure as in adults.

Overall, the DRV exposure data, based on PopPK modelling for the paediatric population for the proposed regimen, indicate lower trough values and somewhat higher AUC values at steady state in 6-12 yr old children as compared to adults, indicating that the proposed regimen is acceptable.

All 8 participants in Cohort 2 remained virologically suppressed and none experienced virologic failure.

The acceptability and swallowability of the film-coated tablet were considered adequate by the CHMP.

3.3. Uncertainties and limitations about favourable effects

A DRV dose of 675 mg is proposed for children aged ≥6 to <12 years and weighing ≥25 kg. This dose is aligned with the approved DRV dose in combination with 100 mg rtv for patients weighing ≥30 to <40 kg. Extending this dose to a body weight of 25 kg is supported by PopPK modelling, but no clinical

data with the 675 mg DRV dose has been generated in patients <30kg. However, three patients with a body weight between 25 and 30 kg received the 600 mg dose according to the protocol.

The PK parameters from COBI show that the daily exposure to COBI (AUC_{0-24h}) for children 6-12 yr old in Cohort 2 in study 216-0128 were on average 1.7-fold, 2.0-fold and 1.7-fold higher than for 12-18 yr old adolescents in Cohort 1 study 216-0218, for 12-18 yr old adolescents in study 292-0106 and adults with HIV-1 infection in study 216-0130, respectively. A similar increase in COBI exposure was observed in children aged 6 to <12 years treated with GENVOYA (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide). GENVOYA has been approved in this age group.

Data generated in Study HTX1006 suggest that acceptability and swallowability of the tablet is acceptable for the target population. Participants enrolled in this study were all HIV-1 infected, ART-experienced patients, and do not represent treatment-naïve paediatric patients who are also part of the proposed target population for the current extension of indication application. This is however not a blocking issue. For patients who have difficulties to swallow the tablet as whole or split it in two, the option of dispersing the film coated tablet in soft food or drinks may offer an alternative.

3.4. Unfavourable effects

The safety profile of DRV/COBI is well-established in adults and adolescents, and given that exposure is comparable, it is not expected to be substantially different in a paediatric setting. The safety assessment of study 216-0128 Cohort 2 (n=8) did not give rise to new safety concerns.

AEs considered related to study drug were reported in 3 participants (Grade 1 product size issue and Grade 1 product taste abnormal [both in the same participant]; Grade 2 vomiting [1 participant]; and Grade 1 vomiting [1 participant]). Overall, no new ADRs were identified.

3.5. Uncertainties and limitations about unfavourable effects

The paediatric study programme is not powered to generate a comprehensive safety database in children and in the data currently presented, no control arm is available for comparison. Rather, exposure of DRV and cobicistat are shown to be comparable to either adults (DRV) or licensed products for this age group (cobicistat in Genvoya). Safety was therefore be extrapolated through a PK/PD-bridge which is in line with EMA guidance.

3.6. Effects Table

Table 31. Effects Table for Rezolsta in paediatric patients

Effect	Short Description	Unit	Treatment	Uncertainties/ Strength of evidence	References
Favourable Effects					
PK	DRV levels		DRV $AUC_{0-24h,ss}$ in the ≥25 to <40 kg group was comparable to DRV $AUC_{0-24h,ss}$ from the reference studies. DRV $C_{0h,ss}$ was 25% to 40% lower in the ≥25 to <40 kg group		

			compared to adults and approximately 60% lower compared to the C228 substudy, but 50% higher compared to the adolescents in the BW ≥40 kg group.		
PK	COBI levels		COBI $AUC_{0\text{-}24h}$ for children 6-12 yr old is on average 1.7- to 2.0-fold higher than for 12-18 yr old adolescents and adults		
Virologic response	Proportion of patients who remained virologically supressed at week 24	n/N (%)	8/8 (100%)	Small sample size (n=8)	Study 216-0128 Cohort 2
Unfavourable Effects					
AEs	Related AEs	n/N	3/8 participants	Small sample size	Study 216-0128 Cohort 2

Abbreviations: n= number of observations; N= number of subjects in the study (intention – to treat)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The extrapolation of efficacy and safety from adults to paediatric patients is in accordance with regulatory practice in the field of HIV. The PD target is expected to respond in the same manner to similar plasma concentrations of the HIV antivirals in both adult and paediatric patients.

Overall, the DRV exposure data, based on PopPK modelling for the paediatric population, for the proposed regimen indicate somewhat lower trough values and somewhat higher AUC values at steady state in 6-12 yr old children as compared to adults, indicating the proposed regimen is acceptable to the CHMP.

The safety profile is well-established in adults and adolescents. The safety assessment of study 216-0128 Cohort 2 is limited but does not give rise to new safety concerns. No cases of virologic failure have been seen. The development of resistance mutations is important, as these may also have an impact on future ARV treatment options. Moreover, as the target population are growing children, potential effects on growth or (pubertal) development are also of importance.

3.7.2. Balance of benefits and risks

The CHMP is of the opinion that the overall data presented supports the efficacy and safety for an extension of the therapeutic indication of Rezolsta.

3.8. Conclusions

The overall benefit-risk balance of Rezolsta is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rezolsta with new strength (675 mg/150 mg film-coated tablets) is favourable in the following indication:

> *Rezolsta is indicated, in combination with other antiretroviral medicinal products, for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and paediatric patients (aged 6 years and older, weighing at least 25 kg).*
>
> *Genotypic testing should guide the use of Rezolsta (see sections 4.2, 4.4 and 5.1).*

The CHMP therefore recommends the grouped extension and variation of the marketing authorisation for Rezolsta subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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