



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human use (CHMP)

Assessment report on group of an extension of marketing authorisation and an extension of indication variation

Symtuza

International non-proprietary name: Darunavir / Cobicistat / Emtricitabine / Tenofovir alafenamide

Procedure No. EMA/X/0000248421

Note

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



Administrative information

Name of the medicinal product:	Symtuza
MAH	Janssen-Cilag International NV Turnhoutseweg 30 B-2340 Beerse BELGIUM
Active substance:	Darunavir / Cobicistat / Emtricitabine / Tenofovir alafenamide
International Non-proprietary Name/Common Name:	Darunavir / Cobicistat / Emtricitabine / Tenofovir alafenamide
Pharmaco-therapeutic group (ATC Code):	ANTIINFECTIVES FOR SYSTEMIC USE (J05)
Therapeutic indication(s):	Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). Genotypic testing should guide the use of Symtuza.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	800 MG/150 MG/200 MG/10 MG 675 MG/150 MG/200 MG/10 MG
Route(s) of administration:	Oral use
Packaging:	Bottle
Package size(s):	90 (3 x 30) tablets 30 tablets

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List of abbreviations

AE	adverse event
AI	Acceptable intake
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral treatment
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/COBI	cobicistat-boosted atazanavir
AUC _{last}	area under the plasma drug concentration versus time curve from time zero to the last quantifiable concentration
AUC _{tau}	area under the plasma concentration-time curve over the dosing interval tau
BMD	bone mineral density
C _{last}	last observed quantifiable plasma drug concentration
C _{max}	maximum observed plasma concentration
C _{tau}	observed plasma concentration at the end of the dosing interval tau
CL/F	apparent oral clearance
COBI	cobicistat
CSR	clinical study report
D/C/F/TAF FDC	darunavir/cobicistat/emtricitabine/tenofovir alafenamide fixed-dose combination
DRV	darunavir
DRV/COBI	cobicistat-boosted darunavir
DXA	dual-energy x-ray absorptiometry
eGFR _{Schwartz}	estimated glomerular filtration rate calculated using the Schwartz formula
EU	European Union
F (or FTC)	emtricitabine
F/TAF FDC	emtricitabine/tenofovir alafenamide fixed-dose combination
FDC	fixed-dose combination
FOIA	Freedom of Information Act
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus type 1
ICH	International Council for Harmonisation
IRIS	immune reconstitution inflammatory syndrome
LC-MS	Liquid Chromatography- mass spectrometry
LDL	low-density lipoprotein
MCC	microcrystalline cellulose
MedDRA	Medical Dictionary for Regulatory Activities
MO	Major objection
n	number of participants with that observation
N	number of participants
NNTA	N-nitroso-2,4-thiazole amine
PBRER	Periodic Benefit-risk Evaluation Report
PD	pharmacodynamic(s)

Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PopPK	population pharmacokinetics
PSUR	Periodic Safety Update Report
PT	preferred term
Q1	first quartile
Q3	third quartile
RH	Relative humidity
UHPLC	Ultra-High-Performance Liquid Chromatography
UV	Ultraviolet spectrometry

1. Background information on the procedure

1.1. Submission of the dossier

Janssen-Cilag International NV submitted on 30 January 2025 an application for a group of variation and extension application for the following variation:

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

Extension application to add a new strength of 675 mg/150 mg/200mg/10 mg film-coated tablets grouped with an Extension of indication (C.I.6) to include treatment of human immunodeficiency virus type 1 (HIV 1) infection in paediatric patients (aged 6 years and older with body weight at least 25 kg) for SYMTUZA, based on the 24-week interim results from study GS-US-216-0128 (Cohort 2); this is a Phase II/III, multicenter, open-label, multicohort interventional study evaluating efficacy, safety, and pharmacokinetics of Cobicistat-boosted Atazanavir (ATV/co) or Cobicistat-boosted Darunavir (DRV/co) and Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 infected children. As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.8, 5.1, 5.2, 6.1, 6.3, 6.4, 6.5 and 8 of the SmPC are updated. The Annex II, Labelling and Package Leaflet are updated accordingly. Version 9.1 of the RMP has also been submitted. Furthermore, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.4 and to update the list of local representatives in the Package Leaflet.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) (P/0284/2024) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0284/2024) was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, Janssen-Cilag International NV 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.

1.4.2. Scientific advice

Janssen-Cilag International NV received scientific advice from the CHMP on 31 January 2019 (EMA/H/SA/4024/1/2018/PED/II).

1.5. Steps taken for the assessment of the product

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

Rapporteur: Patrick Vrijlandt

The application was received by the EMA on	30 January 2025
The procedure started on	20 February 2025
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 May 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 May 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to Janssen-Cilag International NV during the meeting on	19 June 2025
Janssen-Cilag International NV submitted the responses to the CHMP consolidated List of Questions on	09 September 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	14 October 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to Janssen-Cilag International NV on	13 November 2025
Janssen-Cilag International NV submitted the responses to the CHMP List of Outstanding Issues on	27 January 2026
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 February 2026
The CHMP agreed on a 2 nd list of outstanding issues in writing and/or in an oral explanation to be sent to Janssen-Cilag International NV on	26 February 2026
Janssen-Cilag International NV submitted the responses to the CHMP List of Outstanding Issues on	26 May 2026
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 June 2026
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 Symtuza on	25 June 2026

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The current application is intended to support registration of a scored D/C/F/TAF 675/150/200/10 mg film-coated FDC 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 Applicant:

4.1 Therapeutic indications

Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and paediatric patients (aged 6 years and older with body weight at least 25 kg).

Genotypic testing should guide the use of Symtuza (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 2023, 630 000 people died from HIV-related causes globally. There were approximately 39.9 million people living with HIV at the end of 2023, of whom 1.4 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 2023 globally, 120.000 being children 0-14 years old. (WHO FACT sheet and UNAIDS Global HIV & AIDS statistics 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 D/C/F/TAF 800/150/200/10 mg (EU: Symtuza®) FDC film-coated tablet is indicated in the EU, for once daily use, 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. The D/C/F/TAF 800/150/200/10 mg FDC film-coated tablet was developed by Janssen in collaboration with Gilead Sciences, Inc. (Gilead).

In addition, a scored D/C/F/TAF 675/150/200/10 mg film-coated FDC tablet for once-daily use was developed by Janssen in collaboration with Gilead for use in HIV-1 infected paediatric patients aged ≥ 6 years and weighing ≥ 25 kg to < 40 kg, who are either ART-naïve or ART-experienced.

The proposed indication is:

Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and paediatric patients (aged 6 years and older with body weight at least 25 kg).

Genotypic testing should guide the use of Symtuza (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 is one 675 mg darunavir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide tablet once daily taken with food.

ART experienced paediatric patients

One 675 mg darunavir/150 mg cobicistat/200 mg emtricitabine/10 mg tenofovir alafenamide tablet once daily taken with food may be used in patients with prior exposure to antiretroviral medicinal products but without DRV-RAMs and who have plasma HIV-1 RNA < 100 000 copies/mL and CD4+ cell count $\geq$ 100 cells $\times$ 10⁶/L (see section 5.1).*

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

2.3. Type of Application and aspects on development

2.3.1. Legal basis

The legal basis for this application refers to:

Article 10b of Directive 2001/83/EC, as amended – relating to applications for fixed combination products.

2.4. Quality aspects

2.4.1. Introduction

Symtuza 800/150/200/10 mg film-coated tablets are already authorised for the treatment of adults and adolescents (aged 12 years and older, weighing at least 40 kg). The current application is intended for registration of a new lower strength for once-daily use in HIV 1 infected children aged $\geq$ 6 years and weighing $\geq$ 25 to <40 kg.

The finished product is presented as a scored film-coated tablet containing 675/150/200/10 mg of darunavir/cobicistat/emtricitabine/tenofovir alafenamide respectively as active substances. The product contains darunavir as the ethanolate solvate, cobicistat adsorbed on silicon dioxide and tenofovir alafenamide as the fumarate salt.

Other ingredients are:

- tablet core: colloidal anhydrous silica (E551), croscarmellose sodium (E468), magnesium stearate (E572), and cellulose microcrystalline (E460(i));
- tablet coating: polyethylene glycol (macrogol 3350), polyvinyl alcohol (partially hydrolysed), titanium dioxide (E171), talc (E553b), and iron oxide black (E172).

The product is available in white, high density polyethylene (HDPE) bottles with a silica gel desiccants (contained in a separate sachet or canister) fitted with polypropylene (PP) child resistant closures with induction seals.

2.4.2. Active Substance

The active substances are not described in the Ph. Eur. They are already approved for commercial use in Symtuza 800/150/200/10 mg, film coated tablets. The new proposed strength 675/150/200/10mg contains the same active substances, from the same sources, as the commercially available strength. No changes regarding the active substances compared to the currently approved strength are proposed; this is acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as an oval-shaped, blueish grey to grey, scored film-coated tablet (22 x 11 mm) containing 675 mg of darunavir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide as active substances. The new proposed strength for paediatric patients is not dose proportional to the currently approved strength. The excipients are well-known and usual for this type of dosage form. No overages are used in the manufacture of Symtuza 675/200/150/10 mg tablets.

The quality target product profile (QTPP) was suitably defined (Table 2) and the critical quality attributes were identified.

Table 1. quality target product profile

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 ethanolate/ 150 mg cobicistat/ 200 mg emtricitabine/ 10 mg tenofovir alafenamide fumarate	Appearance, Identification, Assay, Uniformity of Dosage Units
Purity	Sufficiently low level of impurities/degradation products	Chromatographic Purity
Microbiological Purity	Sufficiently low level of bioburden, complying with ICH requirements	Microbiological Purity
Drug Release Profile	Immediate release	Dissolution
Container Closure System	HDPE bottle with child-resistant closure and induction seal liner and a desiccant	Appearance, Assay, Chromatographic Purity, Dissolution, Water Content
Shelf life	Minimum 36 months shelf life	Appearance, Assay, Chromatographic Purity, Dissolution, Microbiological Purity

The development of the product has been described, the choice of excipients is justified, and their functions have been explained. Development of the proposed strength was based on previous experience with the formulation and manufacturing development of the 800/150/200/10 mg strength (G001). The choices of the container closure system and manufacturing process are justified. The quantitative formulation designated as G002 was adjusted during development to improve manufacturability and resulted in the commercial formulation G004.

To facilitate the administration to patients unable to swallow the tablet whole, the proposed film-coated tablets bear a score line allowing them to be broken in half. Each piece should be consumed immediately after splitting to ensure the entire dose is administered. The acceptability/swallowability for the target population either as whole or split tablets, was demonstrated in a phase 1 study (TMC114FD2HTX1006). While administration of the proposed product using food or drink vehicles has been referenced in the clinical acceptability study, all study participants chose to swallow the whole or split tablet with water, and therefore alternative administration using a food/drink vehicle, and the associated compatibility studies, are not considered necessary.

A bioequivalence study was performed where the proposed product was compared to the four active substances as single agents or combined tablets (i.e., darunavir 600 mg and 75 mg tablets, emtricitabine/tenofovir alafenamide 200/10 mg tablets, and cobicistat 150 mg tablets).

The bioequivalence study was performed with formulation G002, which was slightly different to the commercial formulation G004. The two formulations were bridged through comparative dissolution studies in four different media (pH 1.2, 4.5, 6.8, and the QC media). The bridging was not initially acceptable as the dissolution profiles were not demonstrated to be similar due to excessive variability for different active substances in different media resulting in a Major Objection (MO1). In response, the applicant submitted a bootstrapping analysis – the profiles were not similar if the 5 minute timepoint was included but profiles were similar when that timepoint was omitted. It was argued that the timepoint is not relevant since tablets are to be taken with food which results in an extended residence

time in the stomach, with dissolution occurring over a longer period. This was accepted and the MO1 was considered resolved.

The CHMP raised another MO requesting the applicant to provide additional data to confirm the representativeness of the test biobatch in relation to typical commercial batches of test product and the acceptability of the test biobatch (e.g. its assay versus the reference biobatch) in line with the EMA guideline on the investigation of bioequivalence.

The applicant confirmed that the size of the batch used in the bioequivalence studies was considered full commercial size at its time of manufacture. Furthermore, the operating principles and control strategy are the same for both the batch used in the bioequivalence studies (CBXXB) and the proposed commercial product, the equipment only varying in size. Comparative batch data according to the release specifications and IPC results were provided, demonstrating the representativeness of the biobatch. Furthermore, comparative dissolution studies were conducted and profiles considered to be similar, as per MO1. Overall, it is concluded that the test and reference medicinal product batches used in the bioequivalence batches adhere to the requirements of the EMA guideline on the investigation of bioequivalence and MO2 was thus resolved.

As with the authorised strength, two dissolution methods are used to control the finished product, due to different solubility profiles of the four active substances. The proposed dissolution methods are the same as those used for the already approved product, and the applicant has shown the suitability of these conditions for the proposed commercial formulation (G004). The parameters are in line with Ph. Eur. 2.9.3, and the higher rotation speed has been justified in relation to coning observed at a lower speed and minimising of artefacts. The selection of media and the use of a surfactant (for the darunavir dissolution method) has been discussed in terms of sink conditions and pH dependency, and this justification is considered applicable for the proposed paediatric formulation.

The container closure system is a white, high density polyethylene (HDPE) bottle containing 30 tablets, fitted with polypropylene (PP) child resistant closure with induction seal. The packaging is common for this type of dosage form, and the container closure system is similar to that used for the already approved strength. The container closure system materials comply with the current European Regulation for materials intended to come into contact with food EC 1935/2004, including Regulation (EU) No 10/2011 on Plastic Materials and Articles Intended to Come into Contact with Food. The suitability of these materials is further demonstrated by the results obtained from stability studies.

2.4.3.2. Manufacture of the product and process controls

The finished product manufacturing and batch release sites are stated in the dossier. Satisfactory evidence of GMP compliance has been provided.

The manufacturing process consists of 8 main steps: initial blending, 2nd blending, granulation, final blending, compression, preparation of coating suspension, film coating and packaging. The product is manufactured using conventional manufacturing techniques. However, since the amount of tenofovir alafenamide (TAF) is <2%, it is considered a non-standard manufacturing process.

A flow chart and written narrative of the manufacturing process have been provided, and both are sufficiently detailed.

Process validation was conducted on three full scale batches in line with the EMA guideline on process validation for finished products. Ranges for critical and non-critical process parameters were explored, and critical and non-critical process controls were adequately recorded. For each step in the process, suitable in-process controls and process parameters/ranges were defined based on development and

process validation data. In addition, blend uniformity was investigated and found to be adequate, which is especially relevant to the distribution of TAF since it is present at <2%.

The proposed holding time of 12 months for the bulk drug product is considered acceptable based on the stability data provided.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification, analytical procedures, batch analysis

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form including appearance (visual), tablet dimension, identification (UHPLC, UV), assay (UHPLC), chromatographic purity related to darunavir (UHPLC), chromatographic purity related to cobicistat (UHPLC), chromatographic purity related to emtricitabine (UHPLC), chromatographic purity related to tenofovir alafenamide (UHPLC), *N*-nitroso-2,4-thiazoleamine (LC-MS), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), water content (Ph. Eur.), and microbiological purity (Ph. Eur.).

The proposed analytical procedures and corresponding specification limits are adequate for routine control of the finished product at release and shelf life. The proposed limits are generally in line with ICH guidelines and Ph. Eur., and batch release and stability data. The wider limits for some parameters at shelf-life are justified based on the behaviour observed during stability studies.

The potential presence of elemental impurities in the finished product was 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. The information on the control of elemental impurities is satisfactory.

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/applicants 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).

During the procedure, the applicant reported elevated levels of *N*-nitroso-2,4-thiazole amine (NNTA) in already approved Symtuza 800/150/200/10 mg tablets (ranging from 30% to 100% of the Maximum Acceptable Limit (MAL) of 12 ppb with respect to the finished product based on an. (With regard to the authorised product the MAH has followed the foreseen process as per the "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines" (EMA/425645/2020), and the relevant regulatory actions have been followed) acceptable intake (AI) of 18 ng NNTA/day and a maximum daily dose (MDD) of 1.4571 g finished product per day.

In the light of the above, the applicant provided an updated nitrosamine risk assessment, and presented confirmatory testing data for NNTA from three validation batches of the new strength at a single timepoint (20 months) stored under long-term conditions.

However, no trend data, nor any information on impurity behaviour in-use was available. Furthermore, the system suitability acceptance criteria for the applied analytical method were considered too wide. Therefore, the CHMP raised a MO requesting the applicant for further confirmatory testing for NNTA up to the end of shelf-life and also under accelerated, and when relevant, intermediate conditions, to tighten

the NNTA limit in the release specifications, to restrict storage conditions in line with available stability data, to provide in-use stability data, and to tighten the system suitability criteria.

In response, the applicant presented additional confirmatory testing data for NNTA on three validation batches as well as on three registration batches. The validation batches were manufactured using microcrystalline cellulose (MCC) with low nitrite content, whereas nitrite was significantly higher in the MCC used to manufacture the registration batches. The validation batches were stored for 11 months under long-term, accelerated as well as intermediate storage conditions. These batches were 23 months old (from date of manufacture) at time of testing and the NNTA levels measured at all storage conditions were below the acceptable intake limit for all three batches, although levels were higher (up to ~50% MAL) under accelerated conditions. The registration batches were also tested for NNTA after storage for 54 months under both long-term and intermediate storage conditions. These batches were 60 months old at the time of testing (from date of manufacture), i.e. exceeding the proposed shelf life of 36 months. The NNTA levels were below the acceptable intake limit (54-94% MAL) for all batches except for one which was found to be above the acceptable intake limit (106%) when stored at 30 °C/75% RH. The registration batches are considered worst case since testing for NNTA was conducted when the batches far exceeded the proposed shelf-life. NNTA also increased above the AI limit in the in-use studies, conducted with the registration batches, more so at higher temperature and humidity.

The applicant also clarified that, in order to mitigate the formation of NNTA, future commercial batches will be manufactured with MCC with low nitrite content, an acceptable limit for which is included in its specification.

Finally, the system suitability criteria for the analytical method were tightened as requested.

However, since confirmatory results covering only one timepoint for the validation and registration batches are insufficient to fully understand the increase of NNTA during storage and considering that the available confirmatory results on both registration and validation batches show higher levels of NNTA when the batches were stored at higher temperature and humidity, the proposed storage condition and the in-use storage recommendation in the SmPC (section 6.4) was restricted to "Store below 25 °C" for the unopened bottle as packaged for sale as well as during the in-use storage period.

The major objection was therefore considered resolved and the nitrosamines control strategy is acceptable. Nonetheless, the applicant is recommended to generate stability data for NNTA according to the ICH guidelines over the approved shelf-life of the product and re-evaluate the release specifications, storage conditions, and shelf-life (including in use) as appropriate (REC).

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

Batch analysis data for ten commercial scale batches of the finished product including the biobatch were provided. The results were within the specifications and confirm consistency of the manufacturing process.

2.4.3.4. Stability of the product

Stability data were provided from three commercial scale batches stored at 5 °C (up to 3 months), 25 °C / 60% RH (up to 36 months), 30 °C / 75% RH (up to 36 months) and 40 °C / 75% RH (up to 6 months). The conditions are generally in line with ICH Q1A, except for intermediate conditions, but the use of the harsher 30 °C / 75% RH condition is acceptable.

Samples were tested for appearance, assay, chromatographic purity, dissolution, and microbial purity.

Changes were mainly seen in tenofovir alafenamide, and to a lesser extent in cobicistat, where the assay decreases and impurities increase, however all parameters remained within the proposed acceptance criteria. The proposed shelf-life of 3 years is justified by the data, including the confirmatory testing data on NNTA. In view of this data, the temperature storage conditions have been restricted to "Store below 25 °C" as stability for NNTA has only been fully demonstrated under long-term storage conditions (i.e. 25 °C / 60% RH).

The forced degradation studies were assessed for the already approved strength and are considered applicable for the new strength. The storage precaution 'store in original package' to protect from moisture is justified as the active substance tenofovir alafenamide is susceptible to degradation in presence of water. A photostability study was conducted in line with ICH Q1B and the product is not sensitive to light.

The in-use stability period of 6 weeks is justified by the in-use stability data of batches stored at 25 °C / 60% RH. The increase in NNTA observed during the in-use period is considered significant, in particular at 30 °C / 75% and the available data justify the recommendation to store the bottle below 25 °C during the in-use period.

Overall, the stability results justify the proposed shelf life of 3 years, the proposed in-use shelf life and the recommended storage conditions in the proposed container, as stated in the SmPC sections 6.3 and 6.4.

2.4.3.5. Adventitious agents

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

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

In the context of this application no new information has been presented in relation to the active substances; this is acceptable. Information on development, manufacture and control of the finished product have been presented in a satisfactory manner. Two MOs were raised during the procedure concerning the bridging data between the biobatch and the proposed commercial formulation, and the representativeness of the test biobatch. Both were resolved with the provision of additional data and justification. In addition, during the procedure the applicant reported elevated levels of a nitrosamine impurity in batches of the authorised strength of the finished product. Another MO was raised and in response to that an updated nitrosamine risk assessment was provided together with results of confirmatory testing. As a result, the storage conditions for the unopened bottle as packaged for sale, as well as during the in-use storage period, and the release specification limit for NNTA were tightened resolving this MO.

At the time of the CHMP opinion, there was a minor unresolved quality issue pertaining to generating additional stability data and possibly reevaluating the NNTA release specifications, FP storage conditions, and shelf-life, having no impact on the benefit-risk balance of the product.

The results of tests carried out indicate satisfactory 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 the clinic.

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 for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to generate stability data for NNTA according to the ICH guidelines over the approved shelf-life of the product and re-evaluate the release specifications, storage conditions, and shelf-life (including in use) as appropriate.

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

Previously available data on juvenile animals do not indicate any concerns for the paediatric population. It is therefore agreed that the existing non-clinical data and the paediatric clinical data are sufficient to support the extension of indication to children aged ≥ 6 years and weighing ≥ 25 to < 40 kg.

Exposure multiples were calculated based on mean PK exposures from the clinical study GS-US-216-0128 (cohort 2), where the age range of ≥ 6 to < 12 years was investigated. The newly calculated exposure multiples are similar compared to those calculated for the > 12 years population studied previously.

All impurities present are toxicologically qualified.

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 <i>K_{ow}</i>	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

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	OECD 106		
Soil 1 = sandy loam		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	OECD 308		
Sediment 1		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/ <i>P. subcapitata</i>	OECD 201	NOEC	≥43	mg/L	growth rate
<i>Daphnia</i> sp. Reproduction Test/ <i>Daphnia magna</i>	OECD 211	NOEC	19	mg/L	reproduction
Fish, <i>O. mykiss</i>	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/ <i>Chironomus riparius</i>	OECD 218	NOEC	≥444	mg/kg _{dw}	emergence normalised to 10% o.c.
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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
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Bioaccumulation potential - log <i>K_{ow}</i>	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 <i>K_{ow}</i>	4.10 at pH 9	potentially B
	<i>BCF_{KgL}</i>	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} C, M, R STOT RE 1 or 2*	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

Phase II Physical-chemical properties and fate			
Study type	Test protocol	Result	Remarks
Adsorption-Desorption	OECD 106		
Soil 1 = clay loam		$K_{OC, soil 1} = 3624$ 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	OECD 308		
Sediment 1		DT _{50, water 1} = 5.6 d DT _{50, whole system 1} = 507 d	20 °C
Sediment 2		DT _{50, water 2} = 12 d DT _{50, whole system 2} = 408 d	20 °C
Transformation products		>10% = N	

Phase II Aquatic effect studies					
Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>P. subcapitata</i>	OECD 201	NOEC	≥29.3	mg/L	growth rate
<i>Daphnia</i> sp. Reproduction Test/ <i>Daphnia magna</i>	OECD 211	NOEC	≥17.5	mg/L	immobilisation/ reproduction/survival
Fish, <i>P. promelas</i>	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/ <i>Chironomus riparius</i>	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

Substance (INN/Invented Name): emtricitabine			
CAS-number: 143491-57-0			
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential - log <i>K</i> _{ow}	OECD 107	-0.7 at pH 4 -0.7 at pH 7 -0.7 at pH 10	Potential PBT/vPvB: N
PBT/vPvB statement emtricitabine is considered to be not PBT, nor vPvB			
Phase I			
Parameter	Value	Unit	Conclusion
PEC _{SW, default}	1.0	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Phase II Physical-chemical properties and fate			
Study type	Test protocol	Result	Remarks
Adsorption-Desorption	OECD 106		
Sludge 1		<i>K</i> _{OC, sludge 1} = 21.1 L/kg _{oc}	
Sludge 2		<i>K</i> _{OC, sludge 2} = 45.6 L/kg _{oc}	
Ready Biodegradability Test	OECD 301	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308		
Sediment 1		DT _{50, whole system 1} = >100 d	20 °C
Sediment 2		DT _{50, whole system 2} = >100 d	20 °C
Transformation products		>10% = N	

Phase II Aquatic effect studies					
Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>P. subcapitata</i>	OECD 201	NOEC	≥110	mg/L	growth rate
<i>Daphnia</i> sp. Reproduction Test/ <i>Daphnia magna</i>	OECD 211	NOEC	≥110	mg/L	survival/reproduction
Fish, <i>P. promelas</i>	OECD 210	NOEC	6.1	mg/L	weight
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥110	mg/L	total respiration

Phase II Sediment effect studies					
Sediment Dwelling Organism Test/ <i>Chironomus riparius</i>	OECD 218	NOEC	≥200	mg/kg _{dw}	emergence/ development normalised to 10% o.c.

Risk characterisation				
Compartment	PEC	PNEC	RQ	Conclusion
STP	10 µg/L	≥11000 µg/L	<0.001	No risk
Surface water	1 µg/L	610 µg/L	0.001	No risk

Groundwater	0.25 µg/L	61 µg/L	0.004	No risk
Sediment	8.16 µg/kg _{dw}	≥2000 mg/kg _{dw}	≤0.004	No risk

Substance (INN/Invented Name): tenofovir			
CAS-number: 147127-20-6			
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential - log <i>K_{ow}</i>	OECD 107	-3.8 at pH 2 -4.3 at pH 7	Potential PBT/vPvB: N
PBT/vPvB statement	tenofovir is considered to be not PBT, nor vPvB		
Phase I			
Parameter	Value	Unit	Conclusion
PEC _{SW, default}	0.054	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Phase II Physical-chemical properties and fate			
Study type	Test protocol	Result	Remarks
Adsorption-Desorption	OECD 106		
Soil 1		<i>K_{OC, soil 1}</i> = 351 L/kg _{oc}	
Soil 2		<i>K_{OC, soil 2}</i> = 1091 L/kg _{oc}	
Soil 3		<i>K_{OC, soil 3}</i> = 671 L/kg _{oc}	
Sludge 1		<i>K_{OC, sludge 1}</i> = 14 L/kg _{oc}	
Sludge 2		<i>K_{OC, sludge 2}</i> = 50 L/kg _{oc}	
Ready Biodegradability Test	OECD 301	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308		
Sediment 1		DT _{50, water 1} = 2.0 d DT _{50, sediment 1} = 28.9 d DT _{50, whole system 1} = 10.4 d	20 °C
Sediment 2		DT _{50, water 2} = 3.5 d DT _{50, sediment 2} = 142 d DT _{50, whole system 2} = 32.7 d	20 °C
Transformation products		>10% = Y	3 transformation products

Phase II Aquatic effect studies					
Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>P. subcapitata</i>	OECD 201	NOEC	32	mg/L	growth rate
<i>Daphnia</i> sp. Reproduction Test/ <i>Daphnia magna</i>	OECD 211	NOEC	100	mg/L	Reproduction
Fish, <i>P. promelas</i>	OECD 210	NOEC	≥10	mg/L	survival, growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/ <i>Chironomus riparius</i>	OECD 218	NOEC	1706	mg/kg _{dw}	emergence, normalised to 10% o.c.

Risk characterisation				
Compartment	PEC	PNEC	RQ	Conclusion

STP	0.53 µg/L	≥100,000 µg/L	<0.001	No risk
Surface water	0.053 µg/L	≥1000 µg/L	<0.001	No risk
Groundwater	0.013 µg/L	≥100 µg/L	<0.001	No risk
Sediment	6.0 µg/kg _{dw}	17,060 mg/kg _{dw}	<0.001	No risk

2.5.5. Discussion on non-clinical aspects

No new non-clinical studies have been submitted for the current variation, which is acceptable.

Considering the above data from Phase I and Phase II, Darunavir, Cobicistat, Emtricitabine and Tenofovir are not expected to pose a risk to the environment. A bioaccumulation potential is not indicated based on the log KOW < 4.5. A definitive PBT/vPvB assessment is not required for all 4 substances.

2.5.6. Conclusion on non-clinical aspects

There are no objections to the approval of the current variation from a non-clinical perspective.

2.6. Clinical aspects

2.6.1. Clinical pharmacology

Table 4. Overview of clinical studies

Study (Phase, Status)	Description	Treatment	# Participants	Main Endpoints
GS-US-216-0128 (Phase 2/3, ongoing) Cohort 2 ^a	DRV/COBI + F/TAF FDC in HIV-1-infected, ART-experienced, virologically suppressed ^b children (≥6 to <12 years and ≥25 to <40 kg)	DRV (dose based on body weight) ^c , COBI (150 mg) and F/TAF FDC (200/25 mg) ^d qd	N=9	• (1st) PK DRV, TAF, and TFV (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), TAF (AUC_{last}, C_{max}, C_{last}, CL/F, V_z/F), FTC (AUC_{last}, AUC_{tau}, C_{max}, C_{tau}, CL/F, V_z/F), TFV (AUC_{last}, C_{max}, C_{tau}, CL/F, V_z/F) • (2nd) Virologic response at Weeks 24 and 48 • (2nd) Change in CD4+ cell count and CD4+ percentage at Weeks 24 and 48 • (2nd) Safety over 48 weeks • (2nd) Acceptability and palatability of COBI and F/TAF FDC through Week 48
TMC114IFD10 07 (Phase 1, completed)	DRV, COBI, FTC and TAF administered as scored FDC tablet compared to administration of the separate tablet formulations under fed conditions in healthy adults (≥18 to <55 years)	DRV/COBI 675/150mg/200/10 mg FDC single dose and DRV (600+75 mg) + COBI (150 mg) + TFC/TAF (200/10 mg) single dose	N=37 ^e	Bioequivalence of DRV, COBI, FTC and TAF when administered as scored DRV/COBI/FTC/TAF FDC tablet compared to coadministration as separate tablet formulations

^a Data from Cohort 2 described are based on Interim Analysis 3 (data cutoff date: 30 January 2024) of Study GS-US-216-0128, including 9 participants in Cohort 2 who received DRV/COBI + F/TAF FDC and who had completed at least Week 24 on the study at the data cutoff date for Interim Analysis 3. Data from participants who received ATV/COBI + F/TAF FDC in Cohort 2 are included in Interim Analysis 3 but are not relevant for this submission. For the purpose of Interim Analysis 3, all participants were enrolled following the implementation of Protocol Amendment 7, 8, or 9.

^b Although Protocol Amendment 8 allowed enrollment of viremic participants (HIV-1 RNA ≥50 copies/mL) in Cohort 2, all 9 participants enrolled in Cohort 2 for which data are described in this Clinical Overview Addendum were virologically suppressed.

^c The recommended daily dosage of DRV based on body weight according to the local Product Information was to be given and was not to exceed the recommended adult dosage.

^d The dose of TAF in the 200/25-mg F/TAF FDC used in the study was higher than in the D/C/F/TAF 675/150/200/10-mg FDC of interest (25 mg versus 10 mg)

^e 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.

2.6.1.1. Pharmacokinetics

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.

Bioanalytical methods

Validated analytical methods for DRV, COBI, FTC, TAF and TFV have been applied, showing that the methods are accurate and precise. In study validation during study sample analysis showed acceptable accuracy and precision. Incurred sample reanalysis were within normal criteria.

Population PK modeling for DRV

The previously developed PopPK model in adults for DRV in combination with COBI was updated to describe the data from the current analysis dataset, for example, by re-estimating selected parameters

and updating the covariate 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. pcVPCs stratified by body weight sufficiently captured the central tendency and variability of the data across all 3 weight bands. The updated PopPK model is considered fit-for-purpose, as was previous concluded.

COBI, FTC, TAF, and TFV are already approved in children weighing ≥ 25 kg at the proposed doses. No simulations were performed, as doses were already accepted, but popPK analysis were used for co-variate analysis.

The PopPK simulations show that for paediatric patients in the weight band ≥ 25 to <40 kg a DRV/COBI regimen of 675/150 mg qd results in comparable or slightly higher (up to 34% higher at 25 kg) DRV AUC_{0-24h} and comparable or slightly lower (up to 33% lower at 39 kg) DRV C_{0h} with respect to adults. For paediatric patients weighing 25 to <40 kg receiving DRV/COBI 675/150 mg qd, DRV C_{0h} below 55 ng/ml (protein-binding adjusted EC₅₀ for wild-type virus) is estimated to occur in <1% of paediatric patients. Distribution plots of DRV AUC_{0-24h} and C_{0h} in paediatric patients compared to adults (study FD2HTX3001) were provided, however, the plots did not contain observed data. On request, the applicant provided plots with observed data, showing that the model predictions and observed data are aligned.

In study GS-US-216-0128, based upon non-compartmental data, for COBI, FTC, TAF and TFV, a higher exposure was observed in paediatric subjects compared to adults. For COBI this was a known observation based upon previous data and considered not of safety concern. For FTC, popPK analysis including 6 Phase 2/3 studies (GS-US-292-0106, GS-US-292-1515, GS-US-236-0112, GS-US-311-1269, GS-US-380-1474 and GS-US-216-0128) in paediatric participants infected with HIV-1, the observed higher FTC exposure is mainly driven by the lower bodyweight, however, exposures overlap with dose in adolescents and adults, and the 200 mg FTC dose is approved for use in adults and paediatric patients weighing at least 25 kg, in combination with other antiretrovirals. For TAF, the main difference in the observed exposures is due to the difference in TAF dose, i.e., 25 mg in study GS-US-216-0128. In addition, comparison with adult data showed an overlap in exposures and comparison with other data in children >25 kg receiving 25 mg TAF (study GS-US-380-1474 receiving B/F/TAF) and study GS-US-292-0106 receiving E/C/F/TAF) showed comparable exposures. TAF 10 mg is recommended for use with agents requiring a PK enhancer, such as DRV. For TFV the main difference in the observed exposures is due to the difference in TAF dose (25 mg vs. 10 mg, respectively). Taking into account 2.5-fold difference in TAF dose, the TFV values would be in the upper quartile of adult data, but still overlapping. Moreover, the 10 mg dose in children >25 kg is in line with that for instance indicated for Genvoya in this patient group.

Bioequivalence (study TMC114IFD1007)

The single dose, randomized, open-label, 2-treatment, 2-sequence, 4-period replicate crossover study, evaluated the bioequivalence of the 675/150/200/10 mg FDC tablet vs. the separate co-administered tablets, i.e., 600 mg + 75 mg DRV + 150 mg COB + 200/10 mg FTC/TAF. The separate tablets were administered in the paediatric study GS-US-216-0128.

A FDC of 200 mg FTC and 10 mg TAF was used, as 10 mg TAF is not commercially available as a single agent. The replicate crossover design allowed for intra-individual comparisons as each participant acts as their own control.

Fed conditions were applied in the BE study, as Symtuza. DRV/COB/TFV/TAF 800/150/200/10-mg should be administered with food, in line with all other DRV-based regimens. In accordance with the

EMA guidance on bioequivalence, therefore, in the BE study subjects received a standardized high-fat breakfast prior to administration of study intervention.

The PK results showed that DRV, COBI, FTC and TAF administration as a scored FDC tablet (DRV/COBI/FTC/TAF 675/150/200/10 mg) was bioequivalent to the coadministration as the separate available tablet formulations (DRV 1×600 mg + 1×75-mg tablet +COBI 1×150 mg tablet + FTC/TAF 1 x 200/10 mg tablet), under fed conditions. For all 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% (see Table 5). Although the high intra-individual variability observed for TAF, also for TAF 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%.

Table 5. Statistical Summary of PK parameters after oral administration of Test treatment A (D/C/F/TAF 675/150/200/10-mg as 1×FDC tablet) and Reference treatment B (DRV as 1×600-mg and 1×75-mg tablet, COBI as 1×150-mg tablet and F/TAF as 1×200/10-mg FDC tablet) under fed conditions in healthy adult participants; PK data analysis set (n=32; study TMC114FD2HTX1007)

Geometric means				
PK parameter	Reference	Test	Geometric mean ratios (%)	90% CI (%)
DRV:				
C_{max} (ng/ml)	6340	6217	98.06	94.10 – 102.18
AUC_{0-t} (ng.h/ml)	70047	71969	102.74	98.11 – 107.60
COBI:				
C_{max} (ng/ml)	885	829	93.67	89.63 – 97.90
AUC_{0-t} (ng.h/ml)	6141	5984	97.45	93.18 – 101.91
FTC:				
C_{max} (ng/ml)	1802	1777	98.64	93.66 – 103.89
AUC_{0-t} (ng.h/ml)	9978	10038	100.60	98.83 – 102.40
TAF:				
C_{max} (ng/ml)	113	119	105.23	90.86 – 121.87
AUC_{0-t} (ng.h/ml)	106	120	113.41	106.82 – 120.41

The FDC tablet used in study TMC114FD2HTX1007 (formulation G002) was slightly different to the commercial formulation. In vitro dissolution data have been presented to support the acceptance of the commercial formulation compared to the formulation used in the BE study (see Quality assessment).

2.6.1.2. Pharmacodynamics

Mechanism of action

DRV is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (KD of 4.5 x 10⁻¹²M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

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

FTC is a nucleoside analogue of 2'-deoxycytidine. FTC is phosphorylated by cellular enzymes to form FTC triphosphate. FTC triphosphate inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase (RT), which results in DNA chain-termination.

TAF is a phosphonoamidate prodrug of tenofovir (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation through hydrolysis by cathepsin A, TAF is more efficient than tenofovir disoproxil in concentrating tenofovir in peripheral blood mononuclear cells (PBMC) (including lymphocytes and other HIV target cells) and macrophages. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits HIV replication through incorporation into viral DNA by the HIV RT, which results in DNA chain-termination.

Primary and Secondary pharmacology

No PK/PD analyses for efficacy or safety were performed in Study 216-0128.

Exposure-response analysis for safety was conducted for the TAF (and TFV) component by Gilead using pooled data from children ≥ 2 to < 12 years of age living with HIV-1 administered F/TAF-containing regimens from 4 paediatric studies (292-0106, 311-1269, 380-1474, and 216-0128) with 10- and 25-mg doses of TAF to evaluate the relationship between TAF and TFV exposures and bone and renal safety endpoints. No clinically meaningful exposure-response relationship was observed between TAF or TFV exposures and changes in bone and renal safety endpoints in children ≥ 6 to < 12 years with body weight ≥ 25 to < 40 kg.

Table 6. Summary of Results From Exposure-Response Analysis of Bone and Renal Safety Endpoints at Week 24 and Week 48 Versus Plasma TAF and TFV Pharmacokinetic Parameters Intensive PK Analysis Set, By Group Group 1: Pooled Age 6 to < 12 years and Weight >= 25 kg

	TAF AUClast			TAF Cmax			TFV AUCtau			TFV Cmax		
	N	Coefficient	p-value	N	Coefficient	p-value	N	Coefficient	p-value	N	Coefficient	p-value
Change from Baseline in Spine BMD Height-age Z-Score												
Week 24	47	-0.078	> 0.05	47	-0.085	> 0.05	48	-0.166	> 0.05	48	-0.157	> 0.05
Week 48	42	-0.122	> 0.05	42	-0.145	> 0.05	42	-0.201	> 0.05	42	-0.228	> 0.05
Change from Baseline in TBLH BMD Height-age Z-Score												
Week 24	50	0.093	> 0.05	50	0.043	> 0.05	51	-0.008	> 0.05	51	0.026	> 0.05
Week 48	44	0.026	> 0.05	44	-0.104	> 0.05	44	0.096	> 0.05	44	0.081	> 0.05
Change from Baseline in Spine BMD												
Week 24	47	-0.119	> 0.05	47	-0.062	> 0.05	48	-0.071	> 0.05	48	-0.061	> 0.05
Week 48	42	-0.145	> 0.05	42	-0.075	> 0.05	42	-0.064	> 0.05	42	-0.070	> 0.05
Change from Baseline in Total Body Less Head BMD												
Week 24	50	0.193	> 0.05	50	0.221	> 0.05	51	0.104	> 0.05	51	0.175	> 0.05
Week 48	44	-0.014	> 0.05	44	0.006	> 0.05	44	0.296	> 0.05	44	0.312	0.0392
Change from Baseline in eGFR by Schwartz Formula												
Week 24	78	0.060	> 0.05	78	0.061	> 0.05	80	0.099	> 0.05	80	-0.014	> 0.05
Week 48	68	-0.193	> 0.05	68	-0.184	> 0.05	69	-0.026	> 0.05	69	-0.142	> 0.05
Change from Baseline in Serum Creatinine												
Week 24	78	-0.163	> 0.05	78	-0.154	> 0.05	80	-0.178	> 0.05	80	-0.108	> 0.05
Week 48	68	0.061	> 0.05	68	0.031	> 0.05	69	0.112	> 0.05	69	0.146	> 0.05

BMD = bone mineral density. TBLH = total body less head. The correlation coefficients and p-values were derived from Pearson's correlation between change from baseline in safety endpoints and log-transformed PK parameters.
For bone safety endpoints (spine BMD height-age Z-score, TBLH BMD height-age Z-score, spine BMD and total body less head BMD), the data from studies GS-US-216-0128 Cohort 2 and Cohort 3, GS-US-292-0106 Cohort 2 and Cohort 3, and GS-US-311-1269 Cohort 2 Group 1 and Cohort 2 Group 2 were included.
For renal safety endpoints (eGFR by Schwartz formula and serum creatinine), the data from studies GS-US-216-0128 Cohort 2 and Cohort 3, GS-US-292-0106 Cohort 2 and Cohort 3, GS-US-311-1269 Cohort 2 Group 1 and Cohort 2 Group 2, and GS-US-380-1474 Cohort 2 and Cohort 3 were included.

2.6.2. Discussion on clinical pharmacology

The scored DRV/COBI/FTC/TAF 675/150/200/10-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 675/150/200/10-mg FDC film-coated tablet is based on the clinical development programs of the single agents of DRV, COBI, FTC and TAF 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/FTC/TAF 675/150-mg FDC film-coated tablet that is bioequivalent to the single agents of DRV, COBI, FTC/TAF administered concomitantly as the commercially available tablet formulations (DRV 1x600-mg and 1x75-mg tablet + COBI 1x150-mg tablet + FTC/TAF 1 x 200/10 mg). 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.

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.

The PK results showed that DRV, COBI, FTC and TAF administration as a scored FDC tablet (DRV/COBI/TFC/TAF 675/150/200/10 mg) was bioequivalent to the coadministration as the separate available tablet formulations (DRV 1x600 mg + 1x75-mg tablet + COBI 1x150 mg tablet + TFC/TAF 1 x 200/10 mg tablet), under fed conditions. For all 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%. Although the high intra-individual variability observed for TAF, also for TAF 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%.

The PopPK simulations show that for paediatric patients in the weight band ≥ 25 to <40 kg a DRV/COBI regimen of 675/150 mg qd results in comparable or slightly higher (up to 34% higher at 25 kg) DRV AUC_{0-24h} and comparable or slightly lower (up to 33% lower at 39 kg) DRV C_{0h} with respect to adults.

Distribution plots of DRV AUC_{0-24h} and C_{0h} in paediatric patients compared to adults (study FD2HTX3001) were provided. Plots with observed data show that the model predictions and observed data are aligned.

In study GS-US-216-0128, based upon non-compartmental data, for COBI, FTC, TAF and TFV, a higher exposure was observed in paediatric subjects compared to adults. For COBI this was a known observation based upon previous data and considered not of safety concern. For FTC, the observed higher FTC exposure is mainly driven by the lower bodyweight, however, exposures overlap with dose in adolescents and adults, and the 200 mg FTC dose is approved for use in adults and paediatric patients weighing at least 25 kg, in combination with other antiretrovirals. For TAF and TFV this was mainly driven by a difference in administered dose, i.e., 25 mg in paediatric subjects and 10 mg in adults. Taking into account the difference in dose, an overlap in exposure is observed, although it is acknowledged that this dose normalisation of the data may include an uncertainty, as the actual 10 mg dose has not been studied. TAF 10 mg is recommended for use with agents requiring a PK enhancer, such as DRV. The data has been sufficiently worded in the SmPC section 5.2 for the current procedure. As the applicant indicated that a separate Type II Variation with the Interim CSR for Study GS-US-216-0128 describing the 48-week data will be submitted (PIP study). In this submission, the applicant should consider including PK data in paediatric subjects showing the actual and/or estimated values of all relevant analytes (including TFV) in a tabular form in the SmPC section 5.2, rather than a general description, to allow readers to understand better that the systemic exposure is comparable and how this has been concluded.

2.6.3. Conclusions on clinical pharmacology

Overall, the available PK data and PopPK modelling, indicate that PK exposures for the components of the D/C/F/TAF 675/150/200/10-mg FDC in children (aged ≥ 6 years and weighing ≥ 25 to <40 kg) are comparable to those observed for the D/C/F/TAF 800/150/200/10-mg FDC in adults and adolescents (aged ≥ 12 years and weighing ≥ 40 kg). Together with the bioequivalence of the D/C/F/TAF 675/150/200/10-mg FDC formulation versus single components (Study FD2HTX1007), this supports the extrapolation of established clinical safety data from adults and adolescents to the younger paediatric population.

The data has been sufficiently worded in the SmPC section 5.2 for the current procedure. As the applicant indicated that a separate Type II Variation with the Interim CSR for Study GS-US-216-0128 describing the 48 week data will be submitted (PIP study). In this submission, the applicant should consider including PK data in paediatric subjects showing the actual and/or estimated values of all relevant analytes (including TFV) in a tabular form in the SmPC section 5.2, rather than a general description, to allow readers to understand better that the systemic exposure is comparable and how this have been concluded.

2.6.4. Clinical efficacy

Table 7. Overview of main clinical studies

Study (Phase, Status)	Description	Treatment	# Participants	Main Endpoints
GS-US-216-0128 (Phase 2/3, ongoing) Cohort 2 ^a	DRV/COBI + F/TAF FDC in HIV-1-infected, ART-experienced, virologically suppressed ^b children (≥6 to <12 years and ≥25 to <40 kg)	DRV (dose based on body weight) ^c , COBI (150 mg) and F/TAF FDC (200/25 mg) ^d qd	N=9 ^e	• (1st) PK DRV, TAF, and TFV (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), TAF (AUC_{last}, C_{max}, C_{last}, CL/F, V_z/F), FTC (AUC_{last}, AUC_{tau}, C_{max}, C_{tau}, CL/F, V_z/F), TFV (AUC_{last}, C_{max}, C_{tau}, CL/F, V_z/F) • (2nd) Virologic response at Weeks 24 and 48 • (2nd) Change in CD4+ cell count and CD4+ percentage at Weeks 24 and 48 • (2nd) Safety over 48 weeks • (2nd) Acceptability and palatability of COBI and F/TAF FDC through Week 48
TMC114FD2HT X1006 (Phase 1, completed)	Scored film-coated D/C/F/TAF FDC tablet administered as a placebo-matched tablet in HIV-1-infected children (≥6 to <12 years and ≥25 to <40 kg)	Placebo ^f single dose	N=24 ^g	Ease and acceptability of swallowing the D/C/F/TAF FDC placebo-matched tablets ^h

^a Data from Cohort 2 described are based on Interim Analysis 3 (data cutoff date: 30 January 2024) of Study GS-US-216-0128, including 9 participants in Cohort 2 who received DRV/COBI + F/TAF FDC and who had completed at least Week 24 on the study at the data cutoff date for Interim Analysis 3. Data from participants who received ATV/COBI + F/TAF FDC in Cohort 2 are included in Interim Analysis 3 but are not relevant for this submission. For the purpose of Interim Analysis 3, all participants were enrolled following the implementation of Protocol Amendment 7, 8, or 9.

^b Although Protocol Amendment 8 allowed enrollment of viremic participants (HIV-1 RNA ≥50 copies/mL) in Cohort 2, all 9 participants enrolled in Cohort 2 for which data are described in this Clinical Overview Addendum were virologically suppressed.

^c The recommended daily dosage of DRV based on body weight according to the local Product Information was to be given and was not to exceed the recommended adult dosage.

^d The dose of TAF in the 200/25-mg F/TAF FDC used in the study was higher than in the D/C/F/TAF 675/150/200/10-mg FDC of interest (25 mg versus 10 mg)

^e Participants included in the SAS. For the definitions of analysis sets, refer to Mod2.7.3/Sec1.2.1.

^f Placebo tablet similar 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.

^g 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.

^h Irrespective of the mode of intake (as a whole or as a split tablet).

2.6.4.1. 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 rtv for patients weighing ≥30 to <40 kg. COBI 150 mg qd was shown to be generally safe and well-tolerated throughout its development and increased 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 E/C/F/TAF 150/150/200/10-mg FDC (Genvoya SmPC 2022), ie, for use in patients weighing ≥25 kg.

F/TAF 200/10 mg and F/TAF 200/25 mg are approved for treatment of HIV-1 infection in the EU in combination with other ARV agents for the treatment of HIV-1 infection in adults and adolescents aged ≥12 years, with a weight ≥35 kg (Descovy SmPC 2023). This formulation contains the same dose of FTC as in the approved Truvada FDC (FTC/TDF 200/300 mg) for use in the same indication (Truvada

SmPC 2024) and as Emtriva, approved for use in adults and children from 4 months and older (Emtriva SmPC 2023). TAF 25 mg is recommended for use with an ART not requiring a PK enhancer, and TAF 10 mg for use with an ART requiring a PK enhancer, such as DRV (Descovy SmPC 2023). TAF 10 mg is also approved as part of the E/C/F/TAF 150/150/200/10 mg FDC for use in adults and paediatric patients weighing ≥ 25 kg (Genvoya SmPC 2022).

Based on the PopPK simulations, no clinically meaningful differences in exposure of the components of the D/C/F/TAF FDC in paediatric patients compared to exposure of these components in adults and adolescents were observed.

2.6.4.2. Main study(ies)

3.3.1. 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 Paediatric Subjects

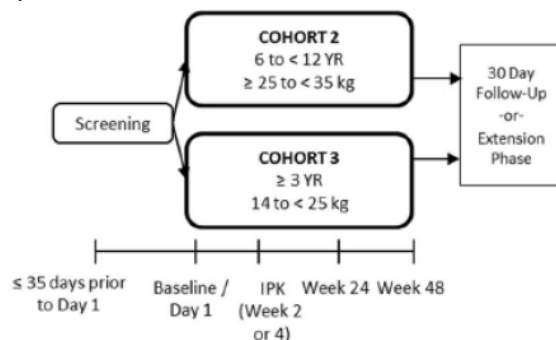
Methods

This is an open-label, multicenter, multicohort study evaluating PK, safety, and efficacy of COBI in combination with ATV or DRV with or without F/TAF (Cohorts 1 to 4); and the PK, safety, and efficacy of F/TAF in participants on an F/TAF-containing ARV regimen (Cohorts 2 to 5) in HIV-infected paediatric participants.

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

A total of approximately 130 paediatric participants ages ≥ 4 weeks to < 18 years will be enrolled to receive study drugs, as defined as below, for 48 weeks plus an additional optional long-term extension (OLE).

Figure 2. Study schema



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

Cohort 2: $n \geq 23$

After Protocol Amendment 9, Cohort 2 weight range will be modified to ≥ 25 to < 40 kg. Participants enrolled within the original weight band (≥ 25 to < 35 kg) will be part of Cohort 2 Group 1 and will receive ATV/co or DRV/co + F/TAF. Participants weighing ≥ 35 to < 40 kg will be enrolled in Cohort 2 Group 2 and will receive DRV/co + F/TAF.

Group 1: $n \geq 23$ (minimum of $n = 14$ on ATV/co + F/TAF and minimum of $n = 9$ on DRV/co + F/TAF).

Group 2: No minimum number for Group 2 receiving DRV/co + F/TAF is specified.

Participants will enroll as follows:

Cohort #	Group	Age Range	Weight Range	ATV/co + F/TAF	DRV/co + F/TAF
2	Group 1	6 to < 12 years	≥ 25 to < 35 kg	n ≥ 14	n ≥ 9
	Group 2		≥ 35 to < 40 kg	Not applicable	No minimum

For Cohort 2, once the minimum number of participants taking ATV/co or DRV/co completes their IPK visit, data from the respective treatment may be analysed.

Replacement participants may be enrolled for participants whose IPK data are not evaluable, or who do not complete all IPK procedures for reasons other than discontinuation due to treatment-related AEs. Participants who discontinue due to treatment-related AEs will not be replaced.

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 <40 kg at screening
- Stable antiretroviral regimen 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 must be on once daily dosing or must switch to once daily at or prior to Day 1. Participants in Cohorts 2 and 3 will switch their NRTI backbone to F/TAF.
 - Participants undergoing dose modifications to their ARV regimen for growth or who were switching medication formulations were considered to be on a stable ARV regimen.
 - 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 $\geq$ 50 copies/mL and on a stable regimen.
- For virologically suppressed participants, unconfirmed virologic elevations of $\geq$ 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.
- Adequate hematologic and hepatic function.
- Adequate renal function: eGFR $\geq$ 90 mL/min/1.73 m² using the Schwartz formula.

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

- Screening CD4 cell count $<$ 200 cells/ μ l
- 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 8).

Table 8. GS-US-216-0128: Summary of Study Treatments

	Treatment Regimen
Cohort 2 ($\geq$ 6 to $<$ 12 years of age, weighing $\geq$ 25 to $<$ 40 kg)	COBI 150-mg tablet + F/TAF 200/25-mg tablet + ATV ^a or DRV ^a

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

Objectives

The primary objectives, related to DRV/co or (F)/TAF, 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 $\geq$ 25 to $<$ 40 kg (6 to $<$ 12 years of age)
- To evaluate the steady-state PK of TAF and confirm the dose of F/TAF in HIV-1 infected paediatric participants weighing $\geq$ 25 to $<$ 40 kg (6 to 12 years of age)
- To evaluate the safety and tolerability of DRV/co and F/TAF through 24 weeks in paediatric participants with HIV-1 weighing $\geq$ 25 to $<$ 40 kg (6 to $<$ 12 years of age)

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

- To evaluate the efficacy of DRV/co and F/TAF through 24 weeks in paediatric participants with HIV-1 weighing $\geq$ 25 to $<$ 40 kg (6 to $<$ 12 years of age)

- To evaluate the safety, tolerability, and efficacy of DRV/co and F/TAF through 48 weeks in paediatric participants with HIV-1 weighing ≥ 25 to < 40 kg (6 to < 12 years of age)

Outcomes/endpoints

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

- PK parameter AUCtau for DRV, tenofovir alafenamide (TAF), and tenofovir (TFV)
- The incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities through Week 24

The secondary endpoints, related to DRV/co and F/TAF, 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
 - AUClast, Cmax, Clast, CL/F, and Vz/F for TAF
 - AUClast, AUCtau, Cmax, Ctau, CL/F, and Vz/F for emtricitabine (FTC)
 - AUClast, Cmax, Ctau, CL/F, and Vz/F for TFVI
- 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/ μ L), 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 $\geq 96\%$ 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 9).

Table 9. Sample Size and Power for Analytes DRV and TAF (Used With DRV) for Cohort 2 and Cohort 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%

- 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 March 27, 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 PBMC PK Analysis Set included all participants who (1) are enrolled into the study, (2) have received at least 1 dose of study drug and (3) have at least 1 nonmissing concentration data of TFV-DP. The PBMC PK Analysis Set will be used for PK analyses of TFV-DP.

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 $\geq$ 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, $\geq$ 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/ μ L) 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 10. A total of 9 participants were enrolled and received at least 1 dose of study drug. At the Week 24 data-cut date (30 January 2024), 3 (33.3%) participants had completed the main (48-week treatment) phase and had entered the extension phase. Six (66.6%) participants were on the study drug in the main phase. No participants had discontinued treatment due to efficacy-related reasons.

Table 10. Disposition of Participants in Study GS-US-216-0128 (Cohort 2); All Screened Participants

	Cohort 2
Participants enrolled, N	9
Main Phase (48-week Treatment Phase)	
Participants who completed study drug, n (%)	3 (33.3)
Participants Still on Study up to the Data Cut Date, n (%)	6 (66.7)
Participants who prematurely discontinued study drug, n (%)	0 (0.0)
Withdrew consent	3 (37.5)
Extension Phase	
Participants who entered Extension Phase, n (%)	3 (33.3)
Participants still on study drug up to the data cutoff date	3 (100.0)

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 [GS-US-216-0128-Interim Analysis 3 Clinical Study Report/Table 15.8.1.3.1](#).

Recruitment

First participant first visit: 11 May 2017. Data-cut date/last participant last visit for this report: 30 January 2024.

Participants included in this interim analysis were enrolled at 6 sites in South Africa, 1 site in the United States of America, and 1 site in Zimbabwe.

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 11.

The median (range) age was 10 (8; 12) years and median (range) weight was 29.0 (25.2; 39.7) kg. The study included 88.9% female participants and 88.9% black participants.

All participants were virologically suppressed at baseline (HIV 1 RNA <50 copies/mL). The median (range) baseline CD4+ cell count was 929 (584; 1,232) cells/μL and all participants had a baseline CD4+ cell count ≥350 cells/μL. The median (range) baseline CD4+ percentage was 36.2 (31.0; 43.9)%. The median (range) time since HIV 1 diagnosis was 9.0 (5.0; 11.0) years. The most common mode of HIV-1 infection was vertical transmission (8 [88.9%] participants). Eight out of 9 participants were asymptomatic.

Table 11. Main Demographic and Baseline Characteristics, and Baseline HIV Disease Characteristics in Study GS-US-216-0128 (Cohort 2); SAS

	Cohort 2 (N=9)
Main Demographic and Baseline Characteristics	
Age (years)	
Mean (SD)	10 (1.4)
Median	10
IQ range	(9; 11)
Range	(8; 12)
Sex at birth, n (%)	
Male	1 (11.1)
Female	8 (88.9)
Race, n (%)	
American Indian or Alaska Native	0
Asian	0
Black	8 (88.9)
Native Hawaiian or Pacific Islander	0
White	0
Other	1 (11.1)
Baseline Weight (kg)	
Mean (SD)	29.9 (4.76)
Median	29.0
IQ range	(26.0; 31.6)
Range	(25.2; 39.7)
Main Baseline HIV Disease Characteristics	
HIV-1 RNA categories (copies/mL), n (%)	
<50	9 (100.0)
≥50	0
CD4+ cell count (/μL)	
Mean (SD)	898 (208.9)
Median	929
IQ range	(773; 1,029)
Range	(584; 1,232)
CD4+ percentage (%)	
Mean (SD)	37.0 (5.41)
Median	36.2
IQ range	(31.6; 42.7)
Range	(31.0; 43.9)
HIV disease status, n (%)	
Asymptomatic	8 (88.9)
Symptomatic HIV infection	1 (11.1)
AIDS	0
Years since participant diagnosed with HIV	
Mean (SD)	8.1 (2.09)
Median	9.0
IQ range	(7.0; 9.0)

Table 11. Main Demographic and Baseline Characteristics, and Baseline HIV Disease Characteristics in Study GS-US-216-0128 (Cohort 2); SAS

	Cohort 2 (N=9)
Range	(5.0; 11.0)

Modified from [GS-US-216-0128-Interim Analysis 3 Clinical Study Report /Tab7](#) and [Tab8](#).

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 12. At Week 24 the percentage of participants with HIV-1 RNA <50 copies/mL in the FAS was 100% (9/9 participants). At Week 48 the percentage of participants with HIV-1 RNA <50 copies/mL in the FAS was 33.3% (3/9 participants), while 6 participants had not reached the Week 48 window by the data-cut date.

Table 12. 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

	DRV/COBI + F/TAF FDC (N=9)
FDA Snapshot Algorithm - Week 24	
Virologic Failure at Week 24, n (%)	0
Virologic Success at Week 24, n (%)	
HIV-1 RNA <50 copies/mL	9 (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	3 (33.3)
No Virologic Data in Week-48 Window, n (%)	
Did not Reach the Week-48 Window by the Data Cutoff Date	6 (66.7)

Week-24 window was between: Day 141 and 210 (inclusive). Week-48 window was between: Day 295 and 378 (inclusive).

Modified from [Mod5.3.5.2/GS-US-216-0128-W24-IA3-C2&3-CSR/Tab11](#) and [Tab12](#).

Source: [Mod5.3.5.2/GS-US-216-0128-W24-IA3-C2&3-CSR/Sec9.3.1](#).

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 13.

Table 13. 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

	N	DRV/COBI + F/TAF FDC (N=9)	
		Mean (SD)	Median (Range)
CD4+ Cell Count (cells/μL)			
Baseline	9	898 (208.9)	929 (584; 1,232)
Week 24	9	901 (261.0)	843 (506; 1,321)
Week 48	3	887 (247.4)	862 (653; 1,146)
Change From Baseline			
Change From Baseline at Week 24	9	3 (146.7)	72 (-267; 214)
Change From Baseline at Week 48	3	-133 (200.7)	-167 (-314; 83)
CD4+ Percentage (%)			
Baseline	9	37.02 (5.409)	36.20 (31.00; 43.90)
Week 24	9	37.69 (7.416)	39.80 (21.40; 45.70)
Week 48	3	37.93 (7.050)	35.40 (32.50; 45.90)
Change From Baseline			
Change From Baseline at Week 24	9	0.67 (4.871)	0.60 (-9.60; 8.70)
Change From Baseline at Week 48	3	-2.43 (7.850)	0.90 (-11.40; 3.20)

On-treatment data included all data collected up to 1 day after permanent discontinuation of study drug or all available data for participants who were still on study drug. Six participants had not reached the Week-48 window by the data cutoff date.

Modified from [Mod5.3.5.2/GS-US-216-0128-W24-IA3-C2&3-CSR/Tab15.9.3.1](#) and [Tab15.9.3.2](#).

Source: [Mod5.3.5.2/GS-US-216-0128-W24-IA3-C2&3-CSR/Sec9.3.3](#).

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.

2.6.4.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14. Summary of efficacy for trial GS-US-216-0128

Title: A Phase 2/3, Multicenter, Open-label, Multicohort Study Evaluating Pharmacokinetics (PK), Safety, and Efficacy of Cobicistat-boosted Atazanavir (ATV/co) or Cobicistat-boosted Darunavir (DRV/co) and Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1-Infected, Virologically Suppressed Paediatric Participants			
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:		48 weeks (Cohort 2)
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		30 days
Hypothesis	No formal statistical testing was planned		
Treatments groups	DRV/co + F/TAF		DRV/co + F/TAF, 48 weeks, N = 9
Endpoints and definitions	Secondary endpoint	Virologic response (snapshot)	Virologic success at Week 24: 9 (100.0)
			Virologic success at Week 48: 3 (33.3)
			No data in week 48 window: 6 (66.7)

Title: A Phase 2/3, Multicenter, Open-label, Multicohort Study Evaluating Pharmacokinetics (PK), Safety, and Efficacy of Cobicistat-boosted Atazanavir (ATV/co) or Cobicistat-boosted Darunavir (DRV/co) and Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1-Infected, Virologically Suppressed Paediatric Participants			
Study identifier	GS-US-216-0128 EU CT number: 2013-001402-28 NCT number: NCT02016924		
	Secondary endpoint	CD4+ cell count Median Change From Baseline	Week 24: 72 (-267; 214) Week 48: -167 (-314; 83)
Database lock	20 May 2024 (data cutoff date: 30 January 2024)		
Notes	None of the participants experienced virologic failure and none met criteria for postbaseline resistance testing		

2.6.4.4. Clinical studies in special populations

Not applicable

2.6.4.5. In vitro biomarker test for patient selection for efficacy

Not applicable

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

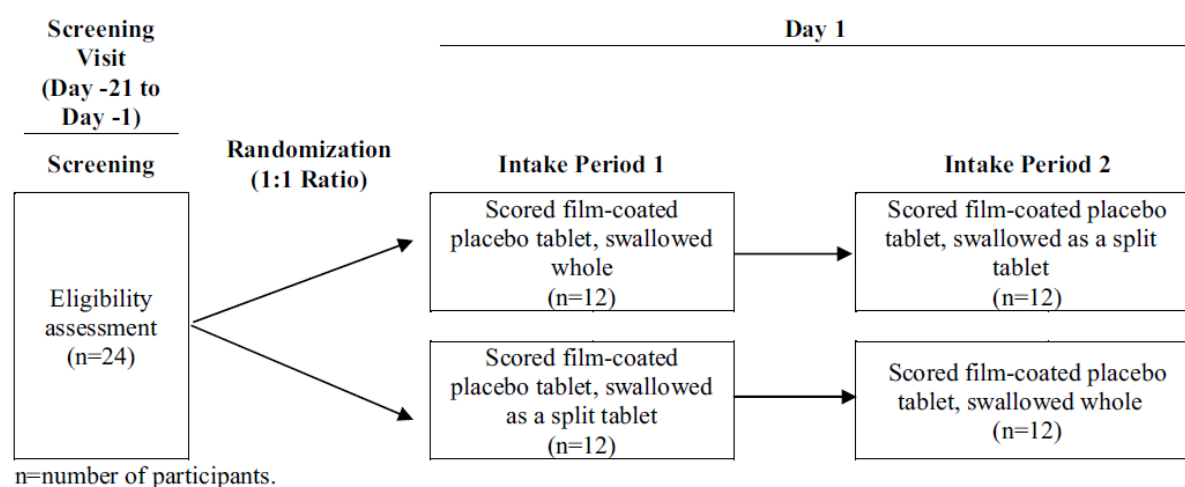
Not applicable

2.6.4.7. 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.

Study design: 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 3 for a schematic overview of the study.

Figure 3. Schematic Overview of the Study (Study TMC114FD2HTX1006)



Treatments: 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).

Participants: 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.

Objectives: 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: 1) 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, 2) to assess the ease of splitting the placebo-matched scored film-coated D/C/F/TAF FDC tablet.

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).

Outcomes

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 15. 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 15. 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)

Table 15. 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

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 16.

Table 16. Swallowability/Acceptability Questionnaires (Participant); Intent-to-treat (TMC114FD2HTX1006)

Questionnaire Response	Current ARV Treatment (N=24) n (%)	D/C/F/TAF FDC-Whole (N=24) n (%)	D/C/F/TAF FDC-Split (N=24) n (%)
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 17. 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 17. Swallowability/Acceptability Questionnaires (Caregiver); Intent-to-treat (TMC114FD2HTX1006)

Questionnaire Response	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 (%)
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](#)

2.6.5. Discussion on clinical efficacy

In support of the current variation, data from Interim Analysis 3 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+F/TAF or DRV/co+F/TAF administered in HIV-1 infected treatment-experienced, virologically suppressed paediatric subjects. Only data from Cohort 2 receiving DRV/co + F/TAF is taken into consideration. A total of 9 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. No clinical data has been generated in patients < 30 kg, as patients with a body weight between 25 and 30 kg received 600mg DRV in Study 216-0128 Cohort 2. 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 AUC_{0-24h,ss} and similar or slightly lower DRV C_{0h,ss} compared to adults. The 200/10 mg F/TAF regimen is already approved for use in paediatric patients 6-12 years of age as part of the Genvoya fixed dose combination regimen. Overall, a D/C/F/TAF 675/150/200/10-mg qd dosing regimen for the weight-band ≥ 25 to < 40 kg in paediatric patients could be acceptable. However, some concerns regarding higher exposures should be adequately addressed (see PK section).

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. The study is part of the agreed PIP.

The efficacy outcomes that have been generated are supportive of the use of Symtuza in HIV-1 infected, virologically suppressed paediatric subjects. All 9 participants in Cohort 2 remained

virologically suppressed and none experienced virologic failure. The changes in CD4+ cell count are 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 not considered of consequence in this assessment, it should be noted that 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.

2.6.6. Conclusions on clinical efficacy

The available efficacy data from Study 216-0128 Cohort 2 are supportive of the use of D/C/F/TAF in HIV-1-infected, virologically suppressed paediatric patients aged ≥ 6 to <12 years and weighing ≥ 25 to <40 kg. All 9 participants remained virologically suppressed and no virologic failures were reported.

Taking into account the established efficacy of D/C/F/TAF in adults and adolescents, and provided that the PK assessment confirms no clinically relevant differences in exposure between the components of the D/C/F/TAF 800/150/200/10 mg FDC in adults/adolescents and the scored D/C/F/TAF 675/150/200/10 mg FDC in children, a similar efficacy profile is expected in the proposed paediatric population.

Overall, no efficacy concerns have been identified based on the data submitted in the current application

2.6.7. Clinical safety

In support of the current variation, safety data from Interim Analysis 3 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.

2.6.7.1. Patient exposure

The median (range) duration of exposure to DRV/COBI + F/TAF FDC was 45.1 (26.3; 131.1) weeks in Study 216-0128 (Cohort 2). All 9 subjects were treated for at least 24 weeks. Six (6) subjects at least reached 36 weeks, 3 of these reached 60 weeks, 2 of these reached 96 weeks and the last subject was treated for 108 weeks.

2.6.7.2. Adverse events

An overall summary of AEs in Study 216-0128 (Cohort 2) through the data cutoff date is provided in Table 18.

No deaths, AEs leading to premature study drug discontinuation, SAEs, or Grade ≥ 3 AEs were reported. In total 8/9 participants (88.9%) reported at least 1 AE, all of which were Grade 1 or Grade 2 in severity. Three (33.3%) participants experienced AEs considered related to study drug by the

investigator: Grade 2 vomiting (1 participant), Grade 1 vomiting (1 participant), and Grade 1 headache (1 participant).

The most frequently reported AEs by PT were: vomiting and headache (each for 2 [22.2%] participants).

Table 18. Overall Summary of Adverse Events in Study GS-US-216-0128 (Cohort 2); SAS

	Cohort 2 (N=9)
Participants experiencing any AE, n (%)	8 (88.9)
Any Grade ≥ 2	4 (44.4)
Any Grade ≥ 3	0
Participants experiencing any AE related to study drug, n (%)	3 (33.3)
Any Grade ≥ 2	1 (11.5)
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-W24-IA3-C2&3-CSR/Tab46](#).

Source: [Mod5.3.5.2/GS-US-216-0128-W24-IA3-C2&3-CSR/Sec11.3](#).

Table 19. Adverse Events Reported For >1 (12.5%) Participant by Preferred Term in Study GS-US-216-0128 (Cohort 2); SAS

	Cohort 2 (N=9)
Participants with 1 or more AE, n (%):	8 (88.9)
Participants with 1 or more AE, by PT, n (%):	
Vomiting	2 (22.2)
Headache	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 2 vomiting [1 participant]; and Grade 1 vomiting [1 participant] and Grade 1 headache [1 participant]).

No new ADRs were identified.

2.6.7.3. Serious adverse events, deaths, and other significant events

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

Bone-related AEs and laboratory tests

No fracture AEs were reported.

Overall, spine and TBLH BMD and height-age BMD Z-scores increased relative to baseline through Week 120 (Table 20). Shifts in spine and TBLH height-age BMD Z-scores from >-2 at baseline to ≤ -2 at some point postbaseline were observed in 1 participant.

Table 20. Spine and TBLH BMD at Baseline and Percentage Change From Baseline, and Height-Age BMD Z-Scores at Baseline and Change From Baseline in Study GS-US-216-0128 (Cohort 2, DRV/COBI + F/TAF FDC subgroup); Spine and TBLH DXA Analysis Sets

	Spine		TBLH	
	N	Median (Q1; Q3)	N	Median (Q1; Q3)
BMD				
Baseline (g/cm ²)	8	0.57 (0.55; 0.60)	9	0.66 (0.64; 0.67)
% change at Week 24	8	3.36 (1.59; 4.68)	9	1.52 (0.00; 3.13)
% change at Week 48	6	4.59 (1.64; 12.50)	6	6.06 (4.55; 9.38)
% change at Week 72	3	24.53 (8.57; 25.00)	3	14.06 (13.64; 16.13)
% change at Week 96	2	24.64 (17.14; 32.14)	2	20.81 (18.18; 23.44)
% change at Week 120	1	28.57 (28.57; 28.57)	1	27.27 (27.27; 27.27)
BMD Z-Score (Height-Age)				
Baseline	8	-1.15 (-1.74; 0.20)	9	-1.15 (-1.93; -0.41)
Change at Week 24	8	0.07 (-0.20; 0.17)	9	-0.18 (-0.27; 0.03)
Change at Week 48	6	-0.11 (-0.27; 0.08)	6	-0.09 (-0.19; -0.08)
Change at Week 72	3	0.26 (-0.45; 0.38)	3	0.29 (0.00; 0.34)
Change at Week 96	2	0.06 (-0.36; 0.48)	2	0.43 (0.25; 0.61)
Change at Week 120	1	0.14 (0.14; 0.14)	1	0.86 (0.86; 0.86)

Modified from [Mod5.3.5.2/GS-US-216-0128-W24-IA3-C2&3-CSR/Tab15.11.9.1.1](#) (spine BMD), [Tab15.11.9.1.2](#) (TBLH BMD), [Tab15.11.9.1.5](#) (spine BMD Z-Score [Height-Age]), and [Tab15.11.9.1.6](#) (TBLH BMD Z-Score [Height-Age]).

Source: [Mod5.3.5.2/GS-US-216-0128-W24-IA3-C2&3-CSR/Sec11.4.1.2](#).

Renal-related Adverse Events and Laboratory Tests

No renal-related AEs (including Fanconi syndrome) were reported.

A gradual increase from baseline in serum creatinine was observed at most time points after Week 4. A decrease from baseline in eGFR_{Schwartz} was observed from Week 4 onwards (Table 21). This decrease was not considered clinically relevant in view of its stabilization and the high eGFR_{Schwartz} values in the 2 participants who already reached Week 96 (124.25 mL/min/1.73m² and 222.89 mL/min/1.73m²).

No Grade 3 or 4 serum creatinine laboratory abnormalities were observed.

Table 21. Changes From Baseline in Serum Creatinine and eGFR_{Schwartz} in Study GS-US-216-0128 (Cohort 2, DRV/COBI + F/TAF FDC subgroup)

	N	Median (Q1; Q3)
Serum Creatinine (mg/dL)		
Baseline	9	0.52 (0.50; 0.54)
Change at Week 1	9	-0.01 (-0.07; 0.01)
Change at Week 4	9	0.02 (-0.06; 0.07)
Change at Week 8	9	0.02 (-0.03; 0.06)
Change at Week 24	9	0.04 (-0.04; 0.09)
Change at Week 48	3	0.06 (0.01; 0.32)
Change at Week 96	2	0.01 (-0.12; 0.14)
eGFR_{Schwartz} (mL/min/1.73m²)		
Baseline	9	144.02 (121.72; 152.20)
Change at Week 1	9	2.39 (-2.66; 27.81)
Change at Week 4	9	-4.80 (-10.77; 20.82)
Change at Week 8	9	-5.64 (-13.87; 12.88)

Table 21. Changes From Baseline in Serum Creatinine and eGFR_{Schwartz} in Study GS-US-216-0128 (Cohort 2, DRV/COBI + F/TAF FDC subgroup)

	N	Median (Q1; Q3)
Change at Week 24	9	-7.28 (-22.94; 8.10)
Change at Week 48	3	-7.44 (-52.35; 6.03)
Change at Week 96	2	23.58 (-21.08; 68.23)

Source: [Mod5.3.5.2/GS-US-216-0128-W24-IA3-C2&3-CSR/Tab15.11.6.2.8](#) (serum creatinine) and [Tab15.11.6.2.22](#) (eGFR_{Schwartz}).

Lipid-related Adverse Events and Laboratory Tests

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

Median fasting values over time of total cholesterol, direct LDL cholesterol, HDL cholesterol, total cholesterol:HDL cholesterol ratio, and triglycerides were generally within normal reference ranges. All graded fasting lipid laboratory abnormalities were Grade 1 or Grade 2.

Glucose-related Adverse Events and Laboratory Tests

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

Median values remained within normal ranges. All graded fasting and nonfasting glucose laboratory abnormalities were Grade 1 or Grade 2 in severity.

Liver-related Adverse Events and Laboratory Tests

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

Median values over time of total bilirubin, direct bilirubin, indirect bilirubin, amylase, ALP, ALT, AST, and lipase were generally within normal reference ranges. No participants had elevations in AST, ALT, total bilirubin, or ALP. No Hy's Law cases were identified. A Grade 3 laboratory abnormality of increased amylase was observed in 1 participant with a Grade 2 result at baseline.

Other Adverse Events and Vital Signs

No **cardiovascular-** or **vital signs-**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).

2.6.7.4. Safety in special populations

Not applicable

2.6.7.5. Immunological events

Not applicable

2.6.7.6. Safety related to drug-drug interactions and other interactions

Not applicable

2.6.7.7. Discontinuation due to adverse events

No AEs leading to study drug discontinuation were reported in Cohort 2.

2.6.7.8. Post marketing experience

Based on the 133,674,452 D/C/F/TAF 800/150/200/10-mg FDC film-coated tablets that were distributed worldwide by the Applicant from launch through 31 August 2024, the estimated exposure to the D/C/F/TAF 800/150/200/10-mg FDC is 366,430 person-years, of which 181,701 person-years reflect exposure in the EU.

PBRERs/PSURs have been generated for the D/C/F/TAF 800/150/200/10-mg FDC covering the period from 21 September 2017 to 20 September 2024, summarising the post marketing safety data obtained by the Applicant. 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 D/C/F/TAF 800/150/200/10-mg FDC continues to demonstrate a favourable benefit-risk profile for its authorised indications.

2.6.8. Discussion on clinical safety

In support of the current variation, safety data from Interim Analysis 3 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 +F/TAF or DRV/co +F/TAF administered in HIV-1 infected treatment-experienced, virologically suppressed paediatric subjects. A total of 9 participants were enrolled and received at least 1 dose of study drug. At the data cut-off date (30 January 2024), 3 (33.3%) participants had completed the main (48-week treatment) phase and had entered the extension phase. At the data cutoff date, all participants who had completed the main phase were continuing to receive study drug in the extension phase. The median (Q1, Q3) duration of exposure to DRV/COBI + F/TAF FDC in Cohort 2 was 45.1 (26.3; 131.1) weeks.

As such, exposure is too limited to reliably assess the safety profile in paediatric patients 6 to 12 years of age. Rather, safety is inferred based on similar exposures as observed in adults and adolescents.

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 2 vomiting [1 participant]; Grade 1 vomiting [1 participant]; and Grade 1 headache [1 participant]). Vomiting and headache are already listed as adverse reactions in section 4.8 of the SmPC. Overall, no new ADRs were identified.

No AEs related to either bone or renal safety endpoints were observed in this small group of paediatric patients. Both spine and TBLH BMD increased relative to baseline through Week 120. Shifts in spine and TBLH height-age BMD Z-scores from >-2 at baseline to ≤ -2 at some point postbaseline were observed in 1 participant. There was an initial small increase in serum creatinine, which stabilised with median values remaining within the normal range. A decrease from baseline in eGFRSchwartz was observed from Week 4 onwards, which did not lead to substantial adverse events or renal laboratory measurements out of reference range. No exposure-response relationship with F/TAF and bone or renal events was observed. However, the data available for this analysis was limited and no firm conclusions can be drawn. Of note, the same C/F/TAF dose has been approved for another HIV FDC (E/C/F/TAF) in paediatric patients weighing at least 25 kg, with similar exposures observed as for DRV/COBI + F/TAF.

2.6.9. Conclusions on clinical safety

Overall, no clinically relevant differences in PK exposures of the components of the D/C/F/TAF 800/150/200/10 mg FDC film-coated tablet (in adults and in adolescents aged ≥ 12 to <18 years and

weighing ≥ 40 kg) and the components of the scored D/C/F/TAF 675/150/200/10-mg FDC film-coated tablet (in children aged ≥ 6 to < 12 years and weighing ≥ 25 kg) were observed, therefore a similar safety and efficacy profile is expected.

No safety concerns have been raised by the data submitted in the current application.

2.7. Risk management plan

2.7.1. Safety Specification

2.7.1.1. Summary of safety concerns

The applicant 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	None

2.7.1.2. 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 applicant. This is agreed.

2.7.1.3. Conclusions on the safety specification

Having considered the data in the safety specification

It is agreed that the safety concerns listed by the applicant are appropriate.

2.7.2. Pharmacovigilance plan

2.7.2.1. Summary of planned additional PhV activities from RMP

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

Study & Status	Summary of Objectives	Safety Concern(s) 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				

No changes to the Pharmacovigilance plan were proposed by the applicant. This is agreed.

2.7.2.2. Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

2.7.3. Risk minimisation measures

2.7.3.1. Routine Risk Minimisation Measures

Not applicable.

No changes were proposed by the applicant. This is agreed.

2.7.3.2. Additional risk minimisation measures

Not applicable.

No changes were proposed by the applicant. This is agreed.

2.7.3.3. Overall conclusions on risk minimisation measures

The PRAC Rapporteur, having considered the data submitted and the empty list of safety concerns in Part II of the RMP, was of the opinion that the routine risk minimisation measures are sufficient to minimise the risks of the product.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 9.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. 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.

2.9. Product information

The MAH took the opportunity to update section 4.4 and 4.8 to include information on reductions in BMD of the spine and of the TBLH $\geq 4\%$ have been reported in paediatric patients receiving other tenofovir alafenamide containing products for 48 weeks.

The MAH took the opportunity to update section 4.6 of the SmPC to include information on the excretion of tenofovir alafenamide in human milk, based on the outcome of the PSUR assessment for Biktarvy EU/1/18/1289 (EMA/PSUR/0000274445), which is applicable to products containing tenofovir alafenamide, including fixed-dose combinations.

2.9.1. User consultation

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

1. The patient information leaflet (PIL) for the Symtuza 800/150/200/10 mg FDC tablet (adult and adolescent indication) has been created starting from the approved REZOLSTA (DRV/COBI 800/150 mg FDC) PIL and additional information, mainly triggered by the emtricitabine and tenofovir alafenamide in the FDC, has been added (DESCOVY (F/TAF) PIL was used where possible). The REZOLSTA PIL is based on the PREZISTA PIL (the “parent”) and includes cobicistat specific language based on the approved TYBOST (COBI) PIL. A justification for not performing user testing for Symtuza was included in the initial Marketing Authorisation Application that has been approved on 21 September 2017.
2. For the extension of the indication of REZOLSTA to adolescents (procedure EMEA/H/C/002819/II/0033) and to paediatric subjects aged ≥ 6 years and weighing at least 25 kg (ongoing procedure EMEA/H/C/002819/X/0054/G), 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 and to the fact that the PIL for REZOLSTA has a similar format as the PIL for PREZISTA 75 mg tablets. The extension of the indication of PREZISTA for children ≥ 6 years was approved on 23 June 2009 (procedure EMEA/H/C/000707/X/20) based on the user testing in 20 participants, ages 14 through 18 years of age. EMA acknowledged that it was not relevant to collect data in children below the age of 14. The Symtuza PIL has a similar format as the REZOLSTA PIL.
3. The proposed updated indication for Symtuza 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 675/150/200/10 mg FDC tablet.
4. 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, COBI and F/TAF in ARV treatment-naïve and treatment-experienced HIV-1 infected adults and adolescents.

3. Benefit risk assessment

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:

Symtuza 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 Symtuza (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, minimize 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 EoI 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 D/C/F/TAF 675/150/200/10 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 and F/TAF FDC from Cohort 2 (N=9) of study 216-0128, combining DRV (dose based on body weight, once daily), COBI (150 mg, once daily), and F/TAF (200/25 mg tablet, once daily) in HIV-1 infected, ART-experienced, virologically suppressed children aged ≥ 6 to < 12 years and weighing ≥ 25 kg.

Further, Study TMC114FD2HTX1006 (also referred to as FD2HTX1006) investigated the acceptability/swallowability the FDC film-coated tablet for use in children aged ≥ 6 to < 12 years using matching placebo tablets, which 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 Symtuza 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 available PK data and PopPK modelling indicate no clinically relevant differences in PK exposures between the components of the D/C/F/TAF 675/150/200/10 mg FDC in children (aged ≥ 6 years and weighing ≥ 25 to < 40 kg) and those of the D/C/F/TAF 800/150/200/10 mg FDC in adults and adolescents (aged ≥ 12 years and weighing ≥ 40 kg). Together with the demonstrated bioequivalence of

the 675/150/200/10 mg FDC formulation to the individual components (Study FD2HTX1007), this supports the extrapolation of established clinical safety data from adults and adolescents to the younger paediatric population.

All 9 participants in Cohort 2 remained virologically suppressed and non-experienced virologic failure.

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

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. The down extension 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 < 30 kg. However, three patients with a body weight between 25 and 30 kg received the 600 mg dose according to the protocol.

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 EoI application.

3.4. Unfavourable effects

The safety profile of Symtuza 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=9) did not give rise to new safety concerns.

AEs considered related to study drug were reported in 3 participants (Grade 2 vomiting [1 participant]; and Grade 1 vomiting [1 participant] and Grade 1 headache [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 the components are shown to be comparable to either adults, adolescents or licensed products for this age group. Safety will therefore be extrapolated which is in line with EMA guidance.

Exposure is too limited to reliably assess the safety profile in paediatric patients ≥ 3 years of age. Rather, safety is inferred based on similar exposures as observed in adults and adolescents.

The Applicant explained that, based on all available data, the observed differences in DRV/COBI exposure for children weighing ≥ 15 to < 25 kg in Study GS-US-216-0128 are not considered clinically relevant. This is based on the following rationale:

- Population PK derived DRV exposures in Cohort 3 of Study GS-US-216-0128 were within the range of those previously observed in adult and paediatric patients, especially with bid DRV dosing, and which were found to be safe and efficacious.
- COBI exposures in Cohort 3 of Study GS-US-216-0128 were in line with those previously observed in the E/C/F/TAF paediatric Study GS-US-292-0106 (Cohort 2 and Cohort 3).
- Based on this, COBI 90 mg qd (as part of the E/C/F/TAF FDC) was approved for the same paediatric population as is the basis of this submission, i.e. children weighing ≥ 15 to < 25 kg.

- Throughout the development of DRV (boosted with either COBI or rlv), there have been no indications for an exposure-response relationship for any AEs.
- Similarly, COBI Phase 2 (GS-US-216-0105) and Phase 3 (GS-US-216-0114) studies using population PK model-derived COBI exposures versus safety parameters revealed no relevant exposure-AE trends.
- Juvenile toxicity studies showed that the toxicological profile of DRV and COBI was comparable to that in adult rats.
- The higher F exposure is mainly driven by the lower body-weight, however, exposures overlap with those in adolescents and adults, and the 200 mg F dose is approved for use in adults and paediatric patients weighing at least 25 kg, in combination with other antiretrovirals.

The rationale and conclusions of the Applicant can be followed. Although DRV AUC_{0-24h} was higher in Cohort 3 vs other studies, the values were still in the same range as those included in the exposure-safety analysis which was submitted as part of the original MAA for Rezolsta. As there was no exposure-safety relation observed, it can be agreed that the increased exposures seen in paediatric patients ≥ 14 to < 25 kg are not likely to be clinically relevant. However, as it cannot be excluded that there are safety aspects associated with this higher exposure that are specific to the paediatric population, i.e. it is uncertain whether the exposure-safety relationship is the same for paediatrics and adults, the Applicant should further follow this post approval (via routine pharmacovigilance activities).

Similarly, COBI exposure (mainly C_{max} and C_{trough}) was higher in study 0128 Cohort 3 vs E/C/F/TAF Cohort 3. Although there is no direct concern based on the information provided by the Applicant and the absence of an exposure-safety correlation in adults, also here this may be different in paediatrics and close attention of any safety signals is warranted.

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Uncertainties / Strength of evidence	References
Favourable Effects					
PK	DRV levels		DRV/COBI/F/TAF regimen qd results in comparable DRV levels as compared to adults		Study 216-0128 Cohort 2
	COBI levels		DRV/COBI/F/TAF regimen qd results in comparable C _{max} levels as compared to adults		Study 216-0128 Cohort 2
	TAF levels		DRV/COBI/F/TAF regimen qd results in comparable AUC _{tau} and C _{max} levels (dose normalised) as compared to adults		Study 216-0128 Cohort 2

Effect	Short Description	Unit	Treatment	Uncertainties / Strength of evidence	References
Virologic response	Proportion of patients who remained virologically suppressed at week 24	n/N (%)	9/9 (100%)	Small sample size (n=9)	Study 216-0128 Cohort 2
Unfavourable Effects					
PK	COBI		DRV/COBI/F/TAF regimen qd results in higher AUCtau and Ctau levels (1.4- and 2.2-fold, respectively) as compared to adults		Study 216-0128 Cohort 2
	F		DRV/COBI/F/TAF regimen qd results in higher AUCtau, Cmax and Ctau levels (2.4-, 2.0- and 1.8-fold, respectively) as compared to adults		Study 216-0128 Cohort 2
AEs	Related AEs	n/N	3/9 participants	Small sample size	Study 216-0128 Cohort 2

Abbreviations:

PK: pharmacokinetics; DRV/COBI/F/TAF: darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DRV: darunavir; COBI: cobicistat; F: emtricitabine; TAF: tenofovir alafenamide; AEs: adverse events

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 available PK data and PopPK modeling, indicate that there are no clinically relevant differences in PK exposures of the components of the D/C/F/TAF 675/150/200/10-mg FDC in children (aged ≥ 6 years and weighing ≥ 25 to < 40 kg) compared to the components of the D/C/F/TAF 800/150/200/10-mg FDC in adults and adolescents (aged ≥ 12 years and weighing ≥ 40 kg), together with the bioequivalence of the D/C/F/TAF 675/150/200/10-mg FDC formulation versus single components (Study FD2HTX1007), allow for the extrapolation of the established clinical safety data from adults and adolescents to the younger paediatric population. 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.

Of note, the same C/F/TAF dose has been approved for another HIV FDC (E/C/F/TAF) in paediatric patients weighing at least 25 kg, with similar exposures observed as for DRV/COBI + F/TAF. Similarly, the DRV dose is aligned with the approved DRV dose in combination with 100 mg rtv.

3.7.2. Balance of benefits and risks

The overall data presented support the efficacy and safety for an extension of the therapeutic indication of Symtuza.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit /risk balance of Symtuza is positive.

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, Symtuza new strength is favourable in the following indication(s):

Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and paediatric patients aged 6 years and older with body weight at least 25 kg.

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

The CHMP therefore recommends the extension(s) of the marketing authorisation for Symtuza subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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)**

Janssen-Cilag International NV 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/0284/2024) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommend the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

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

Extension application to add a new strength of 675 mg/150 mg/200 mg/ 10 mg film-coated tablets grouped with an Extension of indication (C.I.6) to include treatment of human immunodeficiency virus type 1 (HIV 1) infection in paediatric patients (aged 6 years and older with body weight at least 25 kg) for SYMTUZA, based on the 24-week interim results from study GS-US-216-0128 (Cohort 2); this is a Phase II/III, multicenter, open-label, multicohort interventional study evaluating efficacy, safety, and pharmacokinetics of Cobicistat-boosted Atazanavir (ATV/co) or Cobicistat-boosted Darunavir (DRV/co) and Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 infected children. As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2, 6.1, 6.3, 6.4, 6.5 and 8 of the SmPC are updated. The Annex II, Labelling and Package Leaflet are updated accordingly. Version 9.1 of the RMP has also been agreed. The MAH took the opportunity to update section 4.4 and 4.8 to include information on reductions in BMD of the spine and of the TBLH $\geq 4\%$ reported in paediatric patients receiving other tenofovir alafenamide containing products for 48 weeks, to update section 4.6 of the SmPC to include information on the excretion of tenofovir alafenamide in human milk based on the outcome of the PSUR assessment EMA/PSUR/0000274445, to bring the PI in line with the latest QRD template version 10.4 and to update the list of local representatives in the Package Leaflet.

5. Appendix

Not applicable.