EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 September 2022
EMA/807473/2022
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report on grouping of an extension of marketing authorisation and an extension of indication variation

Biktarvy

International non-proprietary name: bictegravir / emtricitabine / tenofovir alafenamide

Procedure No. EMEA/H/C/004449/X/0040/G

## Note

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

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

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# List of abbreviations

AE adverse event

ALT alanine aminotransferase

ART antiretroviral therapy

AST aspartate aminotransferase

B bictegravir

BCLCRSW creatinine clearance calculated using the Schwartz formula

BIC bictegravir

BIC/FTC/TAF bictegravir/emtricitabine/tenofovir alafenamide; coformulated (Biktarvy)

BMI body mass index

BVY bictegravir/emtricitabine/tenofovir alafenamide; coformulated (Biktarvy)

C24 plasma concentration at 24 hours postdose

CI confidence interval

CL/F apparent oral clearance after administration of the drug: CL/F = dose/AUCinf, where dose is the dose of the drug, and AUCinf is the area under the plasma concentration versus time curve extrapolated to infinite time

CLM/F apparent oral clearance for TFV after administration of the drug

COBI cobicistat

CSR clinical study report

DDI drug-drug interaction

DRV darunavir

EFV efavirenz

eGFRSchwartz estimated glomerular filtration rate calculated using the Schwartz formula

EU European Union

EVG elvitegravir

F emtricitabine

F1 relative bioavailability of TAF

FDA (United States) Food and Drug Administration

FDC fixed-dose combination

FTC emtricitabine

GEN elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; coformulated (Genvoya)

HDL high-density lipoprotein

HIV, HIV-1 human immunodeficiency virus, type 1

INSTI integrase strand transfer inhibitor

IQ inhibitory quotient

LDL Low-density lipoprotein

LPV lopinavir

M = E missing = excluded

M = F missing = failure

MedDRA Medical Dictionary for Regulatory Activities

PD pharmacodynamic

PK pharmacokinetic(s)

PopPK population pharmacokinetics

PVC polyvalent cation

Q1, Q3 first quartile, third quartile

QM/F apparent intercompartmental clearance of TFV

QS Quantum satis (Quantity sufficient)

RAM resistance-associated mutation

RAP resistance analysis population

RNA ribonucleic acid

RPV rilpivirine

RTV ritonavir

SAE serious adverse event

SD standard deviation

STR single-tablet regimen

TAF tenofovir alafenamide

TDF tenofovir disoproxil fumarate

ULN upper limit of normal

US, USA United States, United States of America

Vc/F apparent central volume

VcM/F apparent central volume of distribution of TFV

VF virologic failure

VpM/F apparent peripheral volume of distribution of TFV

Vz/F apparent volume of distribution of the drug

WT body weight

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

Gilead Sciences Ireland UC submitted on 28 May 2021 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

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

The MAH applied for an extension application to introduce a new strength (30 mg/120 mg/15 mg film-coated tablets). The extension application is grouped with a type II variation (C.I.6.a) to include treatment of human immunodeficiency virus-1 (HIV-1) infection in paediatric patients at least 2 years of age and weighing at least 14 kg without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir. Sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC and the Package Leaflet are updated to support the extended indication. The RMP (version 3.1) is updated in accordance.

## *1.2. Legal basis and dossier content*

**The legal basis for this application refers to:**

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

The application submitted is composed of administrative information, quality data, clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

## *1.3. Information on Paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0038/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0038/2021 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP (EMEA-001766-PIP01-15-M03).

## *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, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## 1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

## 1.6. Steps taken for the assessment of the product

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

Rapporteur: Jean-Michel Race Co-Rapporteur: Bruno Sepodes

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Liana Gross-Martirosyan

| | |
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| The application was received by the EMA on | 28 May 2021 |
| The procedure started on | 17 June 2021 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 13 September 2021 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 14 September 2021 |
| The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 21 September 2021 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 30 September 2021 |
| The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on | 14 October 2021 |
| The MAH submitted the responses to the CHMP consolidated List of Questions on | 21 January 2022 |
| 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 | 28 February 2022 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 10 March 2022 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on | 24 March 2022 |
| The MAH submitted the responses to the CHMP List of Outstanding Issues on | 21 June 2022 |
| The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 07 July 2022 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 07 July 2022 |
| The CHMP agreed on 2nd list of outstanding issues in writing to be sent | 21 July 2022 |

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| to the MAH on | |
| The MAH submitted the responses to the 2nd CHMP consolidated List of Questions on | 16 August 2022 |
| The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 31 August 2022 |
| 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 Biktarvy on | 15 September 2022 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

The human immunodeficiency virus (HIV) targets the immune system and weakens people's defence against many infections and some types of cancer that people with healthy immune systems can fight off. As the virus destroys and impairs the function of immune cells, infected individuals gradually become immunodeficient. Immune function is typically measured by CD4 cell count. The most advanced stage of HIV infection is acquired immunodeficiency syndrome (AIDS), which can take many years to develop if not treated, depending on the individual. AIDS is defined by the development of certain cancers, infections, or other severe long-term clinical manifestations.

### 2.1.2. Epidemiology

There were approximately 37.6 million people across the globe with HIV in 2020. Of these, 35.9 million were adults and 1.7 million were children (<15 years old). In 2020, 680 000 [480 000–1.0 million] people died from HIV-related causes and 1.5 million [1.0–2.0 million] people acquired HIV.

As of the end of 2020, 27.4 million people with HIV (73%) were accessing antiretroviral therapy (ART) globally. That means 10.2 million people are still waiting. People with HIV who are aware of their status, take ART daily as prescribed, and get and keep an undetectable viral load can live long, healthy lives and have effectively no risk of sexually transmitting HIV to their HIV-negative partner. UNAIDS reports that in 2020, of all people with HIV worldwide: 84% knew their HIV status, 73% were accessing ART, and 66% were virally suppressed.

### 2.1.3. 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 (TB), cryptococcal meningitis, severe bacterial infections, and cancers such as lymphomas and Kaposi's sarcoma.

### 2.1.4. Management

A once daily, single-tablet regimen (STR) has been shown to significantly improve adherence, treatment satisfaction, and virologic outcome for patients infected with HIV-1. Many paediatric patients would also benefit from the availability of a simplified, once daily STR that combined potent efficacy, tolerability, a favourable toxicity profile, a low potential for drug-drug interactions, and practical, convenient dosing.

Six STRs are currently approved in the EU for once daily administration in the treatment of HIV-1 infection in adolescents: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil (EVG/COBI/FTC/TDF), elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF) co-formulated, abacavir/dolutegravir/lamivudine, emtricitabine /rilpivirine/TAF (FTC/RPV/TAF), dolutegravir/lamivudine (DTG/3TC) and darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/COBI/FTC/TAF).

## *2.2. About the product*

Biktarvy (BVY; bictegravir [B; BIC]/emtricitabine [F; FTC]/tenofovir alafenamide [TAF]) is an oral, once daily fixed-dose combination (FDC) that provides a potent and well tolerated regimen for the treatment of patients infected with HIV-1. Biktarvy contains the integrase strand transfer inhibitor BIC, the nucleoside reverse transcriptase inhibitor FTC, and the nucleotide reverse transcriptase inhibitor TAF.

Biktarvy was approved for commercial use in adults in the United States (US) on 07 February 2018 and in the European Union (EU) on 21 June 2018. The indication was extended in the US to include paediatric patients weighing ≥ 25 kg on 18 June 2019, and BVY is recommended as a preferred antiretroviral regimen for children aged ≥ 6 years and weighing ≥ 25 kg in current US Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in Paediatric HIV Infection (Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV 2021).

## *2.3. Type of Application and aspects on development*

The MAH is herewith submitting an application under article 7.2(b) EC No 1234/2008 to extend the Biktarvy marketing authorization with the introduction of an age-appropriate formulation (Biktarvy 30/120/15 mg film-coated tablets), grouped with a Type II C.I.6.a variation to introduce the paediatric indication, use in patients < 18 years of age down to ≥ 2 years of age weighing at least 14 kg.

Study GS-US-380-1474 was performed in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) guideline for Good Clinical Practice (GCP) (Sections 7.5, 8.1.2, and 8.2.2), and the original principles embodied in the Declaration of Helsinki.

## *2.4. Quality aspects*

### 2.4.1. Introduction

The finished product applied for in this line extension is presented as film-coated tablets containing a fixed dose combination of 30 mg of bictegravir, 120 mg of emtricitabine, and tenofovir alafenamide fumarate equivalent to 15 mg of tenofovir alafenamide as active substances.

Other ingredients are:

Tablet core: microcrystalline cellulose (E460) croscarmellose sodium (E468) and magnesium stearate (E470b);

Film-coating: polyvinyl alcohol (E203) titanium dioxide (E171) macrogol (E1521), talc (E553b), iron oxide red (E172) and iron oxide black (E172).

The product is available in white, high-density polyethylene (HDPE) bottle with a polypropylene continuous-thread, child-resistant cap, lined with an induction activated aluminium foil liner. Each bottle contains a silica gel desiccant and a polyester coil as described in section 6.5 of the SmPC.

### 2.4.2. Active Substance

The active substances bictegravir, emtricitabine, and tenofovir alafenamide fumarate are manufactured by the same manufacturers and to the same standards as the approved Biktarvy 50/200/25 mg tablets. No new information is provided for this line extension.

### 2.4.3. Finished Medicinal Product

***Description of the product and Pharmaceutical development***

Biktarvy (BIC/FTC/TAF) fixed-dose combination (FDC) tablets are an immediate-release oral dosage form containing 30 mg of bictegravir (BIC, B), 120 mg of emtricitabine (FTC, F), and 15 mg of tenofovir alafenamide (TAF). BIC/FTC/TAF tablets, 30/120/15 mg, are pink, capsule-shaped, film-coated tablets, debossed with "BVY" on one side and a score line on the other side and measure approximately 14 x 6 mm.

A fixed dose combination of BIC/FTC/TAF is already approved as a 50 mg/200 mg/25 mg film coated tablet. The aim of this pharmaceutical development was to develop a paediatric dosage form containing a lower strength of each active substance.

The excipients used are the same as the ones used for the approved strength 50/200/25 mg tablets except for the colorant. All excipients are well known pharmaceutical ingredients compliant with Ph. Eur. or EU standards for colorants. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report. There are no novel excipients used in the finished product formulation. The choice of this colouring agent in a paediatric preparation is considered acceptable since it was already approved for other paediatric medicines. Differences in colour and debossing are sufficient to distinguish the new and existing formulations.

Formulation development focused on developing a lower strength tablet appropriate for the paediatric population while achieving the established biopharmaceutical performance of BIC sodium, FTC, and TAF as in the approved tablets. Bictegravir sodium is a crystalline, stable, BCS class II compound exhibiting low solubility but high permeability. Emtricitabine is a crystalline BCS class I compound with

high solubility and permeability which degrades by hydrolysis in aqueous solution and to a much smaller degree, in the solid phase. TAF is a BCS class III molecule, highly soluble but poorly permeable, which undergoes pH-dependent hydrolysis in aqueous solution. The formulation used in the relative bioavailability study and phase 3 clinical studies is the same as intended for commercialisation, other than changes in debossing and addition of a score line.

The new tablet is intended for children aged 2 years and above. In the paediatric investigation plan (PIP), the PDCO recommended that an age-appropriate formulation be developed, and that acceptability and palatability data be generated for the smaller tablet since it is nonetheless quite large for the youngest children. This data was provided in clinical studies – however, some tablets were split to aid swallow(contrary to the 50/200/25 mg SmPC instructions - "*tablets should not be chewed, crushed, or split*"). Following a CHMP request, the MAH added a score line to the tablet and amended the SmPC (section 4.2 to state "*For patients who are unable to swallow the tablet whole, the tablet may be split in half and both halves taken one after the other, ensuring that the full dose is taken immediately*." The CHMP recommended the MAH to provide validation data for relevant steps of the revised manufacturing process by December 2022 and 6 months' stability data for the scored tablet by August 2023. The MAH also explained plans for development of an oral suspension as per the PIP. Fulfilment of the PIP is planned by September 2023 which is considered acceptable.

The dissolution method is the same as used for the already approved strength and was developed to accommodate the different solubility and stability profiles of the 3 active substances. Discriminatory power was demonstrated against meaningful changes in composition and process parameters.

The primary packaging is a white HDPE bottle with a polypropylene continuous thread, child-resistant cap, lined with an induction activated aluminium foil liner. Each bottle contains a silica gel desiccant and polyester coil. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

**Manufacture of the product and process controls**

The manufacturing process is considered to be a standard manufacturing process.

The manufacturing description and applied control strategy is considered acceptable. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Process validation will be performed prior to commercial distribution of 30/120/15 mg BIC/FTC/TAF tablets, including the revised process steps associated with introduction of a score line, as defined in the submitted validation protocol. Since the manufacturing process is a standard process, the absence of validation data is considered acceptable.

The proposed holding times for BIC/FTC/TAF final powder blend, BIC/FTC/TAF tablet cores, and BIC/FTC/TAF film-coated tablets taking into account the stability data provided are considered acceptable since confirmation is provided that the finished product shelf life will be calculated in accordance with the Note For Guidance On start of shelf-life of the finished dosage form CPMP/QWP/072/96.

**Product specification**

The finished product release specifications include appropriate tests for this kind of dosage form.

The specifications are the same as those for the approved strength apart one degradant that has only been observed in the 30/120/15 mg strength tablets. The release and shelf-life limits for degradants are considered qualified and acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities and considering experience with the approved formulation. Based on the risk assessment, it can be concluded that no test for elemental impurities is needed.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was submitted, 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). Despite the potential presence of secondary and tertiary amine impurities in the active substances, and the potential presence of nitrosating agents as excipient impurities, the MAH initially concluded that there is no risk of presence of nitrosamine impurities, given the formulation conditions. The CHMP did not except this argument and requested confirmatory testing on representative batches. The MAH provided confirmatory testing results for relevant nitrosamine impurities using a suitably validated and sensitive method and no nitrosamine impurities were detected above the limit of detection (corresponding to 1 ng/tablet). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities the related finished product and no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. The methods for assay and impurities are demonstrated to be stability-indicating.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

**Stability of the product**

Stability data were provided for production scale batches of finished product stored for up to 24 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packaged in the intended commercial container closure system. Samples were tested for appearance, water content, assay, degradation products, dissolution and microbiological quality. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed except for a decrease in TAF assay and commensurate rise in impurity content. However, all parameters remained within their specification limits throughout shelf-life.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability. The finished product is photostable.

Stress studies were carried out on one batch of BIC/FTC/TAF at -20°C for one month and 50 ºC/ambient humidity for two weeks. No significant degradation was observed.

An in-use stability study was performed on one batch at 30 °C/75% for up to 30 days. Stability data for all quality attributes measured comply with the specifications.

Based on the stability data provided, the proposed shelf-life of 36 months when stored in the original package and kept tightly closed to protect from moisture as described in the SmPC (section 6.3) is considered acceptable.

**Adventitious agents**

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

### 2.4.4. Discussion on chemical, pharmaceutical and biological aspects

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

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the benefit/risk ratio of the product. The MAH introduced a score line on the tablet and changed the de-bossing during the procedure to allow sub-division of tablets and facilitate swallowing by patients unable to swallow the whole tablet. The MAH should conduct process validation on relevant steps of the revised process, provide batch analysis data and provide 6 months' stability data on the scored tablets. These points are put forward and agreed as recommendations for future quality development.

### 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. Recommendations 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:

- The MAH should conduct process validation on relevant steps of the revised process and provide batch analysis data on the scored tablets by 31st December 2022.
- The MAH should provide 6 months' stability data on the scored tablets by 31st August 2023.

## *2.5. Non-clinical aspects*

### 2.5.1. Introduction

A comprehensive non-clinical program of pharmacology, pharmacokinetics and toxicology studies was performed to demonstrate the safety and efficacy of bictegravir / emtricitabine / tenofovir alafenamide for the original MAA.

Apart from environmental studies, no new non-clinical data were provided with this application.

## 2.5.2. Pharmacology

The pharmacologic basis to recommend the BIC/FTC/TAF 50/200/25 mg and 30/120/15 mg for the treatment of HIV infection in the paediatric patient population < 18 years of age down to ≥ 2 years of age weighing ≥ 14 kg is scientifically justified based on the non-clinical *in vitro* and *in vivo* efficacy data for the individual components and the combination of the agents presented in this dossier.

No new pharmacology data were provided with this application. This is considered satisfactory.

## 2.5.3. Pharmacokinetics

The pharmacokinetic profiles of BIC, FTC, and TAF are well characterized in multiple animal species and the findings support the use of these agents in combination. Of note, data from clinical studies with the combination demonstrated acceptable tolerability and safety profiles to support use in the paediatric patient population < 18 years of age down to ≥ 2 years of age weighing ≥ 14 kg.

No new PK data were provided with this application. This is considered satisfactory.

## 2.5.4. Toxicology

No juvenile toxicity studies have been conducted with BIC, FTC, TAF, or the combination.

The non-clinical overview includes justifications for the lack of such studies.

According to European Medicines Agency decision P/0038/2021 of 27 January 2021 on the acceptance of a modification of an agreed paediatric investigation plan for bictegravir /emtricitabine / tenofovir alafenamide (Biktarvy), (EMEA-001766-PIP01-15-M03), no juvenile study is required. The prenatal and postnatal reproductive toxicity study of bictegravir in rats has been performed as required and already assessed in the initial submission.

The targeted population in this line extension is the paediatric patient population < 18 years of age down to ≥ 2 years of age weighing ≥ 14 kg. No new studies were recommended by the PedCo, the available data submitted during the initial submission being considered sufficient.

In conclusion, the combination of BIC, FTC, and TAF is not anticipated to exacerbate known toxicities or lead to new toxicities.

## 2.5.5. Ecotoxicity/environmental risk assessment

In the original MAA for Biktarvy, a standard battery of environmental fate and effects studies were conducted to evaluate the environmental risk associated with the use of BIC, FTC and TAF.

At that time, Phase IIb studies for bictegravir were still in progress. Since 2018, the MAH has completed 6 studies, which were submitted with this line extension.

For emtricitabine and tenofovir no new study was provided.

The MAH submitted an updated ERA for the individual substances bictegravir, emtricitabine and tenofovir alafenamide and an updated ERA for the combination. The prevalence of HIV in 2019 for all population in the EU, including paediatric population, has been taken into account. A worst case scenario was used, which is relevant for this line extension.

Relevant residues of BIC, FTC and TAF in the environment were determined and showed low risk to the environment. Approval of this line extension will not lead to any unacceptable risks to aquatic or terrestrial ecosystems.

In conclusion, the use of Biktarvy as a treatment for HIV poses an acceptable risk to the environment.

### 2.5.6. Discussion on non-clinical aspects

A comprehensive non-clinical program of pharmacology, pharmacokinetics and toxicology studies was performed and demonstrated the safety and efficacy of bictegravir / emtricitabine / tenofovir alafenamide for the original MAA.

There are no anticipated clinically relevant pharmacokinetic or toxicological interactions expected in the BIC/FTC/TAF FDC in the paediatric population.

Overall, the toxicology programme revealed that combination of BIC, FTC, and TAF does not exacerbate known toxicities or lead to new toxicities. BIC, FTC, or TAF have not shown significant adverse effects as individual agents in reproductive and developmental toxicity studies. The combination of the 3 components is not expected to have an altered reproductive toxicity profile as compared with that of the individual agents.

The BIC/FTC/TAF 50/200/25 mg and 30/120/15 mg are considered to have low potential for toxicity in the paediatric patient population < 18 years of age down to ≥ 2 years of age weighing ≥ 14 kg and the existing non-clinical data supports the proposed use.

From the results of ERA studies, no significant environmental safety issues were identified.

### 2.5.7. Conclusion on the non-clinical aspects

The overall existing non-clinical programme to date, including data from the combination and individual drug studies, supports the efficacy and safety of BIC/FTC/TAF 50/200/25 mg and 30/120/15 mg in the sought indication.

Apart from environmental studies, no new non-clinical data were provided with this extension application which is in in accordance with the CHMP Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (EMEA/CHMP/SWP/258498/2005, January 2008).

Concerning the environmental risk assessment, new studies were provided, which allowed to conclude that approval of this line extension will not lead to any increased risk to aquatic or terrestrial ecosystems.

## *2.6. Clinical aspects*

### 2.6.1. Introduction

***GCP aspects***

The clinical trials were performed in accordance with GCP as claimed by the MAH.

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

**Tabular overview of clinical studies**

**Table 1. Clinical Study Included in this Submission**

| Study Number | Study Design | Subject Population | Treatment Regimen | CSR and Narrative Locations |
|---|---|---|---|---|
| GS-US-380-1474 | Phase 2/3, open-label, multicenter, multicohort, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of the B/F/TAF FDC in HIV-1 infected, virologically suppressed adolescents and children. | Cohort 1: ≥ 12 to < 18 years of age, weight ≥ 35 kg; n = 50<br>Cohort 2: ≥ 6 to < 12 years of age, weight ≥ 25 kg; n = 50<br>Cohort 3: ≥ 2 years of age, weight ≥ 14 kg to < 25 kg; n = 22<br>HIV-1 infected adolescents (Cohort 1) and children (Cohorts 2 and 3) virologically suppressed (HIV-1 RNA < 50 copies/mL or undetectable if the limit of detection of the local assay used was ≥ 50 copies/mL) for ≥ 6 months prior to screening on a stable antiretroviral regimen comprising 2 nucleoside reverse transcriptase inhibitors plus a third agent; $eGFR_{Schwartz}$ ≥ 90 mL/min/1.73m$^2$ at screening; and no documented or suspected resistance to FTC, tenofovir , or INSTIs including, but not limited to, the reverse transcriptase resistance mutations K65R and M184V/L. | Cohorts 1 and 2: Adult-strength fixed dose combination (FDC) tablet of B/F/TAF (50/200/25 mg) administered orally, once daily, at approximately the same time each day, without regard to food.<br>Cohort 3: Low-dose FDC tablet of B/F/TAF (30/120/15 mg) administered orally, once daily, at approximately the same time each day, without regard to food. | CSR: GS-US-380-1474 Interim Analysis 2<br>Narrative: m2.7.4 Section 1.2.3 |

$eGFR_{Schwartz}$ = estimated glomerular filtration rate calculated using the Schwartz formula; FDC = fixed dose combination; INSTI= integrase strand transfer inhibitor
Note: Six subjects in Cohort 3 attained a weight ≥ 25 kg during the study and were switched to the adult-strength B/F/TAF 50/200/25 mg tablet as appropriate for this weight band.

## 2.6.2. Clinical pharmacology

### *2.6.2.1. Pharmacokinetics*

#### 2.6.2.1.1. Introduction

Biktarvy (BIC/FTC/TAF) is an oral, once daily fixed-dose combination (FDC) that provides a regimen for the treatment of patients infected with HIV-1.

Biktarvy contains the integrase strand transfer inhibitor BIC, the nucleoside reverse transcriptase inhibitor FTC, and the nucleotide reverse transcriptase inhibitor TAF. Biktarvy was approved in adults in the United States (US) on 07 February 2018 and in the European Union (EU) on 21 June 2018.

Prior to this application, the BIC/FTC/TAF 50/200/25 mg FDC was indicated in the EU for the *treatment of adults infected with HIV-1 without present or past evidence of viral resistance to the integrase inhibitor class, FTC, or tenofovir (TFV)*.

A once daily, single-tablet regimen (STR) has been shown to significantly improve adherence, treatment satisfaction, and virologic outcome for patients infected with HIV-1. Many paediatric patients would also benefit from the availability of a simplified, once daily STR that combined potent efficacy,

tolerability, a favourable toxicity profile, a low potential for drug-drug interactions, and practical, convenient dosing. BIC/FTC/TAF may provide an improved option for paediatric patients for whom it would be better to avoid the potential for adverse reactions arising from less tolerated agents such as ritonavir (RTV)-boosted protease inhibitors or central nervous system adverse events (AEs) due to EFV. Additionally, as BIC, FTC, and TAF are not clinically relevant inhibitors or inducers of major human drug-metabolizing enzymes or transporters, there is low potential for BIC/FTC/TAF to cause drug-drug interactions (DDIs). Because no PK enhancer such as COBI or RTV is required to maintain BIC plasma concentrations, the DDI potential of BIC/FTC/TAF is lower than that of other approved agents. The reduced risk of DDIs is an important benefit in the maintenance of treatment adherence in a paediatric population. Moreover, a TAF-containing regimen would be a better choice than a TDF-based regimen in this population due to a more favourable bone and renal profile. The small tablet size of the low-dose BIC/FTC/TAF FDC is expected to provide a further benefit for paediatric patients for whom pill swallowing can be a barrier to treatment compliance.

The low-dose BIC/FTC/TAF 30/120/15 mg tablet was developed to support the Phase 2/3 Study GS-US-380-1474 in paediatric patients with HIV-infection and is the proposed commercial tablet formulation. The designated commercial drug product is an immediate-release FDC tablet containing 30 mg of BIC, 120 mg of FTC, and 15 mg of TAF. BIC is incorporated into the drug product as BIC sodium, and TAF is incorporated into the drug product as the hemifumarate form (referred to as TAF fumarate). Due to the differences in dosage strengths, PK parameters derived using the low-dose BIC/FTC/TAF tablet were normalized by dividing each value by 0.6, the ratio of the test dose/reference dose. The dose-normalized results show the low-dose BIC/FTC/TAF30/120/15 mg tablet demonstrated bioequivalence to the adult-strength BIC/FTC/TAF50/200/25 mg tablet.

The PK of BIC, TAF and TFV (the main metabolite of TAF) in virologically suppressed adolescents ≥ 12 to < 18 years of age weighing ≥ 35 kg and children ≥ 6 to < 12 years of age weighing ≥ 25 kg receiving the adult-strength BIC/FTC/TAF 50/200/25 mg FDC, and children ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving the low-dose BIC/FTC/TAF 30/120/15 mg FDC were estimated by a population PK (PopPK) approach using all available intensive and sparse paediatric plasma concentration data. For BIC, paediatric PK data were derived from Study GS-US-380 1474. For TAF and TFV, paediatric data were derived from Study GS-US-380-1474, E/C/F/TAF Studies GS-US-292-0106 and GS-US-292-1515, and F/TAF Study GS-US-311-1269, as summarised in tables 3 and 4 below, respectively.

**Table 1 : Population Pharmacokinetics of BIC in HIV-1 Infected Paediatric Subjects; Studies included in the PopPK Analysis**

| Study | Study Design/Population | Treatment | Sampling (Intensive/ Sparse) |
|---|---|---|---|
| GS-US-380-1474 | A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the GS-9883/ Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) Fixed Dose Combination (FDC) in HIV-1 Infected Virologically Suppressed Adolescents and Children | Cohorts 1 and 2: adolescents ≥ 12 to < 18 years of age and children ≥ 6 to < 12 years of age weighing ≥ 25 kg B/F/TAF 50/200/25 mg FDC<br>Cohort 3: children ≥ 2 years of age weighing ≥ 14 to < 25 kg B/F/TAF 30/120/15 mg FDC | Intensive + Sparse |

**Table 2: Population Pharmacokinetics of TAF and TFV in HIV-1 Infected Paediatric Subjects; Studies included in the PopPK Analysis**

| Study | Study Design/Population | Treatment | Sampling (Intensive/Sparse) |
|---|---|---|---|
| GS-US-292-0106 | A Phase 2/3, Open-Label Study of the Pharmacokinetics (PK), Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/ Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen in HIV-1 Infected, Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children | Cohorts 1 and 2: adolescents and children ≥ 6 to < 18 years of age, weighing ≥ 25 kg E/C/F/TAF 150/150/200/10 mg<br><br>Cohort 3: children ≥ 2 years of age weighing ≥ 14 to < 25 kg E/C/F/TAF 90/90/120/6 mg | Intensive + Sparse |
| GS-US-292-1515 | A Phase 2/3, Open-Label Study to Evaluate the Safety and Efficacy of E/C/F/TAF in HIV-1-Infected, Virologically Suppressed Adolescents | E/C/F/TAF 150/150/200/10 mg | Sparse |
| GS-US-311-1269 | A Phase 2/3, Open-Label, Multicohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 Infected Children and Adolescents Virologically Suppressed on a 2-Nucleoside Reverse Transcriptase Inhibitor (NRTI)-Containing Regimen | Cohort 1: adolescents ≥ 12 to < 18 years of age, weighing ≥ 35 kg F/TAF 200/25 mg or 200/10 mg<br><br>Cohort 2 Group 1: children ≥ 6 to < 12 years of age, weighing ≥ 25 kg F/TAF 200/25 mg<br><br>Cohort 2 Group 2: children ≥ 2 to < 12 years of age, weighing ≥ 17 to < 25 kg): F/TAF 120/15 mg | Intensive + Sparse |
| GS-US-380-1474 | A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883//F/TAF) Fixed-Dose Combination (FDC) in HIV-1-Infected, Adolescents and Children | Cohorts 1 and 2: adolescents ≥ 12 to < 18 years of age, weighing ≥ 35kg and children ≥ 6 to < 12 years of age, weighing ≥ 25 kg B/F/TAF 50/200/25 mg<br><br>Cohort 3: children ≥ 2 years of age weighing ≥ 14 to < 25 kg): B/F/TAF 30/120/15 mg | Intensive + Sparse |

To confirm the appropriateness of the BIC/FTC/TAF 50/200/25 mg, adult-strength dose in adolescents ≥ 12 to < 18 years of age weighing ≥ 35 kg (Cohort 1) and children ≥ 6 to < 12 years of age weighing ≥ 25 kg (Cohort 2), and low-dose BIC/FTC/TAF 30/120/15 mg in children ≥ 2 years of age weighing ≥ 14 kg to < 25 kg (Cohort 3), exposures of BIC, FTC, and TAF in paediatric subjects were compared with historical data from HIV-1 infected adults treated with BIC/FTC/TAF in the BIC/FTC/TAF Phase 3 pivotal studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878, as appropriate.

A PK equivalence boundary of 70% to 143% was used for Cohorts 1 and 2, and 50% to 200% was used for Cohort 3. The wider PK equivalence boundary specified for Cohort 3 was used to take account of the inherent variability of BIC exposures observed in paediatric subjects ≥ 6 years of age weighing ≥ 25 kg (Cohorts 1 and 2 of Study GS-US-380-1474). This was justified by taking into consideration the available PK, efficacy, and safety data from Phase 3 studies of BIC/FTC/TAF 50/200/25 mg in adults.

Population PK parameters of TAF and intensive PK parameters of FTC were compared with historical PopPK and intensive PK data, respectively, in HIV-infected adults treated with BIC/FTC/TAF. As TFV exposures were not derived in the BIC/FTC/TAF-treated HIV-1 infected adult subjects in the Phase 3 Studies, PopPK parameters of TFV for adolescents and children were compared with those in HIV-1

infected adults receiving GEN, for which safety and efficacy in this population had been previously established.

#### 2.6.2.1.2. Bioanalytical methods

A LC-MS/MS assay procedure was used for determination of plasma concentration of the individual components of Biktarvy (BIC, FTC, and TAF), and TFV, the main metabolite of TAF.

#### 2.6.2.1.3. Pharmacokinetic data analysis

Population PK models were developed to characterize the exposures of BIC, TAF, and TFV in virologically suppressed adolescents and children ≥ 2 years of age weighing ≥ 14 kg in both the PK lead-in and treatment phases using all available intensive and sparse plasma concentration data. Population PK parameters of BIC, TAF, and TFV were predicted and are presented in the subsequent sections. For FTC, PK parameters estimated from analysis of the intensive PK samples from the PK lead-in phase were used. To confirm the appropriateness of the BIC/FTC/TAF doses in virologically suppressed children and adolescents ≥ 2 years of age weighing ≥ 14 kg, PopPK parameters AUCtau and Ctau for BIC were compared to historical PopPK data in HIV-1 infected adults treated with BIC/FTC/TAF using a PK equivalence boundary of 70% to 143% for Cohorts 1 and 2, and a PK equivalence boundary of 50% to 200% for Cohort 3. The wider PK equivalence boundary specified for Cohort 3 was used to take account of the inherent variability of BIC exposures observed in paediatric subjects in Cohorts 1 and 2. This was justified by taking into consideration the available PK, efficacy, and safety data from Phase 3 studies of BVY (BIC/FTC/TAF 50/200/25 mg) in adults (Study GS-US-380-1474 Protocol). Population PK parameters of TAF and intensive PK parameters of FTC were compared to historical PopPK and intensive PK data, as appropriate, in HIV-1 infected adults treated with BVY. As TFV exposures were not derived for BVY-treated HIV-1 infected adults in the Phase 3 studies, PopPK parameters of TFV for adolescents and children were compared to historical PopPK data in HIV-1 infected adults treated with GEN (E/C/F/TAF 150/150/200/10 mg).

#### 2.6.2.1.4. Bioequivalence and Influence of food

The bioavailability of BIC, FTC, and TAF from low-dose BIC/FTC/TAF 30/120/15 mg tablets (Batch FX1701B), was evaluated against the marketed adult-strength BIC/FTC/TAF 50/200/25 mg tablets in Study GS-US-380-4424. Although the production methods are different in the two strengths, both use the same excipients and are fully dose proportional. Due to the differences in dosage strengths, PK parameters derived using the low-dose BIC/FTC/TAF tablet were normalized by dividing each value by 0.6, the ratio of the test dose/reference dose. The dose-normalized results show the low-dose BIC/FTC/TAF 30/120/15 mg tablet demonstrated bioequivalence to the adult-strength BIC/FTC/TAF50/200/25 mg tablet for AUC and Cmax within the pre-specified limits of 70% - 143%. In fact, all comparison were inside the typical acceptance interval of 80-125%. The same low-dose BIC/FTC/TAF 30/120/15 mg tablet formulation was used in all further development, clinical, and stability studies, and is identical to the designated commercial tablet formulation.

The food effect on BIC, FTC, and TAF from low-dose BIC/FTC/TAF 30/120/15 mg tablets, was evaluated again in Study GS-US-380-4424. A high-fat meal had no impact on BIC exposures (AUCinf, AUClast, and Cmax) but delayed the median Tmax of BIC from 1 hour to 4 hours. For FTC, the GLSM ratios and 90% CIs for AUCinf, AUClast, and Cmax were within the PK equivalence boundary of 70% to 143%, and median Tmax was delayed (from 1.00 hour to 2.00 hours) after administration with a high-fat meal. Mean TAF AUCinf increased by 42%, Cmax decreased by 44%, and the median Tmax was delayed (from 0.5 hour to 1.5 hours) after administration with a high-fat meal compared with fasted.

Being BIC and TAF low solubility drugs, food is expected to increase the bioavailability of both drugs. For BIC, in particular, this effect was demonstrated when administered as single agent or as a FDC with TAF and FTC but was not relevant in the low dose FDC. For TAF, the bioavailability increase observed with food after the administration with the FDC formulation is consistent with historical data of TAF as a single agent and as the F/TAF combination. For FTC, being this a BCS class 1 drug, a significant food effect was not expected.

Although these differences in bioavailability of TAF due to concomitant administration with food exist, the BIC/FTC/TAF FDC formulations were administered without regard to food in Phase 2/3 study in HIV-1 infected adolescents and children. As such, it is acceptable to conclude that BIC/FTC/TAF can be administered without regard to food.

#### 2.6.2.1.5. Pharmacokinetics in HIV-1 Infected Paediatric Subjects

The paediatric pharmacokinetics in HIV-1 Infected paediatric subjects for the individual components of Biktarvy BIC, FTC and TAF are summarised below, together with TFV.

- ***BIC* Pharmacokinetics in HIV-1 Infected Paediatric Subjects**

Plasma concentrations of BIC were best described by a 1-compartment model with first-order absorption with a lag time and first-order elimination. The effect of WT (body weight) on CL/F and Vc/F was included using fixed allometric exponents of 0.75 and 1, respectively. The effect of PPI (Proton-pump inhibitor) administration was added to ka and fixed to the value estimated in adults. Asian race on CL/F (−26.9%) and Vc/F (−27.2%) was found to be significant during the stepwise covariate modelling search. No additional covariates were found to significantly affect BIC exposure.

BIC exposures were inversely correlated with WT, percentage changes in BIC exposures ranging from −44.3% to +99.8% (relative to median exposures) for subjects with extreme covariate values (i.e., 5th and 95th WT percentiles). Based on the protocol-defined and weight-based dosing strategy and favourable clinical safety profile, these changes in exposure were not deemed clinically significant.

- ***FTC* Pharmacokinetics in HIV-1 Infected Paediatric Subjects**

Exposures of FTC in adolescents weighing ≥ 35 kg and children weighing ≥ 25 kg receiving adult-strength BVY tablets (BIC/FTC/TAF50/200/25 mg) were compared with pooled intensive PK data from Phase 3 Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878 (N = 77) in HIV-1 infected adult subjects.

In adolescents ≥ 35 kg, FTC AUCtau and Cmax were comparable to those in adults from the Phase 3 BVY studies. FTC Ctau was 31% lower than observed in adults.

In children ≥ 25 kg, FTC Ctau was comparable to that in adults from the Phase 3 BVY studies. FTC AUCtau and Cmax were 42% and 85% higher, respectively, than in adults.

These differences in FTC PK were not deemed clinically relevant based on the favourable safety profile of BIC/FTC/TAF.

Exposures of FTC in children ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving the low dose BVY tablet (BIC/FTC/TAF30/120/15 mg) were compared to pooled intensive PK data from the Phase 3

Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878 (N = 77) in HIV-1 infected adult subjects receiving the adult-strength BVY tablet (BIC/FTC/TAF50/200/25 mg)

In children ≥ 2 years of age weighing ≥ 14 to < 25 kg, FTC AUCtau and Ctau were comparable to those in adult subjects in the Phase 3 BVY studies. FTC Cmax was 81% higher than in adults; this difference was not deemed clinically relevant based on the favourable safety profile of BVY.

- ***TAF* Pharmacokinetics in HIV-1 Infected Paediatric Subjects**

Predicted systemic exposures of TAF in adolescents weighing ≥ 35 kg and children weighing ≥ 25 kg receiving adult-strength BVY tablets (BIC/FTC/TAF 50/200/25 mg) were compared with those from BVY-treated, HIV-1 infected adult subjects in the Phase 3 Studies GS-US-380-1489 and GS-US-380-1490 (N = 486). Tenofovir alafenamide AUCtau and Cmax in BVY-treated adolescents ≥ 35 kg were generally comparable to those in adults.

Tenofovir alafenamide AUCtau and Cmax in children ≥ 25 kg who received adult-strength BVY tablets (BIC/FTC/TAF 50/200/25 mg) were 60% and 33% higher, respectively, compared to adults. Exposures of TAF in children were within the range of safe exposures from historical data in adults for approved F/TAF-containing products. In consideration of the favourable safety profile for BVY in the paediatric population and the lack of an exposure-safety relationship for TAF in the Phase 3 BIC/FTC/TAF development programme, higher TAF exposure in children was not considered clinically relevant.

Predicted systemic exposures of TAF in children ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving low dose BVY tablets (BIC/FTC/TAF 30/120/15 mg) were compared with those from BVY-treated, HIV-1 infected adult subjects in the Phase 3 Studies GS-US-380-1489 and GS-US-380-1490 (N = 486).

Tenofovir alafenamide Cmax in BVY-treated children ≥ 2 years of age weighing ≥ 14 to < 25 kg was comparable to that in adults. The modestly higher (42%) TAF AUCtau was within the range of safe exposures from historical data in adults for approved F/TAF-containing products. In consideration of the favourable safety profile for BIC/FTC/TAF in the paediatric population and the lack of an exposure-safety relationship for TAF in the Phase 3 BIC/FTC/TAF development program, higher TAF exposure in children was not considered clinically relevant.

Plasma concentrations of TAF were best described by a 1-compartment model with sequential zero-order first-order absorption and first-order elimination. The effects of WT on CL/F and Vc/F were included using fixed allometric exponents of 0.75 and 1, respectively. COBI was found to affect F1 (163.6% increase). No additional covariates were found to significantly affect TAF exposure.

TAF exposures were inversely correlated with WT, with percent changes in TAF exposures ranging from −36% to +84.7% (relative to median exposures) for subjects with extreme covariate values (ie, 5th and 95th WT percentiles, respectively). In addition, COBI was the most influential covariate with an increase in TAF exposures of +164%. Based on the protocol-defined, boosted third agent- and WT-based dosing strategy, these changes in exposure have been appropriately accounted for.

- ***TFV* Pharmacokinetics in HIV-1 Infected Paediatric Subjects**

Predicted systemic exposures of TFV in adolescents weighing ≥ 35 kg (Cohort 1) and children weighing ≥ 25 kg (Cohort 2) receiving adult-strength BIC/FTC/TAF were compared with those from GEN-treated,

HIV-1 infected adult subjects in the Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 (N = 841).

Tenofovir AUCtau, Cmax, and Ctau in BVY-treated adolescents ≥ 35 kg were similar to those in adults.

In children ≥ 25 kg, TFV AUCtau and Ctau were comparable to those in adult subjects in the Phase 3 GEN studies. The difference in TFV Cmax (66% higher than in adults) was not deemed clinically relevant based on the favourable safety profile of Biktarvy and were within the range of safe exposures from historical data in adults for approved F/TAF-containing products.

Predicted systemic exposures of TFV in children ≥ 2 years of age weighing ≥ 14 to < 25 kg receiving low dose BVY tablets (BIC/FTC/TAF 30/120/15 mg) were compared with those from GEN-treated, HIV-1 infected adult subjects in the Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 (N = 841)

Tenofovir AUCtau and Ctau in BVY-treated children ≥ 2 years of age weighing ≥ 14 to < 25 kg were comparable to those in adults. The difference in TFV Cmax (37% higher than in adults) was not deemed clinically relevant based on the favourable safety profile of BIC/FTC/TAF, and was within the range of safe exposures from historical data in adults for approved F/TAF-containing products.

Plasma concentrations of TFV were best described by a sequential 1-compartment TAF model and 2-compartment TFV model with first-order elimination. A parallel absorption compartment with first-order process was introduced in the model to describe TFV data in the presence of LPV/r (increase in F of 209.5%). The effects of WT on CLM/F, QM/F, VcM/F, and VpM/F were included using fixed allometric exponents of 0.75 and 1 for clearances and volumes of distribution, respectively. Baseline CLCRSW was found to significantly affect CLM/F. No additional covariates were found to significantly affect TFV exposure.

TFV exposures were inversely correlated with WT, with percentage changes in TFV exposures ranging from −37.4% to +89.9% (relative to the median exposures) for subjects with extreme covariate values (ie, 5th and 95th WT percentiles, respectively). In addition, LPV/r and COBI were the most influential covariates with an increase in TFV exposures of +231% and +164%, respectively. Finally, the effect of baseline CLCRSW was a minimally influential covariate, with percentage changes in TFV exposures ranging from approximately −18.4% to +20.1% (relative to median exposures) for subjects with extreme covariate values (ie, 5th and 95th baseline CLCRSW percentiles, respectively). Based on the protocol-defined, boosted third agent- and WT-based dosing strategy, these changes in exposure have been appropriately accounted for.

#### 2.6.2.1.6. Further PK analysis on BIC, TAF and TFV

- ***Body Weight***

Baseline WT was included as a covariate on CL/F and Vz/F in the final PopPK models for BIC, TAF, and TFV. Consistent with the identified WT effect, exposures for BIC, TAF, and TFV were found to increase at decreasing WT.

- ***Estimated Glomerular Filtration Rate***

*- BIC and TAF*

Baseline CLCRSW was not identified as a statistically significant covariate for BIC and TAF PK in their respective final PopPK models. In paediatric subjects, BIC and TAF exposures were generally similar across the range of baseline CLCRSW values.

*- TFV*

Baseline CLCRSW was identified as a statistically significant covariate for TFV PK in the final PopPK model. This is as expected since TFV is renally eliminated. In paediatric subjects, TFV exposures were generally similar across the range of baseline CLCRSW values.

These findings go in line with the adult population, although all paediatric HIV-1 infected subjects presented normal renal function.

- ***Gender***

Gender was not considered a relevant covariate on the BIC, TAF and TFV popPK models and goes in line with previous findings in the adult population.

- ***Race***

Race was identified as a statistically significant covariate for BIC and TAF PK in their respective final PopPK models once body size was accounted for. However, the limited sample sizes within each race category would prevent a robust quantification of the effects of race on BIC exposures.

#### *2.6.2.2. Pharmacodynamics*

The primary and secondary pharmacology profile of Biktarvy has been previously established for adults. Pharmacodynamic interactions between Biktarvy or its individual component(s) and co-administered medicinal products have only been performed in adults and no specific study in the paediatric population was submitted with the dossier for this application.

During the assessment of this procedure, the MAH submitted however further PK/PD data to provide the quantitative description of the effect of Biktarvy on bone and renal toxicity.

### 2.6.3. Discussion on clinical pharmacology

Study GS-US-380-1474 evaluated the PK, safety, and efficacy of the adult-strength BVY tablet (BIC/FTC/TAF 50/200/25 mg) in virologically suppressed HIV-1 infected adolescents ≥ 12 to < 18 years of age weighing ≥ 35 kg (Cohort 1) and children ≥ 6 to < 12 years of age weighing ≥ 25 kg (Cohort 2), and a low dose BVY tablet (BIC/FTC/TA F30/120/15 mg) in virologically suppressed HIV-1 infected children ≥ 2 years of age weighing ≥ 14 to < 25 kg (Cohort 3). Intensive PK samples collected from the PK lead-in phase (Part A) of each cohort were used to estimate PK parameters for BIC, FTC, TAF and TFV.

Two PopPK studies were presented:

- The first considered a population pharmacokinetic analysis of bictegravir in HIV-1 infected adolescents and children and included data from study GS-US-380-1474 with 122 subjects from >2 to <18 years of age. Two fixed dose combination strengths were considered in the data. The model was developed based on a previously developed model and the addition of covariates was made by forward addition and backward deletion. The final model for BIC was a 1-compartment model with first-order

absorption with a lag time and linear elimination. Weight effects were included on CL/F and Vc/F using fixed allometric exponents of 0.75 and 1, respectively. The effect of proton-pump inhibitor (PPI) administration was added to ka and fixed to the value estimated in adults. In addition, Asian subjects were found to have lower CL/F (26.9% reduction) and Vc/F (27.2% reduction). Between-subject variability was included on CL/F and Vc/F and a combination of additive and proportional error model was used to characterize residual variability. The final model parameters were estimated with good confidence (%RSE <30%), presented low shrinkage (<15%) and were confirmed by bootstrapping. GOF plots were acceptable as well as the presented pcVPC (stratified by weight).

- The second considered a population pharmacokinetic analysis of tenofovir alafenamide and tenofovir following administration of tenofovir alafenamide-containing–fixed-dose combinations in HIV-1-infected adolescents and children. Data was collected across various TAF-based regimens (Studies GS-US-292-0106, GS-US-292-1515, GS-US-311-1269, and GS-US-380-1474) and was used to develop sequential PK model(s) of TAF and TFV in HIV-1-infected adolescents and children. Addition of covariates was again made by forward addition and backward deletion. The final paediatric TAF model, simplified from previous TAF PopPK analysis due to various reproducibility and robustness issues, was described by a 1-compartment model with sequential zero- and first-order absorption and first-order elimination. Between-subject variability was included on the duration of zero-order absorption only and resulted in a high value of 108%. A combined error model was used to characterize residual variability, with the inclusion of between-subject variability on the proportional error term. Baseline WT effects were included on CL/F and Vc/F using fixed allometric exponents of 0.75 and 1, respectively. Cobicistat was found to affect relative bioavailability of TAF (163.6% increase), whereas lopinavir/ritonavir-boosted TAF was found to yield comparable exposure to unboosted TAF. In addition, TAF Vc/F was found to be lower in Asian subjects (-78.8% reduction). No additional covariates were found to significantly affect TAF exposure. The final model parameters were estimated with good confidence (%RSE <10%), presented low shrinkage (<25%) and were confirmed by bootstrapping. GOF plots were acceptable as well as the presented pcVPC (stratified by weight and by booster groups) although missing on the higher observed values and not entirely able to predict the values around Tmax. This was the result of several model simplifications that were made in order to achieve stability. The final paediatric sequential TAF-TFV model was described by the previous sequential 1-compartment TAF model and a 2-compartment TFV model with first-order elimination was found to best describe the TFV paediatric data. A parallel absorption compartment with first-order process was introduced in the model to describe TFV data in the presence of the LPV/RTV booster. Between-subject variability was included on apparent oral clearance of TFV (CLM/F), apparent inter-compartmental clearance of TFV (QM/F), VcM/F, and apparent peripheral volume of distribution of TFV (VpM/F); and a combined proportional and additive error model was used to characterize the Residual Variability. The estimated LPV/RTV effect on TFV relative bioavailability (F) was 209.5% increase. Effects of WT were included on CLM/F, QM/F, VcM/F, and VpM/F using fixed allometric exponents of 0.75 and 1, for clearances and volumes of distribution, respectively. In addition, baseline creatinine clearance derived by Schwartz equation was found to significantly affect CLM/F. No additional covariates were found to significantly affect TAF exposure. Most of the final model parameters were estimated with good precision (%RSE <25%) and presented low shrinkage (<20%). Parameter were also confirmed by bootstrapping. GOF plots were acceptable as well as the presented pcVPC (stratified by weight and by booster groups). Overall, the popPK models was considered to be adequate for the purpose.

### 2.6.4. Conclusions on clinical pharmacology

Data from Study GS-US-380-1474 in paediatric patients were presented and analysed to better characterise exposition in paediatric population.

Based on these PK data, no efficacy concern is expected for paediatric subjects.

Population PK models were developed to characterize the exposures of BIC, TAF, and TFV in virologically suppressed adolescents and children ≥ 2 years of age weighing ≥ 14 kg in both the PK lead-in and treatment phases using all available intensive and sparse plasma concentration data. Population PK parameters of BIC, TAF, and TFV were predicted and also compared to historical PopPK data in HIV-1 infected adults. Results for BIC and TAF were generally similar to the ones obtained based on rich data and non-compartmental PK analysis. Overall, statistical comparisons of BIC, FTC, TAF, and TFV plasma PK parameters between children in Cohort 2 Part A and adolescent subjects in Cohort 1 Part A concluded that exposures in children of Cohort 2 Part A were, in general, higher than the adolescent subjects given that the children in Cohort 2 were from a lower weight band compared to the adolescents, and were administered the same dose as adolescents.

Statistical comparisons of BIC, FTC, TAF, and TFV plasma PK parameters between children in Cohort 3 Part A and adolescent subjects and children in Cohorts 1 and 2 Part A concluded that exposures were generally similar between children in Cohort 3 Part A and adolescents and children in Cohorts 1 and 2 Part A, with less than 27% variation in geometric mean ratio.

The PK/pharmacodynamic (PD) analysis provides support for an advantageous safety profile for TAF, both unboosted and with a boosted third agent, compared with TDF in the paediatric population ≥ 2 years of age weighing ≥ 14 kg.

In general, the pharmacodynamics of Biktarvy have been sufficiently evaluated in the paediatric patients at least 2 years of age and weighing at least 14 kg. No major issues have been identified.

The PK/PD data support the use of the low-dose Biktarvy tablet (BIC/FTC/TAF 30/120/15 mg) in paediatric patients ≥ 2 years of age weighing ≥14 to < 25 kg.

## 2.6.5. Clinical efficacy

### *2.6.5.1. Main study: GS-US-380-1474*

*A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the GS-9883/Emtricitabine/Tenofovir Alafenamide (GS-9883/F/TAF) Fixed Dose Combination (FDC) in HIV-1 Infected Adolescents and Children*

This is an ongoing phase 2/3, open-label, multicenter, multicohort, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity, of the BIC/FTC/TAF FDC in HIV-1 infected, virologically supressed adolescent and children.

Adolescents ≥ 12 to < 18 years of age weighing ≥ 35 kg (Cohort 1) and children ≥ 6 to < 12 years of age weighing ≥ 25 kg (Cohort 2) received 1 adult-strength BIC/FTC/TAF 50/200/25 mg FDC tablet, administered orally, once daily, at approximately the same time each day, without regard to food. Children ≥ 2 years of age weighing ≥ 14 kg (Cohort 3) received 1 low-dose BIC/FTC/TAF 30/120/15 mg FDC tablet, administered orally, once daily, at approximately the same time each day, without regard to food. For each cohort, the study was divided into Parts A and B. Subjects in Part A participated in an intensive PK evaluation at Week 2 or 4. Screening was initiated for Part B following confirmation of BIC PK and short-term safety data from Part A for each cohort.

The PK, safety, and efficacy data presented here are from an interim analysis performed when all subjects in Cohort 1 Parts A and B, and Cohort 2 Parts A and B had completed their Week 96 visit, and all subjects in Cohort 3 Parts A and B had completed their Week 24 visit. Six subjects in Cohort 3 attained a weight

≥ 25 kg during the study and were switched to the adult-strength BIC/FTC/TAF 50/200/25 mg tablet (as appropriate for this weight band). Sensitivity analyses were performed in respect of the main efficacy endpoint (percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US Food and Drug Administration (FDA)-defined snapshot algorithm) and palatability/acceptability assessments, in which subjects who switched from the low-dose BIC/FTC/TAF 30/120/15 mg tablet to the adult-strength BIC/FTC/TAF 50/200/25 mg tablet by virtue of having attained a weight ≥ 25 kg during the main phase of the study were excluded from the Full and Safety Analysis Sets at the appropriate time points.

***Study Participants***

Eligible subjects were HIV-1 infected adolescents (Cohort 1: ≥ 12 to < 18 years of age, weight ≥ 35 kg) and children (Cohort 2: ≥ 6 to < 12 years of age, weight ≥ 25 kg; Cohort 3: ≥ 2 years of age, weight ≥ 14 to < 25 kg) virologically suppressed for ≥ 6 months prior to screening on a stable antiretroviral regimen comprising 2 nucleoside reverse transcriptase inhibitors plus a third agent; eGFR ≥ 90 mL/min/1.73 m2 at screening; and no documented or suspected resistance to FTC, tenofovir or INSTI.

***Treatments***

- **Cohort 1 and 2**: Adult-strength fixed dose combination (FDC) tablet of BIC/FTC/TAF **(50/200/25 mg)** administered orally, once daily, at approximately the same time each day, without regard to food.
- **Cohort 3**: Low-dose FDC tablet of BIC/FTC/TAF **(30/120/15 mg)** administered orally, once daily, at approximately the same time each day, without regard to food.

***Objectives***

The primary objectives for Cohorts 1 and 2 are as follows:

- Part A
  - To evaluate the steady state PK of BIC and confirm the dose of the BIC/FTC/TAF 50/200/25 mg FDC in HIV-1 infected, virologically suppressed adolescents (≥ 12 to < 18 years of age) and children (≥ 6 to < 12 years of age)
- Parts A and B
  - To evaluate the safety and tolerability of the adult strength BIC/FTC/TAF FDC through Week 24 in HIV-1 infected, virologically suppressed adolescents (≥ 12 to < 18 years of age) and children (≥ 6 to < 12 years of age)

The primary objectives for Cohort 3 are as follows:

- Part A
  - To evaluate the steady state PK of BIC and confirm the dose of the BIC/FTC/TAF 30/120/15 mg FDC in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg
- Parts A and B
  - To evaluate the safety and tolerability of the low-dose BIC/FTC/TAF FDC tablet through Week 24 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 to < 25 kg

***Outcomes/endpoints***

- **Efficacy endpoint**:

The efficacy endpoints for Cohorts 1 and 2 are as follows:

- The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm;
- The change from baseline in CD4 cell counts and percentages at Weeks 24 and 48;
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 (missing = failure [M = F] and missing = excluded [M = E] analyses).

The efficacy endpoints for Cohort 3 are as follows:

- The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm;
- The change from baseline in CD4 cell count and percentage at Weeks 24 and 48;
- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 (M = F and M = E analyses).

- **Safety endpoint**

Evaluation of the safety and tolerability of the adult strength BIC/FTC/TAF FDC through Week 24 in HIV-1 infected, virologically suppressed adolescents (≥ 12 to < 18 years of age) and children (≥ 6 to < 12 years of age).

Data are derived from an interim analysis performed when all subjects in Cohorts 1 and 2 had completed their Week 96 visit and all subjects in Cohort 3 had completed their Week 24 visit, or prematurely discontinued study drug.

***Randomisation and blinding (masking)***

This is a non-randomized open-label study.

***Statistical methods***

Efficacy analyses used the FAS, which included all subjects who were enrolled into the study and received at least 1 dose of study drug. The proportions of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 were evaluated using both the US FDA defined snapshot algorithm and M = F and M = E analyses. The 95% CIs for these percentages were constructed using the Clopper-Pearson Exact method.

The CD4 cell count and CD4% data, including change from baseline, were summarized using observed, on-treatment data (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug).

## *Results*

***Participant flow***

A total of 124 subjects were enrolled in the study:

Cohorts 1 and 2 (Age ≥ 6 to < 18 Years and Weight ≥ 25 kg)

Of 116 subjects screened, 102 were enrolled, of whom 100 received study drug. At the data-cut date, 99.0% (99 of 100) of treated subjects had completed study drug in the main (48-week) treatment phase and had entered the extension phase. One subject (1%) prematurely discontinued study drug in the main phase prior to the data-cut date because of an AE. At the data-cut date, 73 subjects were continuing to receive study drug, 22 subjects had completed the study, and 4 subjects had discontinued study drug (1 due to pregnancy, 1 following a parent/guardian decision, and 1 was lost to follow-up).

Cohort 3 (≥ 2 years of age, and weight ≥ 14 to < 25 kg)
Of 22 subjects screened, all were enrolled and received study drug. At the data-cut date, 54.5% (12 of 22) of treated subjects had completed study drug in the main (48-week) treatment phase, and 45.5% (10 of 22) of subjects were continuing to receive study drug in the main phase. No subject prematurely discontinued study drug in the main phase. At the data-cut date, all 12 subjects who completed study drug in the main phase had entered the extension phase and were continuing to receive study drug.

***Conduct of the study***

Subjects were enrolled and treated by 24 investigators at a total of 22 study centers: 8 in South Africa, 3 in Thailand, 1 in Uganda, and 10 in the United States (US).

The protocol was amended 5 times during the course of Study GS-US-380-1474.

- **Protocol deviations:**

Cohorts 1 and 2:

A total of 59 important protocol deviations occurred in 36 subjects in Cohorts 1 and 2 during the study. Of the 36 subjects, 24 subjects had a single important deviation, 6 subjects had 2 important deviations, 4 subjects had 3 important deviations, 1 subject had 5 important deviations, and 1 had 6 important deviations. The most common important protocol deviations were for a treatment compliance issue. Of these 15 deviations, 9 deviations were for treatment compliance less than 70% between 2 scheduled study visits. None of these important protocol deviations affected the overall quality or interpretation of the study data.

There were no important protocol deviations because of COVID-19 pandemic-related study disruption in Cohorts 1 and 2. None of the pandemic-related protocol deviations affected the overall quality or interpretation of the study data.

Cohort 3:

A total of 10 important protocol deviations occurred in 8 subjects during the study. Of the 8 subjects, 6 subjects had a single important deviation and 2 subjects had 2 important deviations. Half of the important protocol deviations (5 of 10) were for missing data.

- **Adherence**

Cohort 1 and 2:

The median adherence rates to study drug up to the Week 24 and 48 visits, and up to the data-cut date, were 98.8%, 98.6%, and 98.3%, respectively. The percentage of subjects with an adherence rate ≥ 95% was 90.0% up to the Week 24 visit, 80.0% up to the Week 48 visit, and 82.0% up to the data-cut date.

Cohort 3:

The median adherence rates to study drug up to the Week 24 and 48 visits and up to the data-cut date were 99.4%, 99.5%, and 99.4%, respectively. The percentage of subjects with an adherence rate ≥ 95% was 86.4% up to the Week 24 visit, 83.3% up to the Week 48 visit, and 86.4% up to the data-cut date.

***Baseline data***

**Subject Demographics and Baseline Disease Characteristics:**

In each 3 cohorts, ages and weights were rather well represented, including subjects with low age (12 years in cohort 1, 6 years in cohort 2, 3 years in cohort 3) and weight (35 kg in cohort 1, 25 kg in cohort 2, 14 kg in cohort 3). Furthermore, in cohort 3, the heaviest subject weighed 24 kg, i.e. the maximum weight limit for this cohort.

Overall, paediatric subjects included in this study are well controlled under their current ARV, without advanced disease. The majority of the included subjects were asymptomatic. No subject had CD4 level <200/µl (>90% with CD4 level >500/µl) and >90% of them have asymptomatic disease.

***Outcomes and estimation***

Cohorts 1 and 2:

Proportion of subjects with Plasma HIV-1 RNA < 50 copies/mL at weeks 24 and 48:

At Week 24, all subjects in both Cohort 1 (Parts A and B) and Cohort 2 (Parts A and B) in the FAS had HIV-1 RNA < 50 copies/mL using the US FDA defined snapshot algorithm.

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

Cohort 1 (Parts A and B): 98.0% (95% CI: 89.4% to 99.9%)
Cohort 2 (Parts A and B): 98.0% (95% CI: 89.4% to 99.9%)
Overall: 98.0% (95% CI: 93.0% to 99.8%)

Using the Missing = Failure and Missing = Excluded imputation methods, the results at Week 24 and Week 48 are as follows:

M = F: Week 24, 100.0% (100 of 100 subjects); Week 48, 98.0% (98 of 100 subjects)

M = E: Week 24: 100.0% (100 of 100 subjects); Week 48, 99.0% (98 of 99 subjects)

Change from Baseline in CD4 Cell Counts and Percentages at Weeks 24 and 48:

CD4 cell counts and CD4% were maintained through Week 48. Mean (SD) baseline CD4 cell counts (FAS) were as follows: Cohort 1, 751 (224.4) cells/µL; Cohort 2, 930 (309.9) cells/µL.

Mean (SD) changes from baseline in CD4 cell count were as follows:
At Week 24: Cohort 1, 14 (190.4) cells/µL; Cohort 2, -24 (237.7) cells/µL
At Week 48: Cohort 1, -22 (164.2) cells/µL; Cohort 2, -40 (158.8) cells/µL

Mean (SD) baseline CD4% (FAS) was as follows: Cohort 1, 33.6 (6.23); Cohort 2, 35.8 (6.97).

Mean (SD) changes from baseline in CD4% were as follows:
At Week 24: Cohort 1, 0.4% (3.75%); Cohort 2, 0.8% (3.55%)
At Week 48: Cohort 1, 0.5% (3.41%); Cohort 2, 0.2% (3.80%)

Percentages of subjects in Cohorts 1 and 2, combined, with HIV-1 RNA < 50 copies/mL at Week 96 determined using the M = F and M = E methods were as follows:

M = F: Week 96, 95.0% (95 of 100 subjects)

M = E: Week 96: 99.0% (95 of 96 subjects)

Cohort 3

Proportion of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using the US FDA-Defined Snapshot Algorithm

At Week 24, 90.9% of subjects in Cohort 3 (Parts A and B) (95% CI: 70.8% to 98.9%) and in the FAS had HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm.

At Week 48, 91.7% of subjects in Cohort 3 Part A (95% CI: 61.5% to 99.8%) and in the FAS had HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm.

Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 Using the Missing = Failure and Missing = Excluded Imputation Methods

Percentages of subjects in Cohort 3 with HIV-1 RNA < 50 copies/mL at Week 24 (Parts A and B) and Week 48 (Part A) determined using the M = F and M = E methods were as follows:

M = F: Week 24, 90.9% (20 of 22 subjects); Week 48, 91.7% (11 of 12 subjects)
M = E: Week 24: 100.0% (20 of 20 subjects); Week 48, 100.0% (11 of 11 subjects)

Change from Baseline in CD4 Cell Counts and Percentages at Weeks 24 and 48

CD4 cell counts and CD4% were maintained through Week 48. Mean (SD) baseline CD4 cell counts (FAS) were as follows: at Week 24 for Cohort 3 Parts A and B, 931 (340.3) cells/µL; at Week 48 for Cohort 3 Part A, 907 (399.2) cells/µL.
Mean (SD) changes from baseline in CD4cell counts were as follows:
At Week 24: Cohort 3 Parts A and B, -126 (264.2) cells/µL
At Week 48: Cohort 3 Part A, -22 (184.6) cells/µL

Mean (SD) baseline CD4% (FAS) was as follows: at Week 24 for Cohort 3 Parts A and B, 33.4 (7.56); at Week 48 for Cohort 3 Part A, 32.9 (7.61).

Mean (SD) changes from baseline in CD4% were as follows:
At Week 24: Cohort 3 Parts A and B, 0.2% (4.42%)
At Week 48: Cohort 3 Part A, -1.1% (3.32%)

***Virology resistance analyses***

Of the 100 subjects in the FAS, 5 subjects (5.0%) in Cohort 1 (none in Cohort 2) met the VF and RAP inclusion criteria through Week 96. In Cohort 1, 4 of the 5 RAP subjects resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drug, resulting in 1 subject in Cohort 1B being included in the final RAP. This subject had M184V, K103N, and Y188H at baseline and at VF, with no treatment-emergent resistance to study drug.

In cohort 3, no subject was qualified for resistance testing.

***Acceptability/palatability***

In Cohorts 1 and 2, no subject reported dissatisfaction with either the palatability of the BIC/FTC/TAF tablet ("Product Taste Normal") or its acceptability in terms of shape and size ("Acceptable Shape and Size") at Baseline/Day 1 and Week 4.

In Cohort 3, the majority of subjects had a neutral ("maybe good or maybe bad/could not taste it") or positive ("good" or "super good") palatability assessment at baseline (90.9%, 20 of 22 subjects) and Week 24 (89.5%, 17 of 19 subjects). The majority of subjects had a neutral or positive acceptability response for ease of swallowing, shape, and size when the study drug was swallowed whole at baseline, Weeks 4, 24, and 48:

- In response to the question "How easy was it to swallow the study drug?", the majority of subjects who swallowed the study drug whole reported "easy" or "super easy" (baseline: 82.4%, 14 of 17 subjects; Week 4: 87.5%, 14 of 16 subjects; Week 24: 75.0%, 12 of 16 subjects; Week 48: 71.4%, 5 of 7 subjects).
- In response to the question "How did the shape of the study drug feel when you swallowed it?", the majority of subjects who swallowed the study drug whole reported "good" or "super good" (baseline: 75.0%, 12 of 16 subjects; Week 4: 93.3%, 14 of 15 subjects; Week 24: 75.0%, 12 of 16 subjects; Week 48: 57.1%, 4 of 7 subjects).
- In response to the question "How did the size of the study drug feel when you swallowed it?", the majority of subjects who swallowed the study drug whole reported "okay" (baseline: 88.2%, 15 of 17 subjects; Week 4: 86.7%, 13 of 15 subjects; Week 24: 81.3%, 13 of 16 subjects; Week 48: 71.4%, 5 of 7 subjects).

For those subjects who split the drug in half, all reported taking each half within 10 minutes (5 subjects each at baseline and Week 4, 3 subjects at Week 24, and 1 subject at Week 48).

## 2.6.6. Discussion on clinical efficacy

Approximately one third of subjects had important protocol deviations, which is important, but no subject was excluded from study for such reasons. These protocol deviations did not raise concerns on the analysis of the results.

In the 3 cohorts adherence was good, with a median adherence rates > 98% in the 3 cohorts, 80% of subjects with adherence ≥95% and no subject with adherence <80%.

Ages and weights were rather well represented, including subjects with low age (12 years in cohort 1, 6 years in cohort 2, 3 years in cohort 3) and weight (35 kg in cohort 1, 25 kg in cohort 2, 14 kg in cohort 3). Furthermore, in cohort 3, the heaviest subject weighed 24 kg, i.e., the maximum weight limit for this cohort.

Overall, paediatric subjects included in this study are well controlled under their current ARV, without advanced disease. The majority of the included subjects were asymptomatic. No subject had CD4 level <200/µl (>90% with CD4 level >500/µl) and >90% of them have asymptomatic disease.

Virological suppression was maintained in most of the enrolled subjects in each cohort as shown by the high proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using the US FDA-Defined Snapshot Algorithm or the Missing = Failure and Missing = Excluded Imputation Methods. CD4 cell counts and CD4% were maintained through Week 48 in each cohort. For cohorts 1 and 2, additional efficacy data at week 96 is available, showing maintenance of virological suppression and

CD4 cell counts and CD4%. In cohort 3, no subjects have experienced virological failure, and only one subject (1%) in cohorts 1-2 have HIV-1 RNA level >50 c/ml at Week 48.

In conclusion, although efficacy results are secondary endpoints, these data are consistent with maintenance of the virological suppression on paediatric subjects treated with the proposed doses of Biktarvy.

Viral resistance analysis indicates that overall, BIC/FTC/TAF was administered in 7 subjects with resistance-associated mutation (RAMs) at baseline: 5 subjects with primary NRTI-RAM (M184V) and 2 subjects with primary INSTI-RAM (E92G, R263K). Five of 100 subjects (5.0%) in Cohort 1 had virological failure. Overall, there was no emergence of BIC, FTC or TFV RAM throughout study. The only one virologic failure of this study had already a FTC-RAM (M184V) at baseline without new emergence at virologic failure.

The number of paediatric subjects with confirmed virologic failure during 96 weeks of treatment with Biktarvy has been low (5.0%) and only in Cohort 1.

Considering the young age of subjects in cohort 3, the acceptability to swallow whole tablets is surprisingly good for such formulation, with only 1 subject/22 who finds it "hard" to swallow whole the tablet. However, it seems that 5 subjects have split the drug in half before intake, although it is specified is SmPC that "the tablets should not be chewed, crushed or split". The MAH clarified that these 6 children (3 to 5 years old, weighing 15-20 kg) did split the paediatric tablet in half, with full adherence rate and without virological failure. Mean PK data available from 3 of these subjects who split the paediatric tablet are consistent with the mean exposures of BIC, FTC and TAF measured in the study GS-US-380-1474 in 22 subjects aged ≥2 years and weighing ≥14 to < 25 kg. However, PK data from only 3 subjects cannot be conclusive on the BIC, FTC and TAF exposures when tablets are split in half.

Considering the high acceptability data from children who have taken the paediatric BIC/FTC/TAF tablets whole or split in half, and the film-coating that is not intended for PK properties (not a long-acting tablet) but rather for taste purpose, language on the possibility to split the tablet in half to facilitate the intake has been added to the Product Information.

### 2.6.7. Conclusions on clinical efficacy

Although the efficacy data from the paediatric study were not primary endpoints, these data could be considered supportive. The study design (non-comparative, limited sample size) and the lack of efficacy data on ART-naïve paediatric subjects somewhat limited the interpretation of these results. Notably, paediatric subjects included in this study are well controlled under their current ARV, without advanced disease.

However, more than 90% of paediatric subjects treated with Biktarvy (i.e., 100 subject weighing ≥25 kg treated with Biktarvy 50/200/25 mg and 22 subjects ≥2 years of age and weighing 14 to <25 kg treated with Biktarvy 30/120/15 mg) have maintained their virologic suppression at Week 48. Based on efficacy analyses at Week 24 and Week 48 using the USFDA defined snapshot algorithm, the rates of virologic suppression (HIV-1 RNA < 50 copies/mL) in the analysed samples were above 90% for Biktarvy, and high rates of virologic suppression were maintained beyond Week 48 in cohorts 1 and 2. There were no clinically relevant changes in CD4 cell counts and CD4%. No subjects developed treatment-emergent drug resistance substitutions in integrase or reverse transcriptase. Combined with PK data, these efficacy results support the use of Biktarvy in these paediatric population at the proposed doses.

## 2.6.8. Clinical safety

### *2.6.8.1. Patient exposure*

Cohort 1 and 2

All 100 paediatric subjects ≥ 6 to < 18 years of age weighing ≥ 25 kg received at least 1 dose of study drug. At the data cut date, the median (Q1, Q3) exposure to study drug in Cohorts 1 and 2 was 151.4 (125.6, 153.5) weeks.

Cohort 3

All 22 paediatric subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg received at least 1 dose of study drug. At the data-cut date, the median (Q1, Q3) exposure in Cohort 3 to study drug was 54.9 (29.3, 66.4) weeks.

In Cohorts 1 and 2, most children received BIC/FTC/TAF for a duration ≥96 Weeks (97%). The percentage of children started to decrease significantly for a duration ≥ 132 Weeks.

In Cohort 3, the duration of BIC/FTC/TAF was much more limited with a duration ≥24 Weeks in 95.5% of patients but only 54.5% of children received BIC/FTC/TAF for ≥36 Weeks. Therefore, the total exposure time to study drug was significantly lower in the younger population (cohort 3 - subjects ≥ 2 years of age weighing ≥ 14 to < 25 kg).

### *2.6.8.2. Adverse events*

*GS-US-380-1474*

Cohorts 1 and 2

86.0% (86 of 100) of subjects (Cohort 1 84.0%, 42 of 50 subjects; Cohort 2 88.0%, 44 of 50 subjects) had at least 1 AE, the majority of which were Grade 1 or 2 in severity and considered not related to study drug.

5 subjects had a Grade 3 or 4 AE (Cohort 1 8.0%, 4 of 50 subjects; Cohort 2 2.0%, 1 of 50 subjects), all considered not related to study drug. One subject, in Cohort 2, had an AE leading to premature study drug discontinuation that was considered related to study drug. No subject had a Stage 3, HIV-1 related opportunistic illness reported during the study.

Cohort 3

77.3% (17 of 22) of subjects had at least 1 AE, the majority of which were Grade 1 in severity and not considered related to study drug. No subject had a Grade 3 or 4 AE, an SAE, or an AE leading to premature study drug discontinuation. One subject had a hepatic AE (Grade 1 abnormal faeces). No subject had a Stage 3, HIV-1 related opportunistic illness reported during the study.

### *2.6.8.3. Serious adverse event/deaths*

**Deaths**

No treatment-emergent death was reported in Cohorts 1, 2 and 3 through the data cut date.

**Serious Adverse Events**

Cohorts 1 and 2

Serious AEs were reported for 5.0% (5 of 100) of subjects in Cohorts 1 and 2; none was considered related to study drug. Appendicitis was reported in 2 subjects, 1 subject in Cohort 1 and 1 subject in Cohort 2. No other SAE was reported for > 1 subject.

Cohorts 3

No SAEs were reported in Cohort 3 through the data-cut date.

#### *2.6.8.4. Treatment-Related Serious Adverse Events*

Cohorts 1 and 2

Adverse events considered related to study drug were reported for 13.0% (13 of 100) of subjects in Cohorts 1 and 2. Among study drug-related AEs, only abdominal discomfort (3.0%, 3 subjects) was reported with greater than single subject incidence. In each case, the abdominal discomfort was Grade 1 in severity and transient.

Cohorts 3

Adverse events considered related to study drug were reported for 13.6% (3 of 22) of subjects. Among study drug-related AEs, none was reported with greater than single subject incidence.

#### *2.6.8.5. Laboratory findings*

Haematology and Chemistry Laboratory Values

There were no clinically relevant changes from baseline in median values for haematology or clinical chemistry parameters. Median values were within the relevant reference ranges.

In cohorts 1 and 2, most subjects (99%; 99 out of 100) experienced at least one laboratory abnormality. The maximum toxicity was grade 1 or 2 for 69%, grade 3 or 4 laboratory abnormalities have been reported in 30% of subjects with the most frequent abnormality as haematuria (16 haematuria grade 3 / 4) which have been reported in all but one case in adolescents and considered by the investigators as related to menses. The other laboratory abnormalities reported have been grade 3/ 4 neutropenia (n= 7), amylase increased grade 3/ 4 (n= 3), hyperkalaemia grade 3 / 4 (n=2).

In cohort 3, most subjects (95.5%, 21 out of 22) had at least one laboratory abnormality with a maximum toxicity grade 1 or 2 for 77.3% of subjects and grade 3 or 4 for 18.2% of subjects. The most common grade 3/ 4 laboratory abnormalities were decreased neutrophils (13.6%, 3 out of 22 subjects).

No subject met Hy's Law criteria, defined as concurrent increases in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN) and total bilirubin > 2 x ULN with alkaline phosphatase < 2 x ULN and no alternative aetiology. There were no clinically relevant changes from baseline in median values for the liver-related laboratory parameters ALT, AST, alkaline phosphatase, or total bilirubin at Weeks 24, 48, 72, or 96.

There were no clinically relevant changes from baseline in median fasting values for total cholesterol, direct low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, total cholesterol: HDL cholesterol ratio, triglycerides, or glucose at Weeks 24, 48, or 96.

Concerning, renal laboratory parameters:

In Cohorts 1 and 2

-Increases from baseline in median values for serum creatinine were observed at Week 1 and through Week 96 and remained within the normal range for this population as shown in the figure below. The median (Q1, Q3) baseline serum creatinine value was 0.53 (0.46, 0.62) mg/dL. Median (Q1, Q3) changes from baseline in serum creatinine at Weeks 24, 48, and 96 were 0.07 (0.01, 0.11), 0.08 (0.03, 0.14), and 0.12 (0.06, 0.18) mg/dL, respectively. A graded laboratory abnormality in serum creatinine (Grade 1) was reported for 1 subject (1.0%, 1 of 100 subjects).

-Corresponding to the results for serum creatinine, decreases from baseline in median values for eGFRSchwartz were observed at Week 1, stabilizing after Week 12 through Week 96. The median (Q1, Q3) baseline eGFRSchwartz value was 150.5 (136.5, 172.5) mL/min/1.73 m2. Median (Q1, Q3) changes from baseline in eGFRSchwartz at Weeks 24, 48, and 96 were -12.5 (-26.0, 2.0), -16.0 (-33.0, -1.0), and -15.5 (-33.5, 0.0) mL/min/1.73 m2, respectively.

In Cohort 3

-Increases from baseline in median values for serum creatinine were observed at Week 4 and stabilized after Week 8. The median (Q1, Q3) baseline serum creatinine value was 0.38 (0.34, 0.43) mg/dL. The median (Q1, Q3) changes from baseline in serum creatinine at Weeks 24 and 48 were 0.07 (0.02, 0.09) and 0.06 (0.03, 0.15) mg/dL, respectively. A graded laboratory abnormality in serum creatinine was reported for 1 subject (4.5%, 1 of 22 subjects). This subject had a transient Grade 4 elevated serum creatinine that resolved 4 days later.

-Corresponding to the results for serum creatinine, decreases from baseline in median values for eGFRSchwartz were observed at Week 1, stabilizing after Week 16. The median (Q1, Q3) baseline eGFRSchwartz value was 160.5 (145.0, 168.0) mL/min/1.73 m2. Median (Q1, Q3) changes from baseline in eGFRSchwartz at Weeks 24 and 48 were -19.0 (-24.0, 4.0) and -8.0 (-38.0, -2.0) mL/min/1.73 m2, respectively.

**Vital signs**

There have been no clinically relevant changes in any vital signs parameter reported in any subject in Cohorts 1, 2 and 3.

**Height and Body Weight**

In Cohort 1

- For Body Weight

Media (Q1, Q3) body weight at baseline and Week 96 was 44.8 (40.0, 56.1) kg and 52.7 (47.4, 67.8) kg respectively.

At baseline, the body weight Z-score was mean (SD) -0.51 (1.393); median (Q1,Q3) -0.54 (-1.55, 0.39). Body weight Z-scores increased during the study. The change from baseline at Week 96 was mean (SD) 0.25 (0.462); median (Q1,Q3) 0.21 (-0.13, 0.58).

- For Height

Median (Q1, Q3) height at baseline and Week 96 was 155.5 (148.5, 159.0) cm and 158.6 (155.6, 165.0) cm respectively.

At baseline, the height Z-score was mean (SD) -1.04 (0.964); median (Q1, Q3) -0.87 (-1.62, -0.41). There were no clinically relevant changes in height Z-scores. The change from baseline at Week 96 was mean (SD) 0.11 (0.427); median (Q1, Q3) 0.06 (-0.04, 0.29)

In Cohort 2

- For Body Weight

Media (Q1, Q3) body weight at baseline and Week 96 was 29.0 (26.9, 32.5) kg and 42.1 (35.9, 49.7) kg respectively.

At baseline, the body weight Z-score was mean (SD) -0.39 (1.1123); median (Q1,Q3) -0.35 (-1.30, 0.45). Body weight Z-scores increased during the study. The change from baseline at Week 96 was mean (SD) 0.55 (0.617); median (Q1,Q3) 0.65 (0.24, 0.90).

- For Height

Median (Q1, Q3) height at baseline and Week 96 was 133.3 (129.5, 139.5) cm and 145.4 (142.0, 152.0) cm respectively.

At baseline, the height Z-score was mean (SD) -1.04 (0.964); median (Q1, Q3) -0.87 (-1.62, -0.41). There were no clinically relevant changes in height Z-scores. The change from baseline at Week 96 was mean (SD) 0.11 (0.522); median (Q1, Q3) 0.19 (-0.20, 0.39)

In Cohort 3

- For Body Weight

Media (Q1, Q3) body weight at baseline and Week 48 was 18.7 (15.2, 21.7) kg and 22.3 (17.4, 25.0) kg respectively.

At baseline, the body weight Z-score was mean (SD) -0.65 (1.073); median (Q1,Q3) -0.35 (-1.47, 0.10). Body weight Z-scores increased during the study. The change from baseline at Week 48 was mean (SD) 0.09 (0.357); median (Q1,Q3) 0.0.13 (-0.22, 0.39).

- For Height

Median (Q1, Q3) height at baseline and Week 48 was 111.3 (100.0, 117.5) cm and 119.5 (106.4, 129.6) cm respectively.

At baseline, the height Z-score was mean (SD) -0.80 (1.118); median (Q1, Q3) -0.53 (-1.74, 0.00). There were no clinically relevant changes in height Z-scores. The change from baseline at Week 48 was mean (SD) 0.16 (0.366); median (Q1, Q3) 0.14 (-0.20, 0.50)

Overall, according to the MAH, there have been no clinically relevant changes from baseline in height and Body weight Z-scores increased during the study.

**Tanner stage Assessments**

In Cohorts 1 and 2, changes in Tanner stages for genitalia in males and breasts in female from baseline to96 were Weeks 24, 48 and 96 were consistent with the paediatric study population aged 6 to <18 years.

In Cohort 3, for subjects ≥6 years of age, changes in Tanner stages for genitalia in males and breasts in females from baseline to Weeks 24 and 48 were consistent with this paediatric population.

**Pregnancy**

Two pregnancies have been reported in subjects included in the Cohorts 1 and 2 through the cut-off date. One pregnancy resulted in a normal healthy baby and the other was reported as resolved without additional information about the outcome.

### *2.6.9. Safety in special populations*

Palatability and Acceptability of PFS Formulation in Paediatric Patients

Palatability and acceptability were assessed to confirm the appropriateness of the adult strength. BIC/FTC/TAF 50/200/25 mg FDC tablet for use in adolescents (≥ 12 to < 18 years of age, weight ≥ 35 kg) and children (≥ 6 to < 12 years of age, weight ≥ 25 kg), and the low-dose BIC/FTC/TAF 30/120/15 mg FDC tablet for use in children ≥ 2 years of age, and weight ≥ 14 to < 25 kg.

Cohorts 1 and 2

No subject in Cohort 1 or 2 reported dissatisfaction with either the palatability of the BIC/FTC/TAF tablet ("Product Taste Normal") or its acceptability in terms of shape and size ("Acceptable Shape and Size") at Baseline/Day 1 and Week 4.

Cohort 3

In Cohort 3, the majority of subjects had a neutral ("maybe good or maybe bad/could not taste it") or positive ("good" or "super good") palatability assessment at baseline (90.9%, 20 of 22 subjects) and Week 24 (89.5%, 17 of 19 subjects).

The majority of subjects had a neutral or positive acceptability response for ease of swallowing, shape, and size when the study drug was swallowed whole at baseline, Weeks 4, 24, and 48.

### *2.6.10. Safety related to drug-drug interactions and other interactions*

Drug-drug interactions

There is low potential for BIC/FTC/TAF to cause drug-drug interactions (DDIs).

Because no PK enhancer such as COBI or RTV is required to maintain BIC plasma concentrations, the DDI potential of BIC/FTC/TAF is lower than that of other approved agents. The reduced risk of DDIs is an important benefit in the maintenance of treatment adherence in a paediatric population.

### *2.6.11. Discontinuation due to AES*

In cohort 1 and 2, adverse events (insomnia, worsening anxiety [both Grade 2]) that led to premature study drug discontinuation were reported for 1 subject (1.0%). Neither AE was serious, although both were considered related to study drug

In cohort 3, No subject discontinued study drug or the study due to an AE in Cohort 3 through the data-cut-off date.

### *2.6.12. Post-marketing experience*

No post-marketing data are included in this submission.

### *2.6.13. Long-term safety profile of Biktarvy*

Three studies have investigated F/TAF-containing regimens in the paediatric population:

1. Biktarvy (BIC/FTC/TAF) (Study GS-US-380-1474) in children/adolescents with human immunodeficiency virus (HIV) infection ≥ 2 to < 18 years of age weighing ≥ 14 kg
2. Elvitegravir [E]/cobicistat (C)/F/TAF (Study GS-US-292-0106) in children/adolescents with HIV infection ≥ 2 to < 18 years of age weighing ≥ 14 kg
3. F/TAF) with a third agent (Study GS-US-311-1269) in children/adolescents with HIV infection ≥ 2 to < 18 years weighing ≥ 17 kg

Additionally, two studies evaluated TDF-containing regimens in the paediatric population:

4. TDF (switched from a zidovudine - or stavudine-containing regimen) with existing antiretroviral (ARV) regimen (Study GS-US-104-0352) in children with HIV infection ≥ 2 to < 16 years of age
5. TDF (Study GS-US-174-0144) in children ≥ 2 to < 12 years of age with hepatitis B (HBV) infection

These studies concern different levels of tenofovir exposure and duration of tenofovir exposure (median exposure of 193 weeks with Biktarvy for 6-12 years and 99 weeks for 2-6 years versus 330 weeks with TDF in GS-US-104-0352 study).

*- Renal Safety in Paediatric Participants Receiving BIC/FTC/TAF and F/TAF-Containing Regimens*

Among participants receiving BIC/FTC/TAF in Study GS-US-380-1474, as well as those receiving E/C/F/TAF in Study GS-US-292-0106 and F/TAF in Study GS-US-311-1269, median values for serum creatinine in each cohort increased from Week 1, with a corresponding decrease in glomerular filtration rate as estimated by the Schwartz equation ($eGFR_{Schwartz}$). The decrease in $eGFR_{Schwartz}$ with an F/TAF-containing regimen was similar or lower than that seen with a TDF-based regimen

Serum creatinine values for participants in all age and weight cohorts in all 3 studies evaluating TAF-based regimens at all visits were within the normal range for age, apart from 3 transient exceptions, and the changes over time were not considered clinically significant. The increases observed are consistent with the physiological increase of serum creatinine with increasing age. Of note, larger median increases observed at later visits in participants ≥ 6 years of age in Studies GS-US-380-1474 and GS-US-292-0106 may reflect that the increase in serum creatinine is steeper in adolescence, especially in boys, as some study participants would have reached adolescence during the long-term follow-up.

The increases in serum creatinine in Study GS-US-380-1474 are also consistent with the known inhibitory effect of BIC on renal creatinine transporters, which contributes to a decrease in tubular secretion of

creatinine and consequent increase in serum creatine. Inhibition of renal creatinine transporters by BIC has previously been shown not to impact glomerular function as demonstrated by an absence of change in the actual glomerular filtration rate measured by iohexol clearance in adults (Study GS-US-141-1487).

3 of 291 participants in these 3 studies had isolated, transient graded serum creatinine laboratory values. Only 1 participant had a Grade 3 or 4 serum creatinine value, which was within the normal range on repeat 4 days later.

The incidence of adverse events (AEs) in the Renal and Urinary Disorders system organ class (SOC) was low in each of the 3 studies. No AE related to renal function led to permanent study drug discontinuation. No AE of renal tubulopathy was reported in any of these studies. In contrast, in Study GS-US-104-0352, 16 participants (3 ≥ 12 years of age, 12 ≥ 6 to < 12 years of age, and 1 < 6 years of age) met the laboratory and clinical definition of proximal renal tubulopathy, which led to TDF discontinuation in 4 participants.

The clinical relevance of changes in renal biomarkers in TAF-containing regimens compared with TDF-containing regimens has been evaluated in a pooled analysis of safety data from 26 studies with TAF- or TDF-containing regimens. The analysis included 9332 adults and children with HIV, with TAF exposure of 12519 person years and TDF exposure of 5947 person years. There were no cases of proximal renal tubulopathy in the TAF group compared with 10 cases in the TDF group, and fewer participants in the TAF group (3 of 6360) discontinued study treatment due to renal AEs than in the TDF group (14 of 2962). Changes in renal biomarkers, including serum creatinine and creatinine clearance calculated using the Cockcroft-Gault equation were seen in both groups but were smaller in those taking TAF (i.e., with lower TFV exposures than in those taking TDF), supporting the contention that the changes observed in these biomarkers with TAF-containing regimens do not translate to clinically relevant outcomes.

*- Bone Safety in Paediatric Participants Receiving BIC/FTC/TAF or F/TAF-Containing Regimens*

Bone mineral density (BMD) was assessed in paediatric participants receiving E/C/F/TAF in Study GS-US-292-0106 and F/TAF in Study GS-US-311-1269 with dual-energy x-ray absorptiometry (DXA) scans at Weeks 24 and 48, and then every 48 or 24 weeks, in the respective studies.

Median spine and total-body-less-head (TBLH) BMD values for children ≥ 6 to < 12 years of age and weighing ≥ 25 kg in Cohort 2 in Study GS-US-292-0106 increased at each study visit through Week 240. Height and age (HA) BMD Z-scores did not change notably from baseline, indicating that subjects mineralized bone at rates consistent with those of the reference population. Changes in spine and TBLH HA BMD Z-scores observed in studies of TAF-containing regimens were similar or smaller than those observed in studies evaluating with a TDF-containing regimen.

It is important to consider these median changes in the context of any decreases ≥ 4% in BMD and/or shifts in an HA BMD Z-score from > −2 to ≤ −2 in individual participants, as well as other potentially confounding factors. Overall, in Cohort 2 of Study GS-US-292-0106, 10 of 50 participants had a ≥ 4% decrease in spine BMD at some time point; 3 of these 10 participants plus 1 additional participant had a ≥ 4% decrease in TBLH BMD at some time point. Of note, 9 of the 11 participants with a ≥ 4% decrease in either spine or TBLH BMD were enrolled at a single site; despite concerns about site-specific issues, investigations at the site identified no technical issues with the DXA scanner or with the performance of the DXA procedures. The spine is rich in metabolically active trabecular bone, and deficits after exposure to antiretroviral drugs are most readily apparent early in a treatment protocol. The largest percentage of participants exhibiting a ≥ 4% decrease in spine BMD was at Week 24 (10 of 50 participants [20%]); at subsequent visits, a smaller percentage of participants met this threshold decline (6 of 39 participants [15.4%] at Week 144; 1 of 17 participants [5.9%] at Week 192; and 0 of 9 participants at Week 240). Similarly, the percentage of participants with a ≥ 4% decrease in TBLH BMD ranged from 3.9% to 5.8% at Weeks 24 through 96, with no participant meeting this threshold

in this cortical bone-rich site from Weeks 144 through 240. At their most recent DXA assessment, 5 of 50 (10%) participants showed a ≥ 4% decrease in spine BMD, while none showed a decrease of this magnitude in TBLH BMD. Only 1 of the 5 participants who had a decrease from baseline in spine BMD ≥ 4% at their last visit had a clinical shift in HA BMD Z-score from > −2 to ≤ −2; this participant had no associated AE.

Intensive pharmacokinetic (iPK) sampling was conducted in a subset of participants enrolled in Study GS-US-292-0106. Based on $AUC_{tau}$ and $C_{max}$, TFV exposures were similar in Cohort 2 participants with and without a ≥ 4% decrease in spine BMD, although numbers of participants were small. Consequently, the BMD changes do not appear to be dependent on TFV exposure.

The diagnosis of osteoporosis and osteopenia in children is appropriate only when both low bone mass (BMD Z-score ≤ −2) and a clinically significant fracture history are present. In Cohort 2 of Study GS-US-292-0106, 2 female participants, respectively, each had a traumatic bone fracture, neither of which was considered related to study drug by the investigator. Spine and TBLH BMD progressively increased from baseline in both participants, and neither had a shift in spine or TBLH BMD HA Z-scores from > −2 to ≤ −2 at any time.

In children ≥ 2 years of age weighing ≥ 14 to <25 kg (n = 27) in Cohort 3 in Study GS-US-292-0106, no initial decrease in spine or TBLH HA BMD Z-scores was observed; median changes from baseline at Week 48 were 0.14 and −0.06, respectively. Two participants in Cohort 3 had a decrease ≥ 4% in spine BMD at 1 or more time points and one of these 2 participants also had a decrease ≥ 4% in TBLH BMD; neither had a shift in HA BMD Z-score from > −2 to ≤ −2.

Although the number of participants is smaller, BMD data obtained from Study GS-US-311-1269 also support the long-term safety of TAF-containing products in children < 12 years of age. Median spine and TBLH HA BMD and Z-scores improved or remained stable through a median of up to 113.1 weeks. No participant in Study GS-US-311-1269 had a decrease in BMD ≥ 4% at any time point. Three participants (2 in Cohort 1 and 1 in Cohort 2) had postbaseline shifts in spine or TBLH HA BMD Z-scores from > −2 to ≤ −2; an AE of decreased bone density was reported for 1 of the 3 participants.

Median decreases in HA BMD Z-scores were similar or smaller in Studies GS-US-292-0106 and GS-US-311-1269 (F/TAF-based regimen) studies than in Study GS-US-104-0352 (TDF-based regimen) in children ≥ 6 to < 12 years of age, consistent with what was observed at Week 48. These observations are notable as the participants taking boosted third agents in Study GS-US-311-1269 had increased TFV exposures relative to those taking BIC/FTC/TAF in Study GS-US-380-1474.

Assessing the impact of TFV exposure on bone health is challenging as a deficit in bone mineralization is common in children with HIV receiving ARV drugs, and is likely multifactorial, including local socioeconomic conditions, HIV infection, chronic immune host activation, and the nature of the ARV drugs administered. A number of studies have reported the association of older ARV drugs, especially protease inhibitors such as lopinavir and atazanavir, with increased bone turnover, accelerated bone loss, and a higher prevalence of decreased BMD. In addition, longitudinal assessments of changes in bone health in children with HIV and the link to clinical outcomes are limited. Nonetheless, the overall increases in BMD values observed in study participants ≥ 6 to < 12 years old receiving F/TAF or E/C/F/TAF are consistent with a rate of mineralization expected for children with HIV in this age range.

Biomarkers of bone formation (such as osteocalcin, bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide) and resorption (such as N-telopeptide, C-telopeptide), as well as parathyroid hormone, 25-OH vitamin D, and 1,25-$OH_2$ vitamin D were assessed in the TAF and TDF studies. In general, in participants < 12 years of age, the serum markers were stable or increased, and were consistent with reference ranges for this age group, where available. Interpretation of bone turnover markers is confounded by intrasubject as well as inter-subject variability; variability is related to factors

such as seasonality, circadian rhythm, fasting, physical activity, menstruation, age, sex, ethnicity, and vitamin D deficiency. Serum 25-OH vitamin D was stable or decreased, while serum 1,25-$OH_2$ vitamin D increased over time. Vitamin D deficiency is common globally, independent of HIV status or treatment.

Bone fractures were uncommon in all the studies described here and, importantly, the bone fractures identified, including in Study GS-US-380-1474, were the result of trauma and not considered related to study drug.

Data on longer term effects of TAF- and TDF-containing regimens on bone health is available from adults. In an integrated analysis of the safety and efficacy of TAF vs TDF for ART initiation or switch in women in 7 studies, women initiating or switching to TAF had significantly improved hip and spine BMD compared to women taking TDF after 2 years of treatment. Five-year outcomes from 2 phase 3 studies with BIC/FTC/TAF in treatment-naive adults showed mean (standard deviation) % changes in spine and hip were -0.29% (5.29) and -0.23% (5.16), respectively, through Week 240 (data on file). On Week 240 DXA scans in this BIC/FTC/TAF study, 9 of 144 (6.3%) participants with normal spine BMD at Baseline had osteopenia and none had osteoporosis, while 5 of 50 (10%) participants and 2 of 50 (4.0%) participants who had osteopenia at baseline had improved to normal or had worse classification of osteoporosis, respectively. Among 7 participants with osteoporosis at Baseline BMD, 1 had a normal BMD value and 2 had BMD values consistent with osteopenia (n=2) at Week 240.

*Growth and Development in Paediatric Participants Receiving BIC/FTC/TAF or Other F/TAF-Containing Regimens*

No impairment of growth or development was observed among participants in any of studies GS-US-380-1474, GS-US-292-0106, and GS-US-311-1269 in which participants received B/FTAF, E/C/F/TAF, or F/TAF, respectively. Overall, the study participants gained height and weight as would be expected over time, and Z-scores increased. No impact on normal development, as assessed by Tanner stage changes, was noted in participants in any of the studies, including in participants who entered puberty during the course of the studies.

In summary, the above-described long-term safety data in children who received the BIC/FTC/TAF LDT and in children who received the adult strength BIC/FTC/TAF tablet in Study GS-US-380-1474, combined with aggregate data of children receiving other F/TAF-containing regimens (F/TAF in Study GS-US-311-1269 and E/C/F/TAF in Study GS-US-292-0106), reinforces the safety of BIC/FTC/TAF in terms of renal function, bone development and growth in this age group.

## 2.6.14. Discussion on clinical safety

In Cohorts 1 and 2, i.e., in children age ≥6 years <12 years weight ≥25 kg (cohort 2) and ≥12 years to <18 years weight ≥35 kg (cohort 1) (n=100) the most commonly reported AEs were upper respiratory tract infection, cough, diarrhoea, headache, and nasopharyngitis. The overall types of common AEs were consistent with those expected in the study population. Some AEs such as vomiting (8%), arthralgia (6%), rash (6%) abdominal pain (5%) and anxiety (5%) consider as "uncommon" might have been more frequently reported in children compared to what was reported in adults. However, considering the design of the study, open label, no further conclusions can be made. Most AEs reported were grade 1 or 2. Four AEs grade 3 or 4 and 5 SAEs have been reported but none have been considered as related. No deaths have been reported.

Among study drug-related AEs, only abdominal discomfort grade 1 has been reported with greater than single subject incidence (n=3). Half of the AE reported are listed in the section ADR of Biktarvy SmPC. No new safety issue has been identified. No hepatic AE was reported in any subject, neither any Hy's law case.

Most subjects had no graded liver-related laboratory abnormality, and those that were reported were mostly Grade 1; 1 subject, in Cohort 2, had a Grade 3 increased AST and a Grade 4 increased ALT that resolved while on study drug. There were no Grade 4 liver-related laboratory abnormalities reported. No subject met Hy's Law criteria.

Increases in serum creatinine and decreases in eGFR Schwartz were observed, consistent with the known inhibitory effect of BIC on renal creatinine transporters (organic cation transporter 2 and multidrug and toxin extrusion 1), which contributes to a decrease in tubular secretion of creatinine, resulting in an increase in serum creatinine. These changes in serum creatinine were observed from Week 1 and through Week 96, and remained within the normal range for this population, and changes in eGFR Schwartz were observed at Week 1, stabilizing after Week 12 through Week 96. Inhibition of these renal creatinine transporters by BIC has previously been shown not to impact glomerular function as demonstrated by an absence of change in actual glomerular filtration rate measured by iohexol clearance in adults (Study GS-US-141-1487).

Switching to BIC/FTC/TAF was overall well tolerated by virologically suppressed paediatric subjects ≥ 6 to < 18 years of age through a median duration of exposure of 151.4 weeks. Only one subject discontinued study drug twice due to an AE, once because of insomnia and the second time because of anxiety. Both AEs are listed in the Biktarvy SmPC.

In Cohort 3 i.e.,_in children age ≥2 years to <6 years weighing ≥14 kg to <25 kg (n=22), the most commonly reported AEs were upper respiratory tract infection, cough, nasopharyngitis, and vomiting. The overall types of common AEs were consistent with those expected in the study population. Most AEs reported were grade 1 or 2. No Grade 3 or 4 AE, SAE and deaths have been reported. No subjects discontinued the study due to AE in this cohort. One subject had a hepatic AE (Grade 1 abnormal faeces) that was considered not related to study drug. One case of Grade 4 elevated serum creatinine has been reported in Cohort 3. The AE was transient and resolved 4 days later. There have been no renal tubulopathy (including Fanconi syndrome) reported.

Among study drug-related AEs, none was reported in more than one subject. Most AEs reported are listed in section 4.8 of the Biktarvy SmPC.

No safety issue was identified regarding laboratory abnormalities. Increases from baseline in median values for serum creatinine were observed by Week 4 and stabilized after Week 8. The median (Q1, Q3) change from baseline in serum creatinine at Week 48 was 0.06 (0.03, 0.15) mg/dL. Corresponding decreases from baseline in median values for eGFR Schwartz were observed at Week 1, stabilizing after Week 16. Inhibition of these renal creatinine transporters by BIC has previously been shown not to impact glomerular function as demonstrated by an absence of change in actual glomerular filtration rate measured by iohexol clearance in adults (Study GS-US-141-1487).

Switching to BIC/FTC/TAF appeared to be well tolerated by virologically suppressed paediatric subjects ≥ 2 years of age (weighing ≥ 14 kg to < 25 kg). However, safety data have been gathered in a very limited number of patients (n=22) and for a limited duration of exposure duration (duration ≥24 Weeks in 95.5% of patients but only 54.5% of children received BIC/FTC/TAF for ≥36 Weeks). Taking into account the increased TFV exposure in subjects <12 years old compared to adults, the MAH was requested by the CHMP to further discuss the risk of renal and bone toxicity associated to long-term overexposure to TAF with Biktarvy.

Therefore, the MAH provided renal, bone and growth safety data from pooled studies conducted in paediatric patients aged from 2 to 12 years based on different studies conducted in paediatric patients exposed to either TAF-containing regimens (studies GS-US-380-1474 with Biktarvy, GS-US-292-0106 with Elvitegravir [E]/cobicistat (C)/F/TAF and GS-US-311-1269 with F/TAF) or TDF-containing regimens (studies GS-US-104-0352 with TDF for HIV infection and GS-US-174-0144 with TDF for B viral hepatitis).

These data did not identify any new safety concerns. The CHMP noted that a warning on the possible nephrotoxicity after prolonged exposure to TAF had been recently added to the Product Information for Biktarvy (and all TAF-containing products). This wording also applies to the paediatric population and therefore adequately covers for this paediatric extension.

Regarding bone toxicity, it is not possible to draw any firm conclusion on the potential impact on growing bones after prolonged exposure to tenofovir even at low dose and particularly for children aged ≥2 <6 years because of the limited amount of safety data available in this age group and the limited duration of exposure to tenofovir. Notably, Biktarvy will be the first TAF-containing regimen to be authorized in the age group ≥2 <6 years in the EU. For these reasons, as part of this procedure, the safety specifications of the Biktarvy RMP were updated to include as "missing information" - "Long term safety in children aged between ≥ 2 and < 6 years". Additionally, a warning on the potential long-term bone toxicity of TAF on growing bone was added to sections 4.4 and 4.8 of the Biktarvy SmPC.

Overall, 2 pregnancies exposed to Biktarvy have been reported in the GS-US-380-1474 study. One of the 2 pregnancies resulted in a normal healthy baby and the other was reported as "resolved without additional information about the outcome".

In all cohorts no impact on height, body weight and Tanner stage has been identified.

Overall safety data is reassuring with no significant AEs in severity and number. Most AEs were mild and in line with what was expected for the age of the study population. No new clinically relevant safety signals have been identified with the administration of adult or reduced dose to both Cohort 1/2 and 3. Laboratory changes were also non relevant and in line with what expected for this class of medicines. However, the exposure time for the younger cohort 3 is significantly lower compared to the older one.

The available PK data from study GS-US-380-1474 showed higher exposure to emtricitabine and tenofovir disoproxil. For emtricitabine, this overexposure might be associated to more side effects, notably GI, hepatic and haematologic disorders. No safety data suggesting FTC overexposure have been reported in patients <12 years of age despite limited data numerically gathered notably in HIV-infected patients <6 years. For tenofovir alafenamide, long-term data on exposure to another different FDC of elvitegravir /cobicistat /emtricitabine / tenofovir alafenamide rather than bictegravir/emtricitabine/tenofovir alafenamide were provided. The main purpose of the open-label multicenter single-group study conducted in 102 HIV-1 infected patients ≥ 6 to < 18 years of age was to demonstrate long-term safety for EVG/COBI/FTC/TAF co-formulated both on renal function and bone mineral density / fracture risk. In this study, the impact of long-term treatment on renal function and bone density/fracture risk seems to be acceptable. Some cases with significant decrease in bone mineral density (BMD Z-score) without impact (i.e., fracture) have been reported. And compared to the formulation subject of approval the FDC used in this long-term study (EVG/COBI/FTC/TAF co-formulated) has a lower TAF dose (10mg instead of 25/15mg for Biktarvy).

## 2.6.15. Conclusions on clinical safety

The analysis of safety data in support of this application (mainly from the ongoing study GS-US-380-1474) has shown that the overall safety profile of Biktarvy in the paediatric population is acceptable for the target population and it is comparable to its safety in adults. The additional long-term safety data provided as part of the responses to CHMP confirmed this conclusion.

Renal, bone and growth safety data from pooled studies conducted in paediatric patients aged from 2 to 12 years based on other studies conducted in paediatric patients exposed to either TAF-containing regimens or TDF-containing regimens did not identify any new safety concerns.

Regarding bone toxicity, it was not possible to draw any firm conclusion on the potential impact on growing bones after prolonged exposure to tenofovir even at low dose and particularly for children aged ≥2 <6 years because of the limited amount of safety data available in this age group and the limited duration of exposure to tenofovir. Therefore, the RMP safety specifications of Biktarvy were updated to include "Long term safety in children aged between ≥ 2 and < 6 years" as "missing information" and language on the potential long-term bone toxicity of TAF on growing bone was added to sections 4.4 and 4.8 of the SmPC.

## *2.7. Risk Management Plan*

### 2.7.1. Safety concerns

The MAH has submitted a revised RMP within this extension variation, RMP version 4.0 dated 14 July 2022 to replace previous versions of the RMP.

***Summary of safety concerns***

The MAH identified the following safety concerns in the RMP:

**Summary of safety concerns**

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | Safety in pregnancy and lactation<br>Long-term safety in children aged ≥ 2 to <6 years of age |

### Discussion on safety specification

'Long-term safety in children aged ≥ 2 to <6 years of age' has been added as Missing information as requested.

### Conclusions on the safety specification

Having considered the data in the safety specification the PRAC agreed that the safety concerns listed by the MAH are appropriate.

### 2.7.2. Pharmacovigilance plan

#### *2.7.2.1.* Summary of additional PhV activities

Table Part III.3: On-going and planned additional pharmacovigilance activities

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |

| Study Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due dates |
|---|---|---|---|---|
| None | | | | |
| **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** | | | | |
| None | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| **Antiretroviral Pregnancy Registry (APR)**<br><br>Ongoing | To collect information on the risk of birth defects with antiretroviral drugs, including BIC/FTC/TAF, to which pregnant women are exposed. | Safety in pregnancy (missing information) | Submission of interim reports | In the BIC/FTC/TAFPSUR (DLP and periodicity as described in the List of EU reference dates and frequency of submission of PSURs). |
| **GS-US-380-1474 (Cohort 3)**<br><br>Ongoing | To evaluate the pharmacokinetics, safety, tolerability and antiviral activity of the low dose BIC/FTC/TAF tablet through Week 48 in HIV-1 infected, virologically suppressed children ≥ 2 years of age weighing ≥ 14 kg to < 25 kg. | Long term safety in children aged between ≥ 2 and < 6 years (missing information) | Submission of updated analyses including final CSR for Cohort 3 | Anticipated submission by Q1 2025 |

Study GS-US-380-1474 (Cohort 3) was added as additional pharmacovigilance activity to address 'Long term safety in children aged between ≥ 2 and < 6 years'. In addition, the MAH committed to discuss long-term safety in children from ≥ 2 to < 6 years of age, including renal and bone safety, in future Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Reports (PSUR/PBRERs).

#### *2.7.2.2. Overall conclusions on the PhV Plan*

The PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

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

### 2.7.3. Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

| Safety Concern | Routine Risk Minimization Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important identified risk(s)** | | |
| None | N/A | N/A |
| **Important potential risk(s)** | | |
| None | N/A | N/A |
| **Missing information** | | |
| Safety in pregnancy and lactation | Routine risk communication:<br>SmPC section 4.6<br>PL section 2 | *Additional pharmacovigilance activities:*<br>Antiretroviral Pregnancy Registry |
| Long term safety in children aged between ≥ 2 and < 6 years | Routine risk communication:<br>SmPC sections 4.4 and 4.8 | *Additional pharmacovigilance activities:*<br>Ongoing study GS-US-380-1474 (Cohort 3) to address long term safety in virologically suppressed children ≥ 2 years of age weighing ≥ 14 kg to < 25 kg. |

***Overall conclusions on risk minimisation measures***

The PRAC having considered the data submitted was of the opinion that the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

***Summary of the risk management plan***

The public summary of the RMP has been adequately revised in line with other sections throughout the RMP.

### 2.7.4. Conclusion

Risk management plan version 4.0 is acceptable and approved with this procedure.

## *2.8. Pharmacovigilance*

### 2.8.1. Pharmacovigilance system

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

### 2.8.2. 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*

Sections 1, 2, 3, 4.1, 4.2, 4.4, 4.6, 4.7, 4.8, 5.1, 5.2, 6.1, 6.5 and 8 of the SmPC are updated as part

of this procedure. Sections 1, 2, 3, 5 and 6 of the Package Leaflet have been updated accordingly.

### 2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet was submitted by the MAH, which was acceptable.

### 2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Biktarvy (bictegravir / emtricitabine / tenofovir alafenamide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The global burden of HIV and the specific paediatric challenges are well-known. In 2018, 160,000 (110,000–260,000) children aged 0-14 acquired HIV infection globally. In the Western and Central Europe and North America region, the estimated number of children living with HIV in 2013 was 2,800 (2,300–3,600), and it is estimated that over 95% of these children were receiving antiretroviral therapy.

Globally, deaths among children younger than 15 years of age are reported to be declining. At the end of 2018, an estimated 100,000 (64,000–160,000) children aged 0-14 years had died from AIDS-related causes, representing 52% fewer deaths in this age group than in 2012. In North America, Western and Central Europe, fewer than 200 children died from AIDS-related illnesses in 2012.

### 3.1.2. Available therapies and unmet medical need

The current INSTI-based ARV indicated in paediatric subjects are as follows:

- Dolutegravir: available as dispersible tablets and film-coated tablets, indicated in children ≥ 4 weeks of age and weighing ≥3 kg.

- Dolutegravir/lamivudine (DTG/3TC): available as film-coated tablets, indicated in adolescents ≥ 12 years of age and weighing ≥40 kg.

- Elvitegravir/cobicistat/FTC/TAF (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide): available as film-coated tablet, indicated in children ≥6 years old and weighing ≥25 kg for whom alternative regimens are unsuitable due to toxicities.

- Raltegravir: available as granules for oral suspension and chewable tablets, indicated in children weighing ≥3 kg.

A once daily, single-tablet regimen (STR) has been shown to significantly improve adherence, treatment satisfaction, and virologic outcome for patients infected with HIV-1. Six STRs are currently approved in the EU for once daily administration in the treatment of HIV-1 infection in adolescents (≥12 years old): EVG/COBI/FTC/TDF (elvitegravir/cobicistat/FTC/tenofovir disoproxil fumarate), EVG/COBI/FTC/TAF (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide co-formulated), abacavir/dolutegravir/lamivudine, FTC/rilpivirine/TAF (FTC/RPV/TAF), darunavir/cobicistat/emtricitabine/tenofovir alafenamide (DRV/COBI/FTC/TAF) and dolutegravir/lamivudine (DTG/3TC). EVG/COBI/FTC/TAF tablets is the only once daily STR approved in children.

In adults, BIC/FTC/TAF did not respond to an unmet medical need. However, BIC/FTC/TAF may provide an improved option for paediatric patients for whom it would be better to avoid the potential for adverse reactions arising from less tolerated agents such as ritonavir (RTV)-boosted protease inhibitors or central nervous system adverse events (AEs) due to EFV. Additionally, as BIC, FTC, and TAF are not clinically relevant inhibitors or inducers of major human drug-metabolizing enzymes or transporters, there is low potential for BIC/FTC/TAF to cause drug-drug interactions (DDIs). Because no PK enhancer such as COBI or RTV is required to maintain BIC plasma concentrations, the DDI potential of BIC/FTC/TAF is lower than that of other approved agents. The reduced risk of DDIs is an important benefit in the maintenance of treatment adherence in a paediatric population. Moreover, a TAF-containing regimen would be a better choice than a TDF based regimen in this population due to a more favourable bone and renal profile. The small tablet size of the low-dose BIC/FTC/TAF FDC is expected to provide a further benefit for paediatric patients for whom pill swallowing can be a barrier to treatment compliance.

In conclusion, BIC/FTC/TAF can be regarded as an alternative treatment that has a potential benefit in children. Not only because it may improve adherence but also because it has less potential to DDI and a more favourable bone and renal profile.

### 3.1.3. Main clinical studies

This paediatric extension is based on the study GS-US-380-1474. This is an ongoing Phase 2/3 study to evaluate PK, safety, tolerability, and antiviral activity of the BIC/FTC/TAF FDC in HIV-1 infected, virologically suppressed paediatric subjects. This study enrolled children in age and weight-defined cohorts (Cohort 1: ≥ 12 to < 18 years of age weighing ≥ 35 kg; Cohort 2: ≥ 6 to < 12 years of age weighing ≥ 25 kg; Cohort 3: ≥ 2 years of age weighing ≥ 14 to < 25 kg). Subjects from Cohort 3 received a specific low-dose BIC/FTC/TAF tablet.

## *3.2. Favourable effects*

Overall, no clinically relevant differences in BIC exposure parameters were observed in adolescents or children ≥ 2 years of age and weighing ≥ 14 kg. FTC and TFV exposures were higher than in adults but were within the safe and efficacious ranges established in the Biktarvy and EVG/COBI/FTC/TAF co-formulated programs. Based on PK data, no lack of efficacy associated to a lower BIC, FTC or TAF exposure is expected.

At Week 24 and Week 48, high rates of virologic suppression (>90%) were observed in these virologically-suppressed paediatric subjects, and CD4 cell counts remained stable. No subject had treatment-emergent resistance to study drug. Although the efficacy data from this paediatric study

were not primary endpoints, these data could be considered supportive.

## 3.3. Uncertainties and limitations about favourable effects

The design (non-comparative, limited sample size) of study GS-US-380-1474 and the lack of efficacy data on ART-naïve paediatric subjects or patients without virological suppression are very limiting for the interpretation of the efficacy and virology results. Notably, paediatric subjects included in this study are well controlled under their current ARV, without advanced disease. Therefore, these efficacy data may only be relevant for such population, not for ARV-naïve subjects with high viral load and advanced disease for whom Biktarvy is also indicated.

## 3.4. Unfavourable effects

The analysis of safety data (GS-US-380-1474) has shown that the overall safety profile of Biktarvy in the paediatric population seems comparable to the safety of Biktarvy in adults.

Safety data have been gathered in 50 children ≥ 12 to < 18 years of age weighing ≥ 35 kg, 50 children ≥ 6 to < 12 years of age weighing ≥ 25 kg and 22 children ≥ 2 years of age weighing ≥ 14 to < 25 kg). The most commonly reported AEs were upper respiratory tract infection, cough, diarrhoea, vomiting headache, and nasopharyngitis consistent with those expected in the study population. Most AE were grade 1 and 2. No death has been reported. No serious AE nor grade 3 / 4 AE have been considered as related to BIC/FTC/TAF. Only one subject discontinued study drug twice due to 2 AEs both listed in the section ADR of the Biktarvy SmPC. Increases in serum creatinine and decreases in eGFR Schwartz were observed, consistent with the known inhibitory effect of BIC on renal creatinine transporters (organic cation transporter 2 and multidrug and toxin extrusion 1), which contributes to a decrease in tubular secretion of creatinine, resulting in an increase in serum creatinine. Overall, no new safety issue has been identified.

## 3.5. Uncertainties and limitations about unfavourable effects

The review of safety data provided from the study GS-US-380-1474 has shown that some AEs such as vomiting (8%), arthralgia (6%), rash (6%) abdominal pain (5%) and anxiety (5%) considered for Biktarvy as "uncommon" might have been more frequently reported in children compared to what was reported in adults. Considering the design of the study, open-label, no further conclusions can be drawn except that the safety profile of Biktarvy in children ≥ 2 years of age weighing ≥ 14 kg is comparable (and not similar) to that observed in adults with Biktarvy.

Safety data have been gathered in a limited number of children treated for a limited duration notably in children age ≥2 years to <6 years (n=22, approximately half children received BIC/FTC/TAF for ≥36 Weeks).

In order to further evaluate the totality of the PK, safety, and efficacy data for all age cohorts/weight bands, and in particular renal and bone toxicity, more data need to be submitted. In particular, data from the ongoing studies -0128, -1474, -1092 and a final integrated CS report of all the paediatric clinical studies where TAF was used, is recommended by the CHMP to be provided. A final report for study GS-US-292-0106, where most bone data derive from, is also recommended for submission.

## *3.6. Effects Table*

Not applicable.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

At the time of submission of this application, children who required to be treated with INSTI-based therapy would receive DTG or RAL + other ARVs for backbone therapy, which implies taking each ARV individually and increases pill burden, associated with risk of adherence's decrease. A single tablet regimen, EVG/COBI/FTC/TAF co-formulated, is also available but indicated in children ≥6 years old and weighing ≥25 kg for whom alternative regimens are unsuitable due to toxicities.

A single-tablet regimen for paediatric subjects is welcomed for paediatric subjects (especially adolescent subjects). The acceptability and compliance of Biktarvy will be further enhanced by the possibility to split the tablet in halves (although tablets are not scored).

The PK and efficacy data did not highlight efficacy and virologic issues: in comparison to adult subjects, a similar antiviral activity and virologic suppression is expected with the proposed weight-doses of Biktarvy.

Exposures (AUC and Cmax) of emtricitabine and tenofovir are significantly higher (by approximately 40% to 80%) than those usually observed in adults. Although no significant increased toxicity is be expected with emtricitabine, the potential renal safety consequences of long-term tenofovir exposure with the proposed doses, and the impact on growth of paediatric subjects, remain uncertain particularly for children ≥2 <6 years of age. The latter is an important potential safety concern in case of prolonged exposure for all tenofovir-containing products since the level of tenofovir exposure with no negative effects on bone is unknown , which is a particular concern for paediatric patients whose bone are still growing. MAHMAH. Therefore, the RMP safety specifications of Biktarvy were updated to include "Long term safety in children aged between ≥ 2 and < 6 years" as "missing information".

### 3.7.2. Balance of benefits and risks

For paediatric subjects, the availability of a new STR regimen is beneficial. The proposed doses of the combination of bictegravir + emtricitabine/tenofovir alafenamide in paediatric subjects are expected to be as effective as in adults. As regards the safety of bictegravir + emtricitabine/tenofovir alafenamide in children, safety data are limited and uncertainties remain for the long-term safety consequences of tenofovir exposure on renal function, fracture risks and growth, particularly in children ≥2 <6 years of age. Adequate warnings have been included in the SmPC to minimize these risks. The potential long-term safety issues are also expected to be clarified by data awaited from further studies.

## *3.8. Conclusions*

The overall benefit/risk balance of Biktarvy is positive in children and adolescents ≥2 years of age and weighing ≥14 kg.

# 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 Biktarvy 30 mg/120 mg/15 mg is favourable in the following indication:

- Biktarvy is indicated for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and paediatric patients at least 2 years of age and weighing at least 14 kg without present or past evidence of viral resistance to the integrase inhibitor class, emtricitabine or tenofovir.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Biktarvy 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)**

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

An updated RMP should be submitted:

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

***Paediatric Data***

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0038/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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

| Variations approved | | Type | Annexes affected |
|---|---|---|---|
| X.02.III | Annex I 2.(c) Change or addition of a new strength/potency | Line Extension | I, IIIA, IIIB and A |
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Line extension to introduce a new strength 30/120/15 mg grouped with an extension of indication to include paediatric patients at least 2 years of age and weighing at least 14 kg. Sections 1, 2, 3, 4.1, 4.2, 4.4, 4.6, 4.7, 4.8, 5.1, 5.2, 6.1, 6.5 and 8 of the SmPC are updated. Sections 1, 2, 3, 5 and 6 of the Package Leaflet have been updated accordingly. The opportunity was also taken to update the list of local representatives and bring the product information in line with the latest approved QRD template.

RMP version 4.0 was approved with this procedure.