



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2025
EMA/192996/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Emtricitabine/Tenofovir alafenamide Viartis

International non-proprietary name: emtricitabine / tenofovir alafenamide

Procedure No. EMEA/H/C/006469/0000

Note

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



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List of abbreviations

ADR	Adverse drug reaction
AEs	Adverse events
AI	Acceptable intake
AIDS	Acquired immune deficiency syndrome
ANOVA	Analysis of variance
ANVISA	Brazilian Health Regulatory Agency
ART	Antiretroviral therapy
ARV	Antiretroviral
ASMF	Active substance master file
AUC	Area under the plasma concentration-time curve
AUC _(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC _(0-tau)	Area under the concentration-time curve from time 0 to the end of the dosing interval
AUC _{last}	Area under the curve from the time of dosing to the last measurable concentration
AUC_%Extrap_obs	% of the AUC that has been derived after extrapolation
BA	Bioavailability
BE	Bioequivalence
BMI	Body mass Index
CFB	Change from baseline
CHMP	Committee for Human Medicinal Products
CI	Confidence interval
C _{max}	Maximum observed concentration
CRF	Case report form
CRO	Certified Research Organisation
CSR	Clinical study report
CV	Curriculum vitae
CV%	Coefficient of variation %
DESMP	Diethyl p-toluene sulphonyl oxy methyl phosphonate
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European public assessment report
ERA	Environmental Risk Assessment
EU	European Union
FDC	Fixed-dose combination
GC	Gas chromatography
GC-HS	Gas chromatography-headspace
GC-MS/MS	Gas chromatography mass spectrometry/ mass spectrometry
GCP	Good Clinical Practice
GMP	Good manufacturing practice
GMR	Geometric Mean Ratio
HDPE	High density polyethylene
HIV	Human Immunodeficiency Virus
HIV-1	Human immunodeficiency virus type 1
HIV-2	Human immunodeficiency virus type 2
HPLC	High performance liquid chromatography
hr	Hour
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IR	Infrared

K3EDTA	Tripotassium ethylenediaminetetraacetic acid
KF	Karl Fischer titration
LDPE	Low density polyethylene
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MO	Major objection
N	Number of observations
NA	Not Applicable
NCA	National Competent Authorities
NCO	Non-clinical Overview
NMR	Nuclear magnetic resonance
NMT	Not more than
NRTI	Nucleoside reverse-transcriptase inhibitor
OOS	Out of specification
OPA	Orthophthalaldehyde
PD	Pharmacodynamics
PDE	Permitted daily exposure
PE	Polyethylene
PEC _{SW}	Predicted Environmental Concentration for surface water
Ph. Eur.	European Pharmacopoeia
PIs	Protease inhibitors
PK	Pharmacokinetics
ppm	part per million
PXRD	Powder x-ray diffraction
QC	Quality control
(Q)SAR	(Qualitative) Structure activity relationship
RMP	Risk Management Plan
RH	Relative humidity
rpm	revolutions per minute
SAE	Serious adverse event
SmPC	Summary of product characteristics
T _{1/2}	Half-life
t _{1/2}	Terminal phase half-life
TAF	Tenofovir alafenamide monofumarate
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
T _{max}	Time of maximum observed plasma concentration; if it occurs at more than one time point, T _{max} was defined as the first time point with this value
TTC	Threshold of toxicological concern
UPLC	Ultra performance liquid chromatography
US FDA	United States Food and Drug Administration
UV	Ultraviolet
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viartis Limited submitted on 3 June 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Emtricitabine/Tenofovir alafenamide Viartis, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– ‘Generic of a Centrally authorised product’. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 December 2023.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Emtricitabine/Tenofovir alafenamide Viartis is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1) (see sections 4.2 and 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Descovy instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Descovy, 200/10 mg and 200/25 mg, film-coated tablets
- Marketing authorisation holder: Gilead Sciences Ireland UC
- Date of authorisation: 21-04-2016
- Marketing authorisation granted by:
 - Union
- Union Marketing authorisation number: EU/1/16/1099

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Descovy, 200/10 mg and 200/25 mg, film-coated tablets
- Marketing authorisation holder: Gilead Sciences Ireland UC
- Date of authorisation: 21-04-2016
- Marketing authorisation granted by:
 - Union

- Marketing authorisation number: EU/1/16/1099

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Descovy, 200/10 mg and 200/25 mg, film-coated tablets
- Marketing authorisation holder: Gilead Sciences Ireland UC
- Date of authorisation: 21-04-2016
- Marketing authorisation granted by:
 - Union
- Marketing authorisation number: EU/1/16/1099
- Bioavailability study number(s): EMTA-TBZ-1009, EMTA-TBZ-1010, EMTA-TBZ-1011

1.3. Information on paediatric requirements

Not applicable

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

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Elita Poplavska

The application was received by the EMA on	3 June 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	11 September 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 October 2024

The applicant submitted the responses to the CHMP consolidated List of Questions on	24 January 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	26 February 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 March 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	27 March 2025
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	22 April 2025
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	07 May 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Emtricitabine/Tenofovir alafenamide Viartis on	22 May 2025

2. Scientific discussion

2.1. Introduction

This MAA concerns a generic medicinal product: Emtricitabine/Tenofovir alafenamide Viartis 200 mg/10 mg and 200 mg/25 mg film-coated tablets containing the same active substance as per the approved reference product Descovy 200 mg/10 mg and 200 mg/25 mg film-coated tablets, manufactured by Gilead Sciences Ireland. This generic application concerns both strengths. Three BE studies were submitted to support this MAA: fasting and fed studies for 200/25 mg and fasting study for 200/10 mg strength.

Emtricitabine is a NRTI for the prevention and treatment of HIV infection in adults and children in combination with other ARV drugs.

Tenofovir (TFV) is a nucleotide analogue with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, has improved bioavailability, and delivers high systemic exposures of TFV with favourable efficacy and safety data. Identified risks of TDF is nephrotoxicity requiring regular renal monitoring.

Tenofovir alafenamide (TAF) is another oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing either 200 mg/10 mg emtricitabine/tenofovir alafenamide or 200 mg/25 mg emtricitabine/tenofovir alafenamide as active substances. Tenofovir alafenamide is present as the monofumarate salt.

Other ingredients are:

200 mg/10 mg film-coated tablets: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, partially hydrolyzed poly(vinyl alcohol), titanium dioxide (E171), macrogol, talc and black iron oxide (E172).

200 mg/25 mg film-coated tablets: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, partially hydrolyzed poly(vinyl alcohol), titanium dioxide (E171), macrogol, talc and indigo carmine aluminium lake (E132).

Both tablet strengths are available in HDPE bottles with white opaque PP child-resistant closures along with a desiccant.

The 200 mg/25 mg tablets are additionally available in OPA/alu/PE/desiccant/HDPE-alu/PE blisters and perforated unit dose blisters.

2.2.2. Emtricitabine active substance

General information

The chemical name of emtricitabine is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1*H*)-pyrimidinone corresponding to the molecular formula $C_8H_{10}FN_3O_3S$. It has a relative molecular mass of 247.25 g/mol and the following structure:

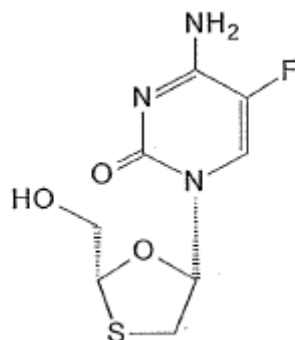


Figure 1: Emtricitabine structure

The chemical structure of emtricitabine was elucidated by a combination of IR, UV, ¹H NMR and ¹³C NMR spectroscopy, mass spectrometry, elemental analysis and x-ray powder diffraction (PXRD).

Emtricitabine is a white to off-white powder, freely soluble in aqueous media from pH 1.2-8. The active substance is non-hygroscopic.

Emtricitabine exhibits stereoisomerism due to the presence of two chiral centres. Enantiomeric purity is controlled routinely in the active substance by chiral HPLC.

Polymorphism has been observed for emtricitabine, and various polymorphic forms exist. The drug substance manufacturer consistently produces same polymorphic form of emtricitabine.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is manufactured by three manufacturers. Satisfactory GMP documentation of the sites has been provided.

Emtricitabine is synthesized in several steps using well defined starting materials with acceptable specification. The route of synthesis of the intermediate from the two proposed manufacturers is similar, differing only in the choice of reagents and solvents. Batch data of emtricitabine manufactured with both sources of the intermediate was provided. All tested parameters were within the specification limits and the quality of the intermediate and the resultant active substance from sources is considered equivalent.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The proposed starting materials have been appropriately justified according to ICH Q11, and their specifications are acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Risk assessments for genotoxic, solvent, elemental and nitrosamine impurities were provided. The risk assessments and applied control measures are considered appropriate.

The active substance packaging has been clearly described and is acceptable, complying with Commission Regulation (EU) No. 10/2011 as amended.

Specification

The active substance specification followed by the finished product manufacturer includes tests for: appearance (visual), solubility (Ph. Eur.), identity (IR, HPLC, PXRD), melting point (Ph. Eur.), specific optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), related substances (HPLC), enantiomeric impurity (chiral HPLC), assay (HPLC), residual solvents (GC), and particle size (Malvern) and other solvent and reagent-related impurities (GC-MS, GC-MS/MS).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

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

Batch analysis data from five production scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data to support the requested re-test period and storage condition is provided.

Stability data from three production scale batches of active substance from the proposed manufacturer, stored in the intended commercial package for up to 18 months under long term conditions (25 °C / 60% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. Photostability testing following ICH guideline Q1B was performed on one batch.

The following parameters were tested: description, identification, melting range, specific optical rotation, loss on drying, enantiomer content, related substances, and assay. The analytical methods used were the same as for release and are stability indicating as demonstrated during forced degradation studies. All tested parameters were within the specifications and no significant trends were observed. Emtricitabine is photostable.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The overall of stability results justify the proposed retest period in the proposed container.

2.2.3. Tenofovir alafenamide monofumarate active substance

General information

The chemical name of tenofovir alafenamide monofumarate is propan-2-yl *N*-[(*S*)-({[2*R*]-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-L-alaninate, (2*E*)-but-2-enedioate (1:1) corresponding to the molecular formula $C_{21}H_{29}N_6O_5P \cdot C_4H_4O_4$. It has a relative molecular mass of 592.55 g/mol and the following structure:

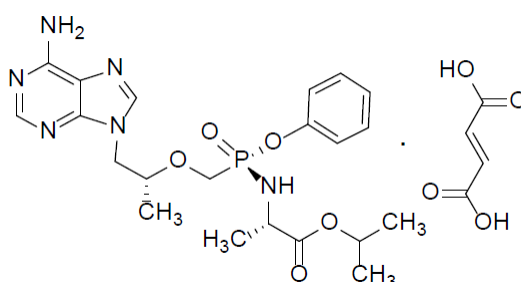


Figure 2: Tenofovir alafenamide monofumarate structure

The chemical structure of tenofovir alafenamide monofumarate was elucidated by a combination of IR, UV, 1H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. The solid-state properties of the active substance were measured by PXRD.

Tenofovir alafenamide monofumarate is a white to off-white or light tan coloured non-hygroscopic powder. The active substance is sparingly soluble in aqueous media across the pH range 1.2-8.0.

Tenofovir alafenamide monofumarate exhibits stereoisomerism due to the presence of three chiral centres. The control strategy has been appropriately justified.

Polymorphism has been observed for active substance. The present process consistently produces the same crystalline which is routinely controlled in the active substance specification. The stability of the polymorphic form throughout the shelf-life of the active substance was demonstrated.

Manufacture, characterisation and process controls

The active substance is manufactured by two manufacturers. Satisfactory GMP documentation of the sites has been provided.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Tenofovir alafenamide monofumarate is synthesized in several steps using well defined starting materials, justified according to ICH Q11, with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Risk assessments for genotoxic, solvent, elemental and nitrosamine impurities were provided. No risk of nitrosamines impurities or elemental impurities was identified, solvents are controlled according to ICH Q3C.

The risk assessment for potentially genotoxic impurities in the initial submission was not considered adequate as the hazard assessment was not conducted according to ICH M7, and impurities with structural alerts present in the starting materials had not been considered, resulting in a major objection (MO). In response, the applicant provided an updated risk assessment, classifying relevant mutagenic impurities according to ICH M7 and providing (Q)SAR results and bacterial reverse mutagenicity assay results as appropriate. All mutagenic impurities are controlled according to ICH M7 option 4 and data has been provided as justification. The MO was thus resolved.

The active substance packaging has been clearly described and is acceptable, complying with EC 10/2011 as amended.

Specification

The active substance specification applied by the finished product manufacturer includes tests for appearance (visual), solubility (Ph. Eur.), identification (IR, HPLC, PXRD), water content (KF), sulfated ash (Ph. Eur.), chiral purity (chiral HPLC), related substances (HPLC), fumaric acid content (HPLC), assay (HPLC), residual solvents (GC-HS), and particle size (Malvern).

Tests included in the specification for the active substance are in line with requirements of ICH Q6A and are considered acceptable. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

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

Batch analysis data from three production scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25 °C / 60% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH)

according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was also conducted. The following parameters were tested: appearance, identification by IR and PXRD, water content, chiral purity by HPLC, related substances and assay. All tested parameters remained unchanged during the testing period under both long-term and accelerated conditions and no significant trends were observed. Furthermore, the active substance was shown to be photostable.

A forced degradation study was performed under stressed conditions, demonstrating that the analytical procedures for impurities and assay are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period without specific storage conditions in the proposed container.

2.2.4. Finished medicinal product

Description of the product and pharmaceutical development

Emtricitabine/tenofovir alafenamide 200 mg/10 mg film-coated tablets are grey, film-coated, rectangle shaped, bevel-edged, biconvex tablets debossed with ET 1 on one side of the tablet and V on the other side.

Emtricitabine/Tenofovir Alafenamide 200 mg/25 mg film-coated tablets are blue, film-coated, rectangle shaped, bevel-edged, biconvex tablets debossed with ET 2 on one side of the tablet and V on the other side.

Both strength tablets are the same size.

The finished product has been developed to be essentially similar to the reference medicinal product Descovy, which is indicated for use in adults and children aged 12 years and older. The proposed finished product has the same qualitative and quantitative composition of active substances, the same pharmaceutical form and the same administration route as the reference product. The same excipients are used in the test product as in the reference product.

The choice and function of excipients was described. Compatibility of the chosen excipients with both active substances was confirmed. All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Both active substances are soluble in aqueous media but have poor flow properties. A granulation approach was therefore developed. The active substance manufacturing processes generate consistent polymorphic form and particle size distributions of both emtricitabine and tenofovir alafenamide fumarate. Specifications have been set based on the batches of active substance used to make the biobatches.

The selected QC dissolution condition is suitably justified. In the initial submission, a wide specification limit was proposed relative to the biobatches resulting in a MO. In response, the applicant tightened the specification limit and the issue was considered resolved.

The applicant investigated discriminatory nature of the proposed dissolution method by manufacturing tablets with minor changes in formulation and process variables. The proposed method was able to distinguish between standard batches and these "bad batches," therefore, the discriminatory power of the dissolution method has been demonstrated.

Bioequivalence was demonstrated for both tablet strengths clinically. Additional studies were conducted to compare dissolution profiles of both strengths of the reference product with the biobatches *in vitro* using the QC dissolution method, and at pH 1.2, 4.5 and 6.8 at least 85% of each active substance was dissolved after 15 minutes in all batches compared. Therefore, release rate is considered similar for test and reference products.

The development of the manufacturing process has been explained, along with optimisation of process parameters for the individual unit operations.

The primary packaging for both strengths is HDPE bottles with white opaque PP child-resistant closures along with a desiccant. The 200 mg/25 mg tablets are additionally available in OPA/alu/PE/desiccant/HDPE-alu/PE blisters and perforated unit dose blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure systems has been validated by stability data, and they are considered adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturer. Satisfactory GMP documentation of the site has been provided.

Adequate information on the manufacturing process and in-process controls is provided. The manufacturing process consists of four main steps: roller compaction, compression, coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by manufacture of three production scale batches of each strength tablet. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. The packaging type and conditions for the bulk were indicated and are acceptable.

Product specification

The finished product release and shelf-life specifications contain tests for description (visual), identification (HPLC, UV), dissolution (UPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), water content (KF), microbial quality (Ph. Eur.), related substances (HPLC), dimensions, and colour test (in house).

The proposed specifications are set in line with ICH guidelines and European Pharmacopoeia requirements. The same limits are proposed for release and shelf-life specifications with the exception of water content and related substances which is considered acceptable based on the stability data. Impurities present above the qualification threshold have been qualified at the specified levels.

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 indicating no significant risk of elemental impurities. Nonetheless, batch analysis data from three batches was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Therefore, no specific controls are required.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No)

726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). The applicant tested three batches of each strength with a suitably sensitive and validated analytical method for nitrosamines potentially present in the finished product. This was based on amines used in the active substance processes which could potentially carry through to the finished product and react with trace nitrite present in the excipients. No nitrosamines were detected and therefore, it is considered that there is no risk of nitrosamine impurities 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 has been presented.

Batch analysis results are provided for three production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

Stability data from three production scale batches of each strength of finished product stored for up to 18 months under long term conditions (25 °C / 60% RH), for up to 12 months under intermediate conditions (30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The batches of the finished product are identical to those proposed for marketing and were packed in both primary packaging formats proposed for marketing. Samples were tested according to the shelf-life specifications.

The results of a photostability study conducted according to ICH Q1B indicate that no protection from light is necessary.

Based on available stability data, the proposed shelf-life of 24 months without specific storage conditions is acceptable for both strengths stored in the HDPE bottles. A shelf-life of 21 months with the instruction “do not store above 30 °C” is acceptable for the blister pack. The storage conditions and shelf-lives are stated in section 6.3 of the SmPC.

Adventitious agents

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

2.2.5. Discussion on chemical, and pharmaceutical 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. A detailed hazard assessment for potentially mutagenic impurities in tenofovir alafenamide fumarate was submitted during the procedure which resolved the related MO. The applicant resolved the second MO by tightening the release and shelf-life specifications for the dissolution method in line with the biobatch data.

2.2.6. 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.

2.2.7. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of emtricitabine and tenofovir alafenamide are well known. As emtricitabine and tenofovir alafenamide are widely used and well-known active substances, the applicant has not provided additional studies and the CHMP agreed that no further non-clinical studies are not required. The non-clinical overview based on literature review was considered appropriate.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Emtricitabine, Tenofovir Alafenamide Tablets 200 mg/10 mg and 200 mg/25 mg is considered unlikely to result in any significant increase in the combined sales volumes for all emtricitabine and tenofovir alafenamide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

Table 1: Summary of main study results

Substance (INN/Invented Name): Emtricitabine, Tenofovir Alafenamide Tablets 200 mg/10 mg, 200 mg/25 mg			
CAS-number (if available): 143491-57-0; 379270-37-8			
PBT screening		Result	Conclusion
<i>Emtricitabine</i>			
Bioaccumulation potential- log K_{ow}	OECD107	-0.91	Potential PBT (N)
Bioaccumulation potential- log K_{ow}	Published literature	-0.43	
<i>Tenofovir alafenamide (as monofumarate salt)</i>			
Bioaccumulation potential- log K_{ow}	OECD107	1.13	Potential PBT (N)
Bioaccumulation potential- log K_{ow}	Published literature	1.61	
Phase I			
Calculation	Value	Unit	Conclusion
<i>Emtricitabine</i>			
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)	1	µg/L	> 0.01 threshold (Y)

<i>Tenofovir alafenamide (as monofumarate salt)</i>			
PEC surfacewater , default or refined (e.g. prevalence, literature)	0.05 and 0.125 (based on dose)	µg/L	> 0.01 threshold (Y)

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. Additionally, the applicant provided regulatory submission documents of the reference product and other marketed medicinal products containing some or all of the active ingredients present in the test product (e.g., Descovy, Emtriva, Genvoya, Viread). The overview justified why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data.

The CHMP considered that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology overall is adequate. The proposed substance and product impurity specification limits which are above the qualification thresholds according to guidelines ICH Q3A and ICH Q3B have been justified with sufficient data. The requested (Q)SAR reports were provided by the applicant to justify the ICH M7 classification of each potentially genotoxic impurity of substance TAF (Impurities 3.2.S.3.2). Classification assigned by the applicant for majority of the compounds is supported by the (Q)SAR reports.

The justification for not submitting a complete ERA was considered acceptable. The present application is pertaining to a generic product, which is assumed to replace existing prescriptions of the originator. Thus, it will not result in an increased environmental exposure to the active ingredients emtricitabine and tenofovir alafenamide.

Non-clinical sections 4.6 and 5.3 of the SmPC are in line with the non-clinical overview and the reference product SmPC.

2.3.4. Conclusion on the non-clinical aspects

The application for Emtricitabine/Tenofovir alafenamide Viartis, film-coated tablets 200 mg/10 mg and 200 mg/25 mg can be approved from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

The applicant has submitted three bioequivalence studies for this MAA and no exemptions were requested. Two of the studies were conducted in healthy adult human subjects under fasting conditions, on both strengths - the highest strength i.e. Emtricitabine/Tenofovir alafenamide Viartis 200mg/25 mg film-coated tablets, and the lowest strength i.e. Emtricitabine/Tenofovir alafenamide Viartis 200mg/10 mg film-coated tablets (both were open-labelled, single-dose, randomised, four-period, two-treatment, two sequence, full-replicate, crossover bioequivalence studies). In addition, the applicant conducted a bioequivalence study in healthy adult human subjects under fed conditions, on the highest strength i.e. Emtricitabine/Tenofovir alafenamide Viartis 200mg/25 mg film-coated tablets.

A bioequivalence study under fasting conditions in this procedure is considered to be the most sensitive condition to detect a potential difference between formulations. In accordance with the administration recommendations provided in the SmPC for the reference product Descovy, the method of

administration is with or without food. Consistently, two of the BE studies for each of the strengths were carried out in a fasted state and are considered as pivotal studies. The presence of food did not affect the area under the curve (AUC) of emtricitabine. In contrast, relative to fasting conditions, the administration of tenofovir alafenamide with a high fat meal (~800 kcal, 50% fat) resulted in a decrease in TAF maximum plasma concentration (C_{max}) (15-37%) and an increase in AUC_{last} (17-77%). Consequently, an additional bioequivalence study has been conducted under fed conditions with the product's most potent formulation, i.e. 200 mg/25 mg and is considered as supportive study. This is in line with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr* and therefore is considered acceptable.

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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

To support the application, the applicant has submitted three bioequivalence studies.

Table 2: Tabular overview of clinical studies

TYPE OF STUDY	STUDY IDENTIFIER	LOCATION OF STUDY REPORT	OBJECTIVE(S) OF THE STUDY	STUDY DESIGN AND TYPE OF CONTROL	TEST PRODUCT(S); DOSAGE REGIMEN; ROUTE OF ADMINISTRATION	NUMBER OF SUBJECTS	HEALTHY SUBJECTS OR DIAGNOSIS OF PATIENTS	DURATION OF TREATMENT	STUDY STATUS; TYPE OF REPORT
BE (Fasting)	EMTA-TBZ-1009	5.3.1.2	The objective of this study is to investigate the bioequivalence of Mylan's Emtricitabine and Tenofovir alafenamide tablets 200/25 mg with DESCOVY® (emtricitabine and tenofovir alafenamide) tablets 200/25 mg in healthy adult human subjects and to monitor the adverse events and also to evaluate the safety of the subjects.	*	Test Product (T): Emtricitabine and Tenofovir Alafenamide Tablets 200 mg/25 mg Oral. Reference Product (R): Descovy® 200 mg/25 mg Film-coated tablets Emtricitabine/Tenofovir alafenamide Oral.	Enrolled subjects: 54 subjects + 01 standby subject Discontinued subjects: 05 subjects. Completed: 49 Subjects.	Healthy Subjects	Single Dose	Complete; Full

TYPE OF STUDY	STUDY IDENTIFIER	LOCATION OF STUDY REPORT	OBJECTIVE(S) OF THE STUDY	STUDY DESIGN AND TYPE OF CONTROL	TEST PRODUCT(S); DOSAGE REGIMEN; ROUTE OF ADMINISTRATION	NUMBER OF SUBJECTS	HEALTHY SUBJECTS OR DIAGNOSIS OF PATIENTS	DURATION OF TREATMENT	STUDY STATUS; TYPE OF REPORT
BE (fed)	EMTA-TBZ-1010	5.3.1.2	The objective of this study was to investigate the bioequivalence of Mylan's Emtricitabine and Tenofovir alafenamide tablets 200/25 mg with DESCovy® (emtricitabine and tenofovir alafenamide) tablets 200/25 mg in healthy adult human subjects and to monitor the adverse events and also to evaluate the safety of the subjects.	*	Test Product (T): Emtricitabine and Tenofovir Alafenamide Tablets 200 mg/25 mg Oral Reference Product (R): Descovy® 200 mg/25 mg Film-coated tablets Emtricitabine/Tenofovir alafenamid Oral	Enrolled subjects: 54 subjects + 02 standby subjects Discontinued subjects: 08 subjects discontinued and 02 subjects replaced. Completed: 46 Subjects.	Healthy Subjects	Single Dose	Complete; Full

TYPE OF STUDY	STUDY IDENTIFIER	LOCATION OF STUDY REPORT	OBJECTIVE(S) OF THE STUDY	STUDY DESIGN AND TYPE OF CONTROL	TEST PRODUCT(S); DOSAGE REGIMEN; ROUTE OF ADMINISTRATION	NUMBER OF SUBJECTS	HEALTHY SUBJECTS OR DIAGNOSIS OF PATIENTS	DURATION OF TREATMENT	STUDY STATUS; TYPE OF REPORT
BE (Fasting)	EMTA-TBZ-1011	5.3.1.2	The objective of this study is to investigate the bioequivalence of Mylan's Emtricitabine and Tenofovir alafenamide tablets 200/10 mg with DESCovy® (emtricitabine and tenofovir alafenamide) tablets 200/10 mg in healthy adult human subjects and to monitor the adverse events and also to evaluate the safety of the subjects.	*	Test Product (T): Emtricitabine and Tenofovir Alafenamide Tablets 200 mg/10 mg Oral. Reference Product (R): Descovy® 200 mg/10 mg Film-coated tablets Emtricitabine/Tenofovir alafenamid Oral.	Enrolled subjects: For Group-I: 24 + 01 subjects (i.e., subject numbers 01 to 24 + Standby-I) For Group-II: 30 + 02 subjects (i.e., subject numbers 25 to 54 + Standby-II & Standby-III) Discontinued subjects: 04 subjects. Completed: 50 Subjects.	Healthy Subjects	Single Dose	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

i. Study EMTA-TBZ-1009: Single-Dose Fasting oral bioequivalence study of Emtricitabine and Tenofovir alafenamide tablets 200/25 mg of Applicant

with DESCOVY (emtricitabine and tenofovir alafenamide) tablets 200/25 mg of Gilead Sciences Ireland UC, in healthy adult human subjects.

Methods

Study design

The study was conducted as an open labelled, single-dose, randomised, four-period, two-treatment, two sequence, full-replicate, crossover bioequivalence study comparing Emtricitabine and Tenofovir alafenamide tablets 200/25 mg of Applicant, with DESCOVY (emtricitabine and tenofovir alafenamide) tablets 200/25 mg of Gilead Sciences Ireland UC, in healthy adult human subjects in healthy adult human subjects under fasting condition.

Population(s) studied

The maximum observed intra-subject variability among primary pharmacokinetic parameters is found to be around ~40%, and the below are the details of sample size calculations. T/R ratio= 115%; Maximum within Reference C.V (%) = ~40%; Significance Level = 5%; Power=80%; Bioequivalence Limits = 80.00% - 125.00%.

Based on the above estimate, a sample size of 46 subjects would be sufficient to establish bioequivalence between formulations. However, taking into account the withdrawal & drop-out subjects, a sample size of 54 subjects are considered for the study.

A total of 54 subjects (+ 1 standby subject) were enrolled in the study and forty-nine (49) subjects completed all 4 periods as per protocol. Four (04) subjects completed 3 periods; one (01) subject completed 1 single period.

Pharmacokinetic and statistical analyses were performed on 50 subjects for Emtricitabine and 53 subjects for Tenofovir alafenamide.

The subjects' weight ranged from 51.2 to 89.73 kg, with a mean weight of 69.34 kg (± 9.335 kg). The subjects' body mass index (BMI) ranged from 19.2 to 29.8 kg/m², with a mean BMI of 24.7 kg/m² (± 2.94 kg/m²).

Analytical methods

A statement on GLP compliance is present in the bioanalytical method validation report and bioanalytical reports. The method for the determination of EMT, TNF and TAF in human plasma was shown to be linear, precise and accurate. The QC values are chosen according to guideline ICH M10. The provided long-term stability data cover the maximum study sample storage period.

Analytical reports related studies EMTA-TBZ-1009, EMTA-TBZ-1010, EMTA-TBZ-1011:

Number of samples collected, analysed and reported is consistent. Integrity of the samples can be confirmed based on the provided information (storage, shipment and stability). Management of repeated sample analyses and missing samples is described adequately. Results of incurred samples reanalysis were well within acceptance criteria. 100% of chromatograms are presented.

Pharmacokinetic variables

$C_{\max}$	: Maximum observed plasma concentration following each treatment.
AUC_{0-t}	: The area under the plasma concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.
$AUC_{0-\infty}$	: The area under the plasma concentration versus time curve from time zero to infinity. Where $AUC_{0-\infty} = AUC_{0-t} + Ct / K_{el}$, Ct is the last measurable concentration and K_{el} is the terminal elimination rate constant.
$T_{\max}$	: Time of the maximum measured plasma concentration.
Residual Area	: Ratio of area under the curve from time zero to last measurable concentration and area under curve from time zero to infinity.
$t_{1/2}$	: The elimination half-life will be calculated as $0.693 / K_{el}$
K_{el}	: First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter will be calculated by linear least squares regression analysis using at least last three or more non-zero plasma concentration values.
$C_{\max}$	: Maximum observed plasma concentration following each treatment.
AUC_{0-72}	: The area under the plasma concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.
$T_{\max}$	: Time of the maximum measured plasma concentration.

Statistical methods

Statistical analysis performed by using SAS software version 9.4 (or higher).

The 90% confidence interval for the geometric LS-means ratio of $C_{\max}$ and AUC_{0-t} , for the test and reference product should be between 80.00% - 125.00% for the natural log-transformed data for Emtricitabine and Tenofovir Alafenamide.

For Emtricitabine and Tenofovir: Concentration data of Subjects who complete the first two periods were considered for the bioequivalence evaluation by using average bioequivalence method. The natural log transformed parameters AUC_{0-t} and $C_{\max}$ for Emtricitabine and $C_{\max}$ and AUC_{0-72} for Tenofovir were statistically analyzed by using the ANOVA model (Proc GLM or any other suitable model). The model included Sequence, Subject (Sequence), Treatment and formulation as fixed effects with a significance level of 0.10. The tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed for $C_{\max}$ and AUC_{0-t} using the two one-sided tests procedure to assess average bioequivalence between the two products.

To conclude bioequivalence, the 90% confidence interval for the ratio of the test and reference products of Emtricitabine should be within the acceptance interval of 80.00% - 125.00%. To meet the acceptance interval the lower limit should be $\geq 80.00\%$ when rounded to two decimal places and the upper limit should be $\leq 125.00\%$ when rounded to two decimal places.

Tenofovir data were provided as supportive evidence for therapeutic outcome.

For Tenofovir Alafenamide: Due to high variable nature of the drug, the pharmacokinetic parameters data of subjects who completed at least two periods with two reference products and/or subjects who

completed minimum two periods with one test and one reference treatments were included in bioequivalence evaluation by using scaled-average-bioequivalence method.

✓ Subjects who received only two reference formulation were included in within reference variability calculation only and were not included in the bioequivalence evaluation.

✓ Subjects who received at least one test and one reference formulation were included in the average bioequivalence method.

Within reference variability was calculated by utilizing the two administrations of Reference Product Descovy (emtricitabine and tenofovir alafenamide) in each subject to ascertain intrasubject or within-subject variability of Reference product (S^2_{WR}) for peak plasma concentration (C_{max}). The ANOVA model (Proc GLM or other suitable procedure) included Sequence, subject (Sequence) and period as fixed effects.

If the intra-subject variability of Reference product for C_{max} was greater than 30% for Tenofovir Alafenamide, the assessment of bioequivalence was performed using the methods for highly variable drugs or drug products described in the EMEA Guideline CHMP/QWP/EWP/1401/98, Rev 1, "Guideline on the Investigation of Bioequivalence".

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00% - 125.00%. The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC_{0-t} where the acceptance range remain at 80.00% - 125.00% regardless of variability.

If within reference variability is < 30%:

The bioequivalence is evaluated as average bioequivalence criteria i.e. 90% CI for C_{max} was within 80.00% - 125.00%.

Suitable statistical tests were described for e.g., studentized residuals >3 etc., to ensure that the calculated intra-subject variability was reliable estimate and that was not because of the outliers.

Results

Table 3: Pharmacokinetic parameters for Emtricitabine (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
$AUC_{(0-t)}$	13421.992	17.9	13082.827	16.5
$AUC_{(0-\infty)}$	13686.025	17.7	13316.792	16.4
C_{max}	2668.168	22.0	2610.584	26.0
T_{max}^*	1.000 (0.500 - 2.330)	-	1.000 (0.500 - 5.000)	-
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 4: Statistical analysis for Emtricitabine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals	CV%*
AUC _(0-t)	102.23	99.60-104.93	7.78
C _{max}	103.05	96.96-109.52	18.29
* estimated from the Residual Mean Squares			

Table 5: Pharmacokinetic parameters for Tenofovir (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
AUC _(0-72h)	204.858	27.2	210.598	27.7
C _{max}	9.291	30.1	9.616	34.0
T _{max} *	1.250 (0.330 - 2.330)	-	1.250 (0.330 - 2.330)	-
AUC _{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
C _{max}	maximum plasma concentration			
T _{max}	time for maximum concentration (* median, range)			

Table 6: Statistical analysis for Tenofovir (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals	CV%*
AUC _(0-72h)	97.61	92.84-102.63	15.01
C _{max}	98.05	91.60-104.95	20.46
* estimated from the Residual Mean Squares			

Table 7: Pharmacokinetic parameters for Tenofovir Alafenamide (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
AUC _(0-t)	226.064	45.5	221.217	44.0
AUC _(0-∞)	231.320	45.0	224.727	43.5
C _{max}	384.601	44.9	384.498	51.5
T _{max} *	0.500 (0.330 - 1.750)	-	0.500 (0.167 - 1.250)	-

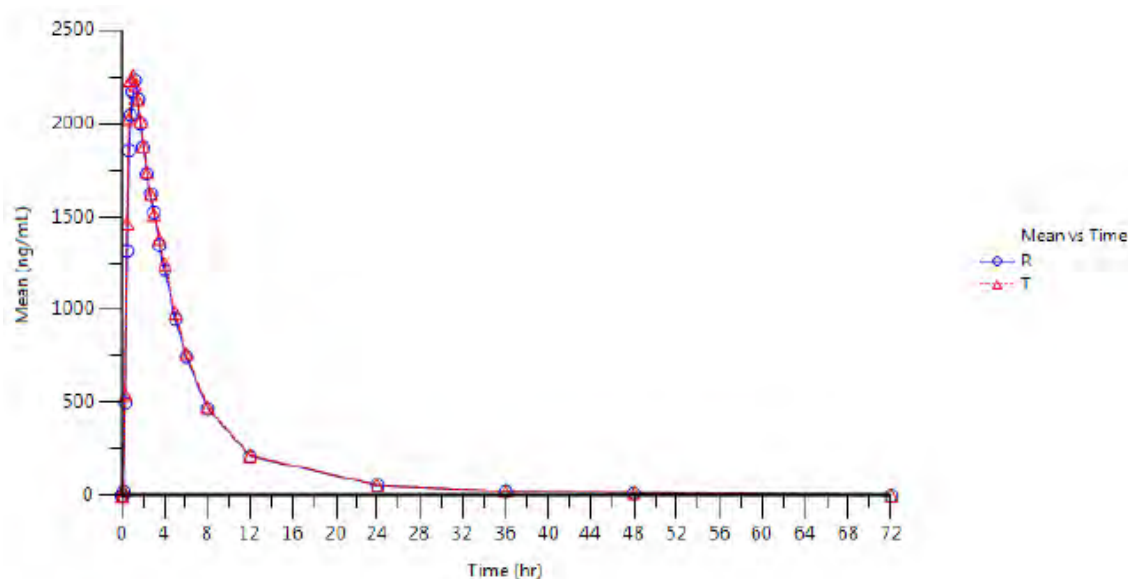
Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
AUC _{0-t}	area under the plasma concentration-time curve from time zero to t hours			
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity			
C _{max}	maximum plasma concentration			
T _{max}	time for maximum concentration (* median, range)			

Table 8: Statistical analysis for Tenofovir Alafenamide (ln-transformed values)

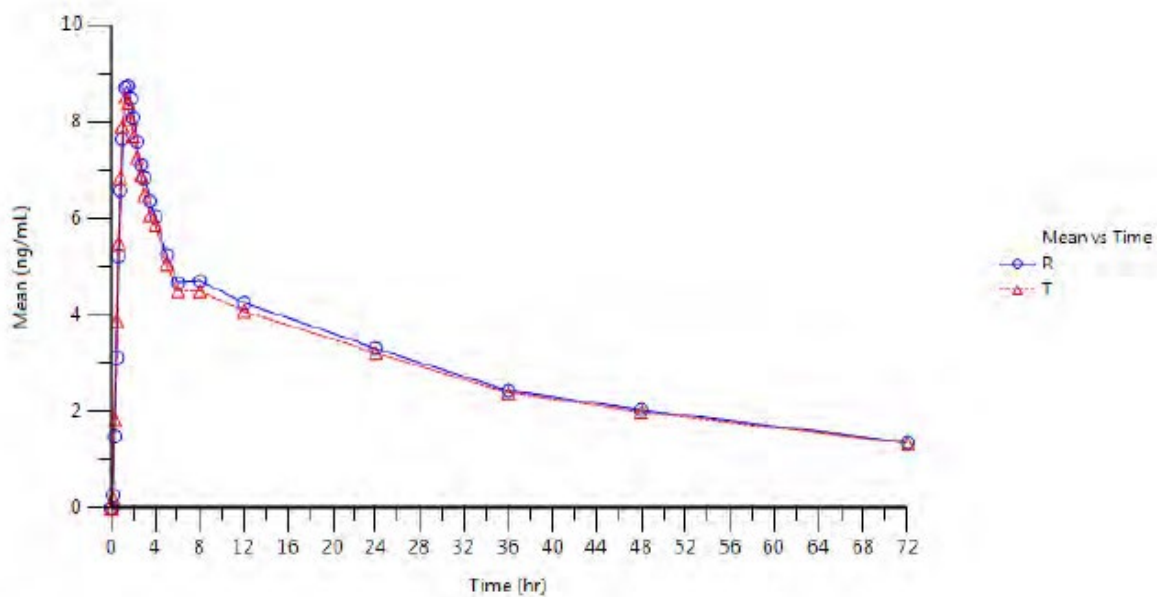
Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC _(0-t)	101.54	95.72-107.71	29.9
C _{max}	100.73	92.38-109.83	35.7
* estimated from the Residual Mean Squares			

Linear Plots of Mean Plasma Concentrations

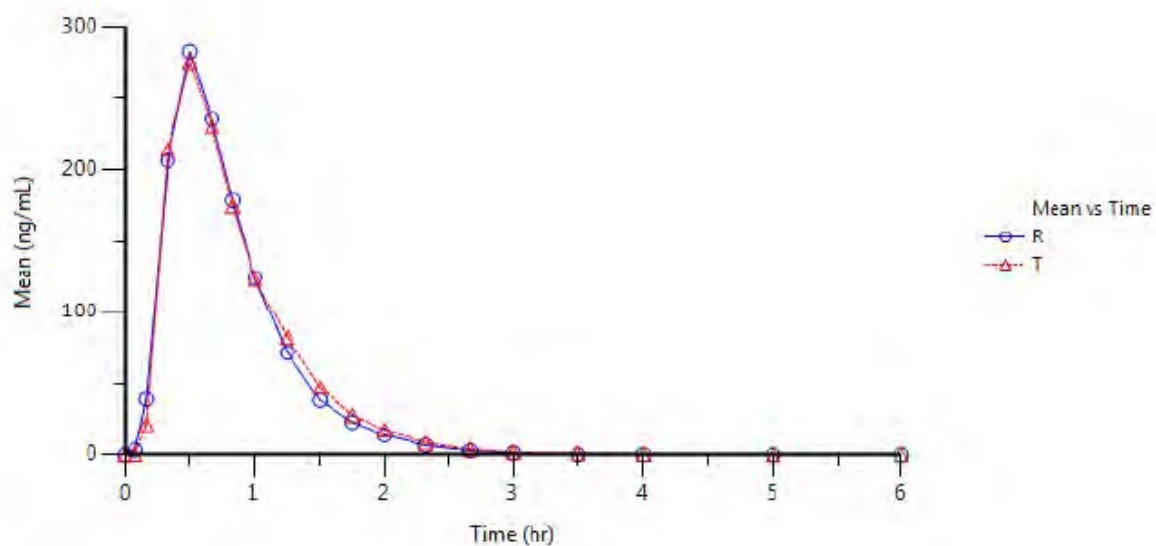
Emtricitabine



Tenofovir



Tenofovir alafenamide



P-values from ANOVA

Emtricitabine

Pharmacokinetic Parameters	p-value for Treatment/Formulation	p-value for period	p-value for Sequence
AUC _{0-t} (hr.ng/mL)	0.1622	0.0150	0.8524
C _{max} (ng/mL)	0.4121	0.6920	0.9447

Source: Sub Section 16.2.6.2.1 of Section 16.2.6.2 of Appendix 16.2.6.

Tenofovir

Pharmacokinetic Parameters	p-value for Treatment/Formulation	p-value for period	p-value for Sequence
AUC ₀₋₇₂ (hr.ng/mL)	0.4227	0.9803	0.0951
C _{max} (ng/mL)	0.6294	0.2753	0.4516

Source: Sub Section 16.2.6.2.1 of Section 16.2.6.2 of Appendix 16.2.6.

Tenofovir Alafenamide

Pharmacokinetic Parameters	p-value for Treatment/Formulation	p-value for period	p-value for Sequence
AUC _{0-t} (hr.ng/mL)	0.6686	0.8046	0.8568
C _{max} (ng/mL)	0.8893	0.0228	0.9048

The applicant's justification for Significant Period Effect For Emtricitabine (AUC_{0-t}) and Tenofovir alafenamide (C_{max}):

Significant period effect could possibly reflect different positioning, timing and degree of physical activity, timing and composition of food/beverages ingested, or the temperature of the water administered in the two periods. The conditions were maintained similar for two periods and the plasma samples of each subject of the two periods are analysed all together and in a sequence in which the blood samples were collected. In each period both products were dosed (Test and Reference).

Safety data

No serious adverse events (SAEs) were reported. One AE (treatment emergent) was reported by one (01) subject over the course of the study. Reported AE was moderate in severity.

There was 1 AE (Diarrhoea) considered at least possibly related to the oral administration of Descovy 200 mg/25 mg Film-coated tablets.

ii. Study EMTA-TBZ-1010: Single-Dose Fed oral bioequivalence study of Emtricitabine and Tenofovir alafenamide tablets 200/25 mg of Applicant with DESCovy (emtricitabine and tenofovir alafenamide) tablets 200/25 mg of Gilead Sciences Ireland UC, in healthy adult human subjects.

Methods

Study design

This was an open labelled, single-dose, randomised, four-period, two-treatment, two sequence, full-replicate, crossover study investigating the bioequivalence of Applicant's Emtricitabine and Tenofovir alafenamide tablets 200/25 mg to Gilead Sciences Ireland UC, of DESCovy (emtricitabine and tenofovir alafenamide) tablets 200/25 mg of following administration of a single, oral dose of 200 mg/25 mg (1 x 200 mg/25 mg) in 54 healthy adult human subjects under fed conditions.

Population(s) studied

The maximum observed intra-subject variability among primary pharmacokinetic parameters is found to be around ~40%, and the below are the details of sample size calculations. T/R ratio= 115%; Maximum within Reference C.V (%) = ~40%; Significance Level = 5%; Power=80%;

Bioequivalence Limits = 80.00% - 125.00%

Based on the above estimate, a sample size of 46 subjects would be sufficient to establish bioequivalence between formulations. However, taking into account the withdrawal & drop-out subjects, a sample size of 54 subjects are considered for the study.

Main criteria for inclusion - healthy, adult non-smoker and non-alcoholic, human subjects aged between 18 to 45 years old (inclusive of both), weighing at least 50.00 kg with a Body Mass Index (BMI) greater than or equal to 18.5 kg/m² but less than or equal to 30.0 kg/m², who were judged to be healthy based on a pre-study physical examination and clinical laboratory tests.

Enrolled subjects – 54 subjects + 02 standby subjects; Discontinued subjects – 08 subjects discontinued and 02 subjects replaced.

Analytical methods

A statement on GLP compliance is present in the bioanalytical method validation report and bioanalytical reports. The method for the determination of EMT, TNF and TAF in human plasma was shown to be linear, precise and accurate. The QC values are chosen according to guideline ICH M10. The provided long-term stability data cover the maximum study sample storage period.

Analytical reports related studies EMTA-TBZ-1009, EMTA-TBZ-1010, EMTA-TBZ-1011:

Number of samples collected, analysed and reported is consistent. Integrity of the samples can be confirmed based on the provided information (storage, shipment and stability). Management of repeated sample analyses and missing samples is described adequately. Results of incurred samples reanalysis were well within acceptance criteria. 100% of chromatograms are presented.

Pharmacokinetic Variables

- C_{max} : Maximum observed plasma concentration following each treatment.
- AUC_{0-t} : The area under the plasma concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.
- AUC_{0-inf} : The area under the plasma concentration versus time curve from time zero to infinity. Where $AUC_{0-inf} = AUC_{0-t} + C_t / K_{el}$, C_t is the last measurable concentration and K_{el} is the terminal elimination rate constant.
- T_{max} : Time of the maximum measured plasma concentration.
- Residual Area : Ratio of area under the curve from time zero to last measurable concentration and area under curve from time zero to infinity.
- $t_{1/2}$: The elimination half-life will be calculated as $0.693 / K_{el}$
- K_{el} : First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter will be calculated by linear least squares regression analysis using at least last three or more non-zero plasma concentration values.

For Tenofovir:

- $C_{\max}$: Maximum observed plasma concentration following each treatment.
- AUC_{0-72} : The area under the plasma concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.
- $T_{\max}$: Time of the maximum measured plasma concentration.

Statistical methods

Statistical analysis performed by using SAS software version 9.4 (or higher).

The 90% confidence interval for the geometric LS-means ratio of $C_{\max}$ and AUC_{0-t} , for the test and reference product should be between 80.00% - 125.00% for the natural log-transformed data for Emtricitabine and Tenofovir Alafenamide.

For Emtricitabine and Tenofovir: Concentration data of Subjects who complete the first two periods were considered for the bioequivalence evaluation by using average bioequivalence method. The natural log transformed parameters AUC_{0-t} and $C_{\max}$ for Emtricitabine and $C_{\max}$ and AUC_{0-72} for Tenofovir were statistically analysed by using the ANOVA model (Proc GLM or any other suitable model). The model included Sequence, Subject (Sequence), Treatment and formulation as fixed effects with a significance level of 0.10. The tests were performed to analyse for statistically significant differences in the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed for $C_{\max}$ and AUC_{0-t} using the two one-sided tests procedure to assess average bioequivalence between the two products.

Note: Tenofovir data was provided as supportive evidence for therapeutic outcome.

For Tenofovir Alafenamide: Due to high variable nature of the drug, the pharmacokinetic parameters data of subjects who completed at least two periods with two reference products and/or subjects who completed minimum two periods with one test and one reference treatments were included in bioequivalence evaluation by using scaled-average-bioequivalence method.

✓ Subjects who received only two reference formulation were included in within reference variability calculation only and were not included in the bioequivalence evaluation.

✓ Subjects who received at least one test and one reference formulation were included in the average bioequivalence method.

Within reference variability was calculated by utilizing the two administrations of Reference Product DESCOVY (emtricitabine and tenofovir alafenamide) in each subject to ascertain intrasubject or within-subject variability of Reference product (S^2_{WR}) for peak plasma concentration ($C_{\max}$). The ANOVA model (Proc GLM or other suitable procedure) included Sequence, subject (Sequence) and period as fixed effects.

If the intra-subject variability of Reference product for $C_{\max}$ was greater than 30% for Tenofovir Alafenamide, the assessment of bioequivalence was performed using the methods for highly variable drugs or drug products described in the EMEA Guideline CHMP/QWP/EWP/1401/98, Rev 1, "Guideline on the Investigation of Bioequivalence".

The geometric mean ratio (GMR) should lie within the conventional acceptance range 80.00% - 125.00%. The possibility to widen the acceptance criteria based on high intra-subject variability does not apply to AUC_{0-t} where the acceptance range remain at 80.00% - 125.00% regardless of variability.

If within reference variability is < 30%:

The bioequivalence is evaluated as average bioequivalence criteria i.e. 90% CI for C_{max} was within 80.00% - 125.00%.

Note: Suitable statistical tests were described for e.g., studentized residuals >3 etc., to ensure that the calculated intra-subject variability was reliable estimate and that was not because of the outliers.

Results

Table 9: Pharmacokinetic parameters for Emtricitabine (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
$AUC_{(0-t)}$	11921.550	17.8	11601.738	22.7
$AUC_{(0-\infty)}$	12195.267	17.8	11869.591	22.5
C_{max}	2000.558	27.2	1839.071	25.0
T_{max}^*	2.000 (0.830 - 4.000)	-	2.670 (0.830 - 4.000)	-
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 10: Statistical analysis for Emtricitabine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals	CV%*
$AUC_{(0-t)}$	105.24	98.63 - 112.30	19.73
C_{max}	109.19	102.24 - 116.62	20.01
* estimated from the Residual Mean Squares			

Table 11: Pharmacokinetic parameters for Tenofovir (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
$AUC_{(0-72h)}$	233.969	23.5	231.745	27.0
C_{max}	8.249	26.6	8.027	29.1
T_{max}^*	3.000	1.250 - 4.000	3.000	1.250 - 5.000
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 12: Statistical analysis for Tenofovir (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals	CV%*
$AUC_{(0-72h)}$	103.25	96.10 - 110.93	21.15
C_{max}	105.25	97.02 - 114.18	24.09
* estimated from the Residual Mean Squares			

Table 13: Pharmacokinetic parameters for Tenofovir Alafenamide (non-transformed values)

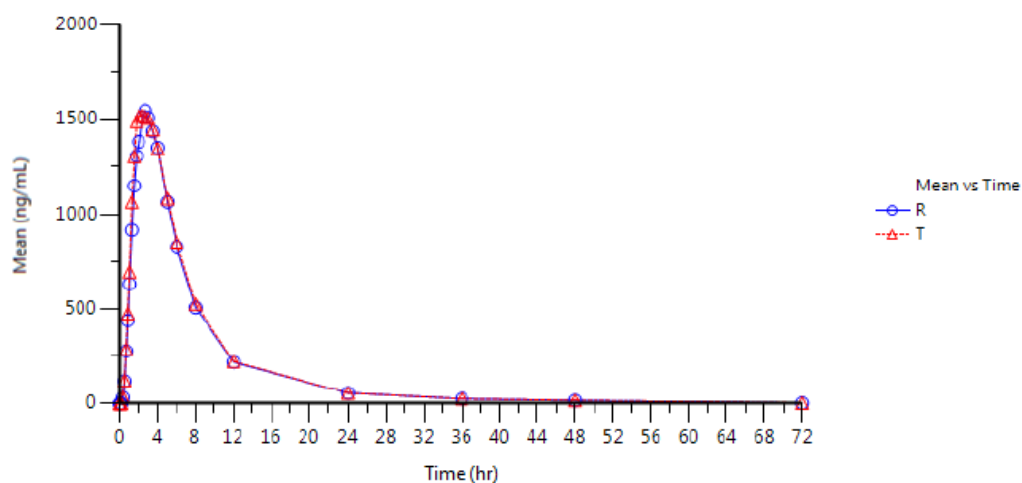
Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
AUC _(0-t)	292.457	35.6	293.232	35.4
AUC _(0-∞)	\$304.806	34.0	\$\$304.634	34.2
C _{max}	250.240	57.7	241.316	66.5
T _{max} *	1.500 (0.500 - 3.500)	-	1.500 (0.670 - 3.500)	-
AUC _{0-t}	area under the plasma concentration-time curve from time zero to t hours			
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity			
C _{max}	maximum plasma concentration			
T _{max}	time for maximum concentration (* median, range)			
\$	n=102 since the subject 24 period-1, subject 26 period-4 and subject 43 and 47 period-2 test product did not fit with linear regression in the terminal phase.			
\$\$	n=102 since the subject 24 period-2 reference product did not fit with linear regression in the terminal phase. Subject 25 reference data was not included in the calculation of within reference as an outlier (Appendix 16.2.6); subject 38 the plasma concentrations reported zero values period-4 test product.			

Table 14: Statistical analysis for Tenofovir Alafenamide (ln-transformed values)

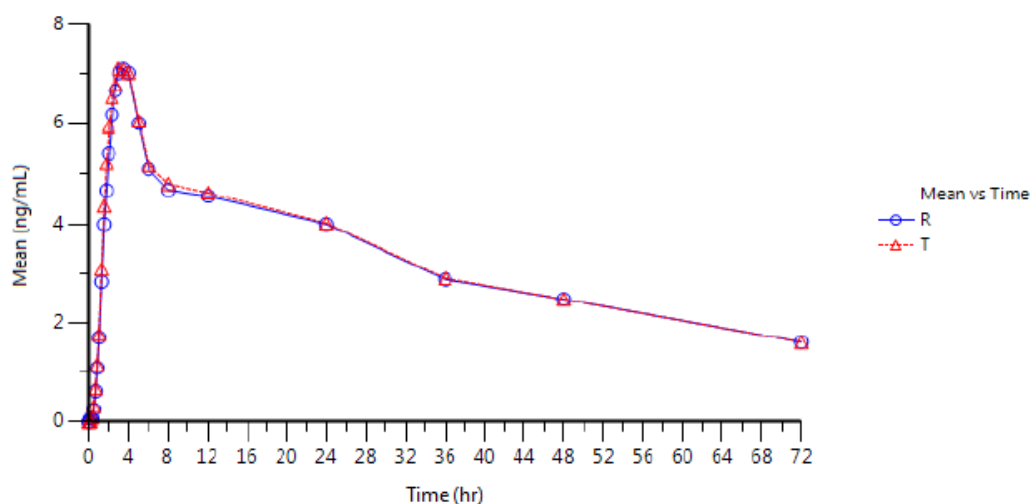
Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC _(0-t)	100.46	95.04 - 106.18	22.3
C _{max}	104.08	96.37- 112.41	37.2
* estimated from the Residual Mean Squares			

Linear Plots of Mean Plasma Concentrations

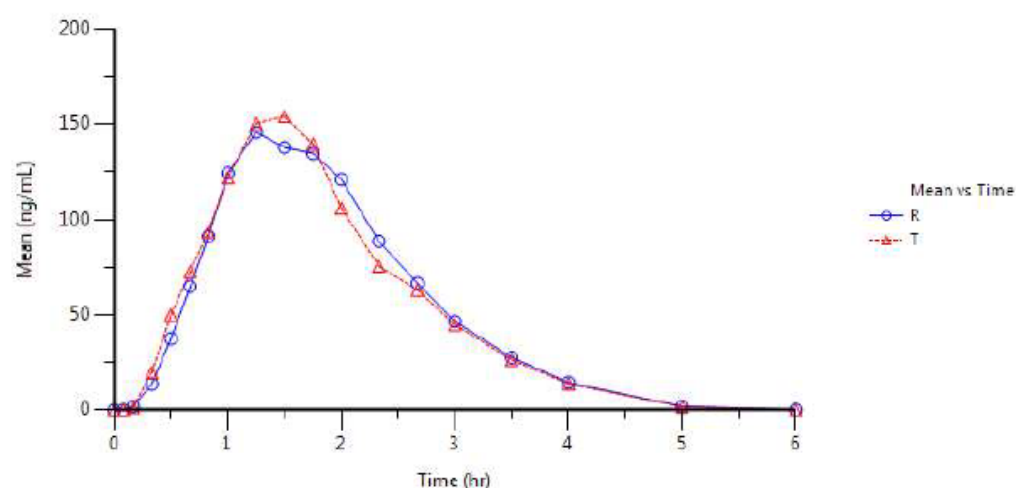
Emtricitabine



Tenofovir



Tenofovir alafenamide



P-values from ANOVA Table

Emtricitabine

Pharmacokinetic Parameters	p-value for Treatment/Formulation	p-value for period	p-value for Sequence
AUC _{0-t} (hr.ng/mL)	0.1930	0.6154	0.7048
C _{max} (ng/mL)	0.0296	0.2697	0.0329

The applicant's justification for Significant Formulation Effect for Emtricitabine (C_{max}):

Significant treatment effect or formulation effect can be present when the treatment mean square is small. Significant difference can occur at the moment the variability is low or the number of volunteers sufficiently high. Decision of equivalence is based on the Schuirmann test and the 90% confidence interval is within the equivalence boundaries. The sequence effect in a bioequivalence study could indicate an unequal carryover effect.

Tenofovir

Pharmacokinetic Parameters	p-value for Treatment/Formulation	p-value for period	p-value for Sequence
AUC ₀₋₇₂ (hr.ng/mL)	0.4584	0.6610	0.6946
C _{max} (ng/mL)	0.2972	0.9417	0.5403

Tenofovir alafenamide

Pharmacokinetic Parameters	p-value for Treatment/Formulation	p-value for period	p-value for Sequence
AUC _{0-t} (hr.ng/mL)	0.8922	<.0001	0.5730
C _{max} (ng/mL)	0.3914	<.0001	0.0608

The applicant's justification for Significant Period Effect For Tenofovir alafenamide (C_{max} and AUC_{0-t}):

Significant period effect could possibly reflect different positioning, timing and degree of physical activity, timing and composition of food/beverages ingested, or the temperature of the water administered in the all periods. The applicant states, the conditions were maintained similar for all the periods. The plasma samples of each subject of all the periods are analyzed all together and in a sequence in which the blood samples were collected. In each period the products were dosed (Test and Reference).

Safety data

No serious adverse events (SAEs) were reported. Three AE's (treatment emergent) were reported by three subjects over the course of the study. Two AEs were mild in severity and one AE was moderate in severity.

There was 1 AE (Vomiting) considered at least possible related to the oral administration of Descovy 200 mg/25 mg Film-coated tablets. There was 1 AE (Headache) considered at least possible related to the oral administration of Emtricitabine/ Tenofovir alafenamide.

There was 1 AE (Vomiting) considered unrelated to the oral administration of Descovy 200 mg/25 mg Film-coated tablets.

iii. Study EMTA-TBZ-1011: Single-Dose Fasting oral bioequivalence study of Emtricitabine and Tenofovir alafenamide tablets 200/10 mg of Applicant with DESCovy (emtricitabine and tenofovir alafenamide) tablets 200/10 mg of Gilead Sciences Ireland UC, in healthy adult human subjects.

Methods

Study design

The study was conducted as an open labelled, single-dose, randomised, four-period, two-treatment, two sequence, full-replicate, crossover bioequivalence study comparing Emtricitabine and Tenofovir alafenamide tablets 200/10 mg of Applicant with DESCovy (emtricitabine and tenofovir alafenamide) tablets 200/10 mg of Gilead Sciences Ireland UC, in healthy adult human subjects under fasting condition.

Group-I

A 14 days' washout separated between period-1 and period-2, 15 days' washout separated between period-2 and period-3 and 17 days' washout separated between period-3 and period-4.

Group-II

A 14 days' washout separated between period-1 and period-2; period-2 and period-3 & period-3 and period-4.

Population(s) studied

The maximum observed intra-subject variability among primary pharmacokinetic parameters is found to be around ~40%, and the below are the details of sample size calculations. T/R ratio= 115%; Maximum within Reference C.V (%) = ~40%; Significance Level = 5%; Power=80%; Bioequivalence Limits = 80.00% - 125.00%

Based on the above estimate, a sample size of 46 subjects would be sufficient to establish bioequivalence between formulations. However, taking into account the withdrawal & drop-out subjects, a sample size of 54 subjects are considered for the study.

A total of 54 subjects + 03 additional subject (standby-I, standby-II & standby-III) (+ 3 standby subject) were enrolled in the study. Study was conducted in two groups. For Group-I: 24 + 01 subjects (i.e., subject numbers 01 to 24 + Standby-I. For Group-II: 30 + 02 subjects (i.e., subject numbers 25 to 54 + Standby-II & Standby-III). Fifty (50) subjects completed 4 periods. Three (03) subjects completed 3 periods, one (01) subject completed 1 single period. For (4) subjects were withdrawn from the study.

The subjects' weight ranged from 52.85 to 94.42 kg, with a mean weight of 69.98 kg (± 9.528 kg). The subjects' body mass index (BMI) ranged from 19.9 to 29.8 kg/m², with a mean BMI of 25.0 kg/m² (± 2.59 kg/m²).

Pharmacokinetic and statistical analyses were performed on 52 subjects for Emtricitabine and 53 subjects for Tenofovir alafenamide.

Analytical methods

A statement on GLP compliance is present in the bioanalytical method validation report and bioanalytical reports. The method for the determination of EMT, TNF and TAF in human plasma was shown to be linear, precise and accurate. The QC values are chosen according to guideline ICH M10. The provided long-term stability data cover the maximum study sample storage period.

Analytical reports related studies EMTA-TBZ-1009, EMTA-TBZ-1010, EMTA-TBZ-1011:

Number of samples collected, analysed and reported is consistent. Integrity of the samples can be confirmed based on the provided information (storage, shipment and stability). Management of repeated sample analyses and missing samples is described adequately. Results of incurred samples reanalysis were well within acceptance criteria. 100% of chromatograms are presented.

Pharmacokinetic variables

Actual time-points of the sample collection were used for the calculation of pharmacokinetic parameters. All concentration values below the lower limit of quantification were set to zero for the pharmacokinetic and statistical calculations.

The following pharmacokinetic parameters were computed for Emtricitabine, Tenofovir and Tenofovir Alafenamide through non compartmental method.

Primary pharmacokinetic parameters were C_{max} and AUC_{0-t} .

Secondary pharmacokinetic parameters were $AUC_{0-\infty}$, T_{max} , Residual area, $t_{1/2}$ and K_{el} .

For Tenofovir the pharmacokinetic parameters were C_{max} and AUC_{0-72} , T_{max} .

The pharmacokinetic variables are adequate and in line with BE guideline.

Statistical methods

Statistical analysis performed by using SAS software version 9.4 (or higher).

The 90% confidence interval for the geometric LS-means ratio of C_{max} and AUC_{0-t} , for the test and reference product should be between 80.00% - 125.00% for the natural log-transformed data for Emtricitabine and TAF.

For Emtricitabine and Tenofovir: Concentration data of Subjects who complete the first two periods were considered for the bioequivalence evaluation by using average bioequivalence method. The natural log transformed parameters AUC_{0-t} and C_{max} for Emtricitabine and C_{max} and AUC_{0-72} for Tenofovir were statistically analyzed by using the ANOVA model (Proc GLM or any other suitable model). The model included Sequence, Subject (Sequence), Treatment and formulation as fixed effects with a significance level of 0.10. The tests were performed to analyze for statistically significant differences in the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed for C_{max} and AUC_{0-t} using the two one-sided tests procedure to assess average bioequivalence between the two products.

To conclude bioequivalence, the 90% confidence interval for the ratio of the test and reference products of Emtricitabine should be within the acceptance interval of 80.00% - 125.00%. To meet the acceptance interval the lower limit should be $\geq 80.00\%$ when rounded to two decimal places and the upper limit should be $\leq 125.00\%$ when rounded to two decimal places.

Tenofovir data was provided as supportive evidence for therapeutic outcome.

For TAF: Due to high variable nature of the drug, the pharmacokinetic parameters data of subjects who completed at least two periods with two reference products and/or subjects who completed minimum two periods with one test and one reference treatments were included in bioequivalence evaluation by using scaled-average-bioequivalence method.

✓ Subjects who received only two reference formulation were included in within reference variability calculation only and were not included in the bioequivalence evaluation.

✓ Subjects who received at least one test and one reference formulation were included in the average bioequivalence method.

Within reference variability was calculated by utilizing the two administrations of Reference Product DESCOVY (emtricitabine and TAF) in each subject to ascertain intrasubject or within-subject variability of Reference product (S2WR) for peak plasma concentration (C_{max}). The ANOVA model (Proc GLM or other suitable procedure) included Sequence, subject (Sequence) and period as fixed effects.

If the intra-subject variability of Reference product for C_{max} was greater than 30% for TAF, the assessment of bioequivalence was performed using the methods for highly variable drugs or drug products described in the EMEA Guideline CHMP/QWP/EWP/1401/98, Rev 1, "Guideline on the Investigation of Bioequivalence".

If within reference variability is $< 30\%$:

The bioequivalence is evaluated as average bioequivalence criteria i.e. 90% CI for C_{max} was within 80.00% - 125.00%.

Note: Suitable statistical tests were described for e.g., studentized residuals >3 etc., to ensure that the calculated intra-subject variability was reliable estimate and that was not because of the outliers.

For Emtricitabine and Tenofovir: (Considering the first two period data)

Determination of biologically implausible (pharmacokinetic) outliers will be based on the observed results (concentration data; such as no detectable plasma concentration following the administration of drug) which are determined to be discordant with the rest of the subjects. Clinical and bioanalytical circumstances will be examined in an attempt to provide insight into the apparent anomalous results. It is the sponsor's intent to complete this study in one cohort. In the event that separate enrolments are necessary to complete the intended number of subjects, appropriate adjustments may be made to the statistical model to reflect the multi-cohort nature of the study.

Additional cohorts will be recruited and dosed under the following conditions:

Recruiting for additional enrolment(s) begin before the end of the final period of the previous enrolment;

Subjects are recruited from the same population, under the same protocol requirements;

dosing of additional cohorts began as soon as practical after their recruitment: and

no two cohorts are dosed on the same day.

Appropriate adjustments will be made to the statistical model to reflect the multi-cohort nature of the study if:

the number of cohorts is less than or equal to 3; and

there are at least 6 subjects in each cohort.

For Emtricitabine:

The group*treatment effect was examined keeping group*treatment effect in ANOVA model. After performing group by treatment effect i.e. treatment*group effect found statistically significant at 5% level of significance for AUC_{0-t}. However, as per recent ICH-M13A guideline "ICH Guideline M13A on bioequivalence for immediate-release solid oral dosage forms, EMA/CHMP/ICH953493/2022" group*treatment effect is not absolutely required to check "BE should be determined based on the overall treatment effect in the whole study population. In general, the assessment of BE in the whole study population should be done without including the group*treatment interaction term in the model". Hence, based on recent guideline ICH-M13A & sponsor request, bioequivalence was determined based on overall treatment effect i.e. with including the group by treatment interaction term in the ANOVA model for evaluation of confidence intervals & as a part of sensitive analysis.

Results

Table 15: Pharmacokinetic parameters for Emtricitabine (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
AUC _(0-t)	12756.159	16.7	12884.189	17.1
AUC _(0-∞)	12986.763	16.7	13092.584	17.0

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
C _{max}	2674.487	32.4	2780.957	27.5
T _{max} *	0.830 (0.500 - 3.500)	-	1.000 (0.500 - 3.000)	-
AUC _{0-t}	area under the plasma concentration-time curve from time zero to t hours			
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity			
C _{max}	maximum plasma concentration			
T _{max}	time for maximum concentration (* median, range)			

* Median, Minimum and Maximum values reported for Tmax

Table 16: Statistical analysis for Emtricitabine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC _(0-t)	99.14	96.15 - 102.22	9.32
C _{max}	94.73	88.28% - 101.64	21.63
* estimated from the Residual Mean Squares			

The group by treatment effect was significant for Emtricitabine component only. Accordingly, as per ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms (EMA/CHMP/ICH/953493/ 2022), have performed an exploratory analysis for AUC_{0-t} and the calculated 90% CI for each group independently and the results are presented below.

BE results for Subjects from 1-24 i.e., Group-1

BE results for Subjects from 1-24 i.e., Group-1 (Annexure M3.3)

Parameter	[T/R] Ratio	90% CI Lower	90% CI Upper
LnAUC _{0-t}	103.64	98.91	108.59

BE results for Subjects from 25-54 i.e., Group-2

BE results for Subjects from 25-54 i.e., Group-2 (Annexure M3.3)

Parameter	[T/R] Ratio	90% CI Lower	90% CI Upper
LnAUC _{0-t}	95.99	92.27	99.86

Considering the above results even though the group by treatment effect was statistically significant, this will not have any impact on the outcome of bioequivalence study.

Table 17: Pharmacokinetic parameters for Tenofovir (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	CV%	Arithmetic mean	CV%
AUC _(0-72h)	77.458	23.7	88.726	21.1
C _{max}	3.386	25.2	3.824	24.1
T _{max} *	1.250 (0.500 - 12.000)	-	1.250 (0.330 - 3.000)	-
AUC _{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity			
C _{max}	maximum plasma concentration			
T _{max}	time for maximum concentration (* median, range)			

* Median, Minimum and Maximum values reported for Tmax. Note: Tenofovir data was provided as supportive evidence for therapeutic outcome. However, BE conclusion based on the Emtricitabine and Tenofovir Alafenamide.

Table 18: Statistical analysis for Tenofovir (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
AUC _(0-72h)	86.80	82.00 - 91.87	16.84
C _{max}	88.30	82.80 - 94.16	19.08
* estimated from the Residual Mean Squares			

Table 19: Pharmacokinetic parameters for Tenofovir Alafenamide (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic mean	CV%	Arithmetic mean	CV%
AUC _{0-t}	104.933	50.2	108.592 ± 56.6007	52.1
AUC _(0-∞)	107.252	49.0	110.851	51.4
C _{max}	165.167	51.1	174.848	49.7
T _{max} *	0.500 (0.330 - 2.000)	-	0.500 (0.167 - 1.500)	-
AUC _{0-t}	area under the plasma concentration-time curve from time zero to t hours			
AUC _{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity			
C _{max}	maximum plasma concentration			
T _{max}	time for maximum concentration (* median, range)			

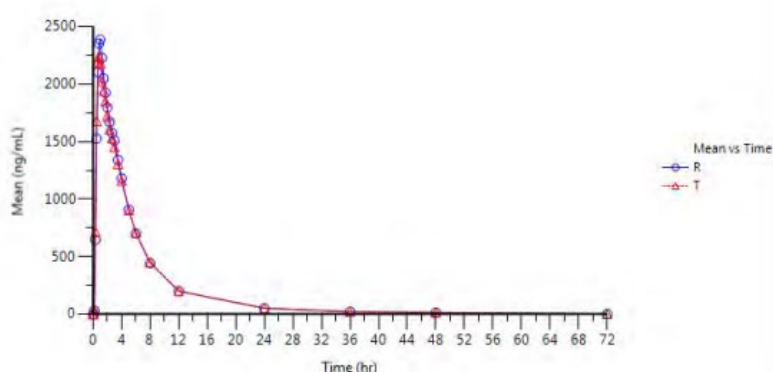
* Median, Minimum and Maximum values reported for Tmax.

Table 20: Statistical analysis for Tenofovir Alafenamide (ln-transformed values)

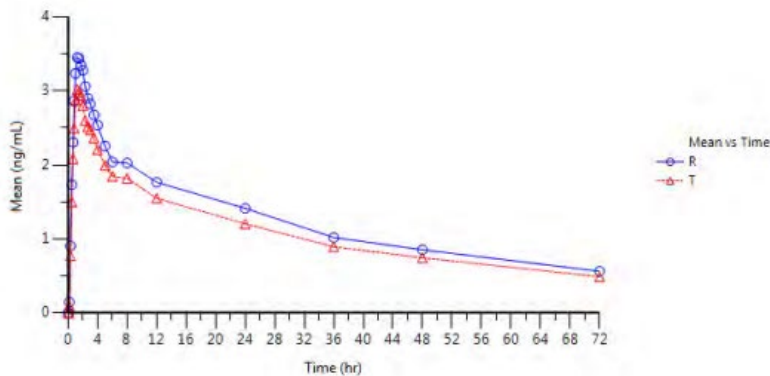
Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	Expanded Acceptance Limits	CV% ISCV of Reference
AUC _(0-t)	98.00	92.15 - 104.22	80.00 - 125.00	28.8
C _{max}	94.23	86.99% - 102.06	80.00 - 125.00	27.9

Linear Plots of Mean Plasma Concentrations

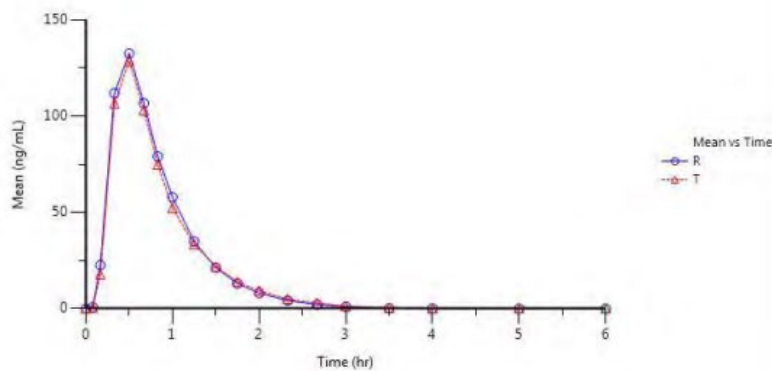
Emtricitabine



Tenofovir



Tenofovir alafenamide



Details for group effect for Drug

This study was conducted in two groups and the group factors were considered in the ANOVA model i.e., sequence, formulation, subject (sequence*group), period (group), group*sequence and treatment*group and there was a 'treatment * group' interaction term statistically significant i.e., the p-value of 'treatment*group' was less than 0.05 for AUC_{0-t} for Emtricitabine. As per ICH M13A guideline, the bioequivalence was determined based on overall treatment effect i.e. without including the group*treatment interaction term in the ANOVA model for evaluation of confidence intervals and statistical analysis also performed without dropping the 'treatment*group' interaction term in the model and provided as an additional information and based on results obtained the 90% confidence limits were also fell well within acceptance range of 80.00% to 125.00%.

Details of p-value for group effect

Parameters	Significant Criteria	AUC _{0-t}
Treatment*Group	P<0.05	0.0368

Overall, all the procedures/conditions related to clinic throughout the study were identical for both groups. The conditions were maintained similar for both the groups in four periods; therefore, it seems

none of these are applicable in this study. Also, in both groups the products were dosed (Test and Reference) by maintaining almost similar environment. Statistical analysis has been performed without including & with including group*treatment interaction term in the ANOVA model. However, bioequivalence was determined based on overall treatment effect i.e. without including the group*treatment interaction term in the ANOVA model for evaluation of confidence intervals. As a part of sensitive analysis, statistical analysis with including group*treatment term in ANOVA model has been provided as additional information. Based on result obtained after keeping group*treatment term in the ANOVA model, 90% CI also fell well within acceptance range of 80.00% to 125.00%.

Each group had equal distribution of subjects (1-24 in group I & 25-54 in group II). There is no significant difference observed in rase, age, weight, height & BMI between both the groups.

For Emtricitabine: P-values from ANOVA

Pharmacokinetic Parameters	p-value for Treatment/Formulation	p-value for period(Group)	p-value for Sequence
AUC ₀₋₄ (hr.ng/mL)	0.6379	0.4497	0.3577
C _{max} (ng/mL)	0.2034	0.2091	0.8276

P-value for Treatment/Formulation, period (Group) and sequence effects were found statistically insignificant on ln-transformed scale for pharmacokinetic parameters AUC_{0-t} and C_{max}.

For Tenofovir: P-values from ANOVA

Pharmacokinetic Parameters	p-value for Treatment/Formulation	p-value for period(Group)	p-value for Sequence
AUC ₀₋₇₂ (hr.ng/mL)	0.0001	0.3237	0.1099
C _{max} (ng/mL)	0.0022	0.7441	0.4150

P-value for period (Group) and sequence effects were found statistically insignificant on ln-transformed scale.

Whereas Treatment/Formulation effect was found statistically significant on ln-transformed scale for pharmacokinetic parameters AUC₀₋₇₂ and C_{max}.

Justification for Significant Formulation Effect (C_{max} and AUC₀₋₇₂):

Significant treatment effect or formulation effect can be present when the treatment mean square is small. Significant difference can occur at the moment the variability is low or the number of volunteers sufficiently high. Significant treatment effect or formulation effect can simply be ignored as the decision of equivalence is based on the Schuirmann test and the 90% confidence interval is within the equivalence boundaries.

For Tenofovir alafenamide: P-values from ANOVA:

Pharmacokinetic Parameters	p-value for Treatment/Formulation	p-value for period(Group)	p-value for Sequence
AUC ₀₋₄ (hr.ng/mL)	0.5877	0.5006	0.2167
C _{max} (ng/mL)	0.2199	0.2453	0.3218

P-value for Treatment/Formulation, period(Group) and sequence effects were found statistically insignificant on ln-transformed scale for pharmacokinetic parameters AUC_{0-t} and C_{max}.

Safety data

No serious adverse events (SAEs) were reported. One AE (treatment emergent) was reported by one subject over the course of the study. The reported AE was moderate in severity.

There was 1 AE (vomiting) considered at least possibly related to the oral administration of Descovy 200 mg/10 mg film-coated tablets.

2.4.2.2. Pharmacokinetic conclusions

Based on the presented bioequivalence studies (EMTA-TBZ-1009, EMTA-TBZ-1010 and EMTA-TBZ-1011) Emtricitabine/Tenofovir alafenamide Viatris, film-coated tablets 200 mg/25 mg and 200 mg/10 mg is considered bioequivalent with Descovy, film-coated tablets 200 mg/25 mg and 200 mg/10 mg (manufactured by Gilead Sciences Ireland UC).

2.4.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Clinical efficacy

No new clinical efficacy studies were presented and no such studies are required for this application.

2.4.4. Discussion on clinical aspects

To support the marketing authorisation application the applicant conducted three bioequivalence studies. Two of the studies were conducted in healthy adult human subjects under fasting conditions, on both strengths - the higher strength i.e. Emtricitabine/Tenofovir alafenamide Viatris 200mg/25 mg film-coated tablets, and the lower strength i.e. Emtricitabine/Tenofovir alafenamide Viatris 200mg/10 mg film-coated tablets (both were open labelled, single-dose, randomised, four-period, two-treatment, two sequence, full-replicate, crossover bioequivalence studies). In addition, the applicant conducted a bioequivalence study in healthy adult human subjects under fed conditions, on the higher strength i.e. Emtricitabine/Tenofovir alafenamide Viatris 200mg/25 mg film-coated tablets.

Information regarding GCP inspections of the clinical and analytical site have been provided. Audit certificates and monitoring reports were included with each study report. The most recent inspections of the clinical site were done by WHO in 2022, ANVISA in 2022 and US FDA in 2022 and 2023. This Clinical Facility was inspected by US FDA in 2023 and the inspection did not reveal any critical findings.

The use of Emtricitabine and Tenofovir alafenamide is well established. Human pharmacology, efficacy and safety of Emtricitabine and Tenofovir alafenamide is well known. The applicant has submitted an analytical clinical overview describing the PD and PK, as well as efficacy and safety data, based on published literature. The clinical aspects of the SmPC are in line with the SmPC of the reference product.

As indicated by the applicant in the clinical overview, a linear PK was observed for emtricitabine in the published literature. No data were available regarding the linearity or non-linearity of tenofovir alafenamide. The pharmacokinetic data on the active substances emtricitabine and tenofovir alafenamide provided in the SmPC of the reference products and relevant published studies were sufficiently robust to support the conduct of the BE studies in the fasting and fed state.

In general, a bioequivalence study should be conducted under fasting conditions, as this is considered to be the most sensitive condition to detect a potential difference between formulations. In accordance with the administration recommendations provided in the SmPC for the reference product Descovy, the method of administration is with or without food. Consistently, two of the BE studies for each of the strengths are carried out in a fasted state. The presence of food did not affect the AUC of emtricitabine. In contrast, relative to fasting conditions, the administration of tenofovir alafenamide with a high fat meal (~800 kcal, 50% fat) resulted in a decrease in TAF C_{max} (15-37%) and an increase in AUC_{last} (17-77%). Consequently, an additional bioequivalence study has been conducted under fed conditions with the product's most potent formulation, i.e. 200 mg/25 mg.

Taking into account that the reported effect of a high fat meal on exposure of TAF can be considered as substance related, rather than formulation-dependent, and the formulation can be administered irrespective of food, the submitted fed study is considered as supportive only and the fasted studies of both strengths as pivotal. The fasted studies are sufficient for the development of the generic formulation.

Additionally, the active substance content for the lower strength is below the 5% threshold of the tablet core weight.

The choice of the reference product is appropriate. In the study report, certificates of analysis have been provided for test and reference product batches. Assay content of active substances between both products does not differ by more than 5 %. The batch size of the test product exceeds the necessary 100,000 units.

The submitted bioequivalence studies have a four-period, two-treatment, two sequence, full-replicate, crossover design. In line with bioequivalence (BE) guideline recommendations CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, a replicate 4-period crossover scheme has been applied, as tenofovir alafenamide is expected to be highly variable. However, for emtricitabine (and pro-drug metabolite tenofovir), concentration data of subjects who only complete the first two periods were selected, thus, adapting to a two period non-replicate study design. The method was pre-specified in the study protocol. Emtricitabine is not presumed to be highly variable. The metabolite tenofovir was tested for supportive purposes only. Therefore, a two period non-replicate study design can be considered applicable for the two substances. The maximum observed intra-subject variability was used for sample size calculations (CV~40%), leading to an estimate sample size of at least 46 subjects. Thus, re-estimating the sample size was not considered necessary in this case. Sample sizes of all three studies are adequate. Population inclusion/exclusion criteria have been described sufficiently. The population was chosen according to guidelines.

Plasma samples were assayed for emtricitabine, tenofovir alafenamide (prodrug) and tenofovir (active metabolite). In line with the SmPC, the elimination half-life of emtricitabine was 10 h, and for tenofovir alafenamide (and tenofovir) it was 0.51 h (and 32.37 h), respectively. According to the BE guideline, the washout period should be at least 5 elimination half-lives.

It can be concluded that washout periods of 14, 15 and 16 days in study EMTA-TBZ-1009, 14 and 15 days in study EMTA-TBZ-1010 and 14, 15 and 17 days in study EMTA-TBZ-1011 are sufficient.

In line with the SmPC, emtricitabine and tenofovir alafenamide are absorbed with reaching C_{max} at 1-2 h and 1 h respectively. The sampling periods cover 72 hours. The sample scheme was planned with sufficient frequency around this time period and C_{max} is not expected to be as the first point of a concentration time curve for any of the studies.

The pharmacokinetic variables and statistical methods are adequate and in line with BE guideline.

For emtricitabine and tenofovir, concentration data of subjects who complete the first two periods were selected for the average bioequivalence method. The natural log transformed parameters AUC_{0-t} and C_{max} for emtricitabine and C_{max} and AUC_{0-72} for tenofovir were statistically analyzed by using the ANOVA model, including terms Sequence, Subject (Sequence), Treatment and formulation as fixed effects.

For tenofovir alafenamide, the pharmacokinetic data of subjects who completed at least two periods with two reference products and/or subjects who completed minimum two periods with one test and one reference treatment were included in bioequivalence evaluation by using scaled-average-bioequivalence method. The widening of the acceptance criteria has been adequately justified for C_{max} CI of tenofovir alafenamide, due to high variability (CV%), and the ANOVA model included terms Sequence, Subject (Sequence) and Period as fixed effects. For TAF C_{max} , expanded CI acceptance limits (76.83 - 130.15%) are calculated based on increased (over 30%) within-subject variability CV%. The resulting CI meets both the expanded and standard BE acceptance limits.

The remainder of primary pharmacokinetic variables AUC_{0-t} and C_{max} 90% confidence intervals for the test and reference product ratios are within 80-125% acceptance range for both emtricitabine and tenofovir alafenamide. The bioequivalence of test and reference products has been proven.

Based on the presented three bioequivalence studies presented (EMTA-TBZ-1009, EMTA-TBZ-1010, EMTA-TBZ-1011), the test products Emtricitabine/Tenofovir alafenamide Viartis film-coated tablets 200mg/25 mg and 200mg/10 mg (test products) compared to the reference products Descovy (emtricitabine and tenofovir alafenamide) film-coated tablets 200mg/25 mg and 200mg/10 mg manufactured by Gilead Sciences Ireland UC (reference products) meet the bioequivalence criteria in terms of rate and extent of absorption after administration of single doses as specified in the protocols.

In relation to safety, the Emtricitabine and Tenofovir Alafenamide Tablets 200 mg/25 mg were well tolerated when administered as a single oral dose of 200 mg/25 mg (1 x 200 mg/25 mg) under both fed and fasting conditions. Similarly, the Emtricitabine/Tenofovir alafenamide Viartis film-coated tablets, 200 mg/10 mg, were also well tolerated when administered as a single oral dose of 200 mg/10 mg (1 x 200 mg/10 mg) under fasting conditions.

In study EMTA-TBZ-1009, five subjects have been excluded from pharmacokinetic analysis. The reasons for exclusion are justified and in accordance with the study protocol. Actual time points of sample collection were used for pharmacokinetic calculations, rendering these deviations to have no significant impact on study results.

No subject had detectable pre-dose plasma levels and no subject reached C_{max} at the first sampling time point, based on individual plasma concentration data provided in the study report. Based on calculations provided in the study report, it was observed that the extrapolated AUC was less than 20% across all subjects and treatments in both the emtricitabine and tenofovir alafenamide groups.

The applicant provided a justification for a statistically significant period effect from ANOVA, reported for emtricitabine (AUC_{0-t}) and tenofovir alafenamide (C_{max}). The justification is considered sufficient, as in each period both products - test and reference - were dosed per the randomisation scheme. The period effect is not expected to influence the comparison. Washout period length was chosen in line with BE guidance to rule out the possibility of a carryover effect.

In study EMTA-TBZ-1010, prior to dosing of each period, a high fat high calorie meal (approximately 800-1000 kcal) was provided. The standardized meal plan is provided in the study protocol.

For tenofovir, it is stated in the study report that three subjects were excluded from the pharmacokinetic and statistical analysis, as pre-dose concentration was greater than 5% of the C_{max} for the test and reference products. In the report appendix (Plasma Concentration Data Listing), the

individual pre-dose concentrations for these three subjects have not been reported. As the metabolite tenofovir is tested for supportive purposes only and the exclusion approach is also pre-specified in the study protocol, the issue was not further.

Subject exclusion from TAF pharmacokinetic analysis on the basis of linear regression in the terminal phase was pre-specified in the study protocol. No value of K_{el} , AUC_{0-inf} or $t_{1/2}$ for Emtricitabine and Tenofovir Alafenamide is reported for cases that do not exhibit a terminal log-linear phase i.e. $R^2 < 0.80$ in the concentration versus time profile.

Based on AUC_%Extrap_obs estimates provided in the study report appendix, it was observed that the extrapolated AUC was less than 20% for subjects in the emtricitabine group. For tenofovir alafenamide group, the exceptions were one subject for reference product in period 2, with estimated AUC_%Extrap_obs 23.309, and one subject for test product in period 2, with estimated AUC_%Extrap_obs 36.924.

The applicant provided a justification for a statistically significant period effect from ANOVA, reported for tenofovir alafenamide (C_{max}) and a significant formulation effect for emtricitabine (C_{max}). The justification is considered sufficient, as in each period both products, test and reference, were dosed per the randomisation scheme. The period effect is not expected to influence the comparison. Washout period length was chosen in line with BE guidance to rule out the possibility of a carryover effect.

In study EMTA-TBZ-1011, a total of four subjects were withdrawn from the study on the grounds of failing to report to the facility as outlined in the study protocol. In the pharmacokinetic/statistical evaluation of parameters for TAF, one of the four subjects was excluded in accordance with protocol. Two of the four subjects were not included in the pharmacokinetic analysis with respect to Emtricitabine and Tenofovir, as only the initial two periods were planned for the protocol-based pharmacokinetic/ statistical data evaluation for Emtricitabine and Tenofovir.

In addition, pre-dose concentrations greater than 5% of C_{max} for tenofovir were found in three subjects. Therefore, these subjects were not included in the pharmacokinetic and statistical analysis for tenofovir in accordance with the established study protocol. In all cases, the reasons for exclusion were justified and in accordance with the study protocol.

Protocol deviations for sample time differed between +04 to +06 minutes. Actual time points of sample collection were used for pharmacokinetic calculations, rendering these deviations to have no significant impact on study results. In period 3, the samples from several subjects were exposed to deviated freezer temperature for approximately 22 minutes. The applicant stated there was no impact of the deviation as the temperature excursion will not have any impact on the integrity of analyte concentration data, since the room temperature (benchtop) stability at approx. 25°C had already been proven during conduct of partial method validation. The temperature deviation occurred during storage of clinical samples in freezer was very well covered within the proven stability temperature duration. In period 2, it was identified that the concerned study personnel miscalculated the scheduled time for post dose vitals. However, the subject vitals were within the normal limits and subject sample was taken as per scheduled time point. Hence, there was no impact on the safety of subject.

As previously outlined in the initial study protocol, the decision to recruit an additional cohort of subjects was made prior to the bioanalysis results becoming available. This approach is in accordance with the ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms - Step 5 (EMA/CHMP/ICH/953493/2022 25 July 2024). In order to mitigate the impact of potential group effects, all groups received their initial dosage at the same clinic within a few weeks of one another. Moreover, the identical protocol requirements and procedures were adhered to for all groups, thus ensuring consistency in the experimental design. The recruitment of subjects was conducted from the same initial pool of participants, thereby ensuring a comparable demographic profile across the groups.

Subjects were randomly assigned to groups and treatment arms (or treatment sequences) at the study outset. The aim was to assign a similar sample size to each group, wherever feasible. This approach is in accordance with the ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms - Questions and answers (EMA/CHMP/ICH/325575/2024).

In the study EMTA-TBZ-1011, a statistically significant group by treatment effect was identified for the emtricitabine component with regard to AUC0-t. The applicant conducted an exploratory analysis for AUC0-t and calculated the 90% CI for each group independently, as requested, in accordance with ICH M13A *Guideline on bioequivalence for immediate-release solid oral dosage forms* (EMA/CHMP/ICH/953493/ 2022). In accordance with the EMA guidelines, the statistically significant group by treatment effect under consideration is not deemed to be the primary bioequivalence criteria. Instead, it is a supplementary tool that may be utilised in the event of the identification of irregular patterns requiring further investigation, when deemed appropriate. It has been demonstrated that the primary pharmacokinetic variable (AUC0-t, 90% CI) for both the test and reference product ratios fall within the acceptable range of 80-125% for both groups, whether considered independently in each group or via analysis of pooled data. This finding confirms that bioequivalence of the test and reference products has been proven and fulfils the primary bioequivalence criteria.

For emtricitabine and TAF based on the ANOVA results, no significant sequence, period and group effect effects were observed for log-transformed pharmacokinetic parameters Cmax, AUC0-t. For emtricitabine and TAF based on the ANOVA results, no significant formulation effects were observed for log-transformed pharmacokinetic parameters Cmax, AUC0-t.

2.4.5. Conclusions on clinical aspects

Based on the presented bioequivalence studies (EMTA-TBZ-1009, EMTA-TBZ-1010, EMTA-TBZ-1011) Emtricitabine/Tenofovir alafenamide Viatris, film-coated tablets 200 mg/25 mg and 200 mg/10 mg is considered bioequivalent with Descovy, film-coated tablets 200 mg/25 mg and 200 mg/10 mg (manufactured by Gilead Sciences Ireland UC).

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Safety in pregnancy and lactation

2.5.2. Pharmacovigilance plan

Summary Table of Additional Pharmacovigilance Activities

Study & Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required Additional Pharmacovigilance Activities				
Antiretroviral Pregnancy Registry	To collect information on the risk of birth defects in patients exposed to emtricitabine/tenofovir alafenamide during pregnancy	- Missing information: Safety in pregnancy	Interim reports	Semi-annual
On-going			Final Report	When 1000 first trimester exposures to each antiretroviral therapy is attained or when a subsequent mechanism for monitoring pregnancy outcomes emerges (e.g., standardized national monitoring program).

2.5.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Missing Information: Safety in pregnancy and lactation	Routine risk minimization measures SmPC section 4.6 PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None Additional pharmacovigilance activities: Antiretroviral Pregnancy Registry (APR)

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

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

2.6.2. 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.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Descovy 200 mg/10 mg film-coated tablets (EMA/H/C/004094; MA issued on: 21 April 2016) and Abevmy 25 mg/ml concentrate for solution for infusion (EMA/H/C/005327, MA issued on: April 21st, 2021). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of emtricitabine and tenofovir alafenamide, film-coated tablets. The reference product Descovy, film-coated tablets 200 mg/25 mg and 200 mg/10 mg (manufactured by Gilead Sciences Ireland UC) is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1).

No non-clinical studies have been provided for this application. The non-clinical overview is based on an overview of published information for the active substance.

From a clinical perspective, this application did not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance. The applicant's clinical overview of these aspects based on information from published literature is considered sufficient.

To support the marketing authorisation application, the applicant conducted three bioequivalence studies. The pivotal studies are two studies conducted in healthy adult human subjects under fasting conditions, on both strengths - the higher strength i.e. Emtricitabine/Tenofovir alafenamide Viartis 200mg/25 mg film-coated tablets, and the lower strength i.e. Emtricitabine/Tenofovir alafenamide Viartis 200mg/10 mg film-coated tablets in comparison with Descovy (emtricitabine and tenofovir alafenamide) tablets 200/25 mg and 200 mg/10 mg respectively, from Gilead Sciences Ireland UC. Both bioequivalence studies were open labelled, single-dose, randomised, four-period, two-treatment, two sequence, full-replicate, crossover bioequivalence studies. In addition, the applicant conducted a bioequivalence study in healthy adult human subjects under fed conditions, on the higher strength i.e. Emtricitabine/Tenofovir alafenamide Viartis 200mg/25 mg film-coated tablets vs Descovy (emtricitabine and tenofovir alafenamide) tablets 200/25 mg from Gilead Sciences Ireland UC, which is considered as a supportive study.

The study designs were considered adequate to assess the bioequivalence of these formulations and were in accordance with the relevant European requirements. The submitted bioequivalence studies have a four-period, two-treatment, two sequence, full-replicate, cross-over design. However, for emtricitabine (and pro-drug metabolite tenofovir), concentration data of subjects who only completed the first two periods were selected, thus, adapting to a two period non-replicate study design. The method was pre-specified in the study protocol. Emtricitabine is not presumed to be highly variable.

The metabolite tenofovir was tested for supportive purposes only. Therefore, a two-period non-replicate study design can be considered applicable for the two substances. The maximum observed intra-subject variability was used for sample size calculations ($CV \sim 40\%$), leading to an estimate sample size of at least 46 subjects. Thus, re-estimating the sample size was not considered necessary in this case.

For emtricitabine and tenofovir, concentration data of subjects who completed the first two periods were selected for average bioequivalence method. The natural log transformed parameters AUC_{0-t} and C_{max} for emtricitabine and C_{max} and AUC₀₋₇₂ for tenofovir were statistically analyzed by using the ANOVA model, including terms Sequence, Subject (Sequence), Treatment and formulation as fixed effects.

For tenofovir alafenamide, the pharmacokinetic data of subjects who completed at least two periods with two reference products and/or subjects who completed minimum two periods with one test and one reference treatment were included in bioequivalence evaluation by using scaled-average-bioequivalence method. The widening of the acceptance criteria has been adequately justified for C_{max} CI of tenofovir alafenamide, due to high variability ($CV\%$), and the ANOVA model included terms Sequence, Subject (Sequence) and Period as fixed effects.

For tenofovir alafenamide C_{max}, expanded CI acceptance limits (76.83 - 130.15%) were calculated based on increased (over 30%) within-subject variability ($CV\%$).

Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulations of products Emtricitabine/Tenofovir alafenamide Viatris film-coated tablets 200mg/25 mg and 200mg/10 mg met the protocol-defined criteria for bioequivalence when compared with the reference products Descovy (emtricitabine and tenofovir alafenamide) film-coated tablets 200mg/25 mg and 200mg/10 mg manufactured by Gilead Sciences Ireland UC. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, AUC_{0-∞}, and C_{max} were all contained within the protocol-defined acceptance range. For tenofovir alafenamide, the resulting CI meets both the expanded and standard bioequivalence acceptance limits.

The primary pharmacokinetic variables AUC_{0-t} and C_{max} 90% confidence intervals for the test and reference product ratios are within 80-125% acceptance range for both emtricitabine and tenofovir alafenamide. The bioequivalence of test and reference products has been demonstrated.

Based on the three bioequivalence studies presented (EMTA-TBZ-1009, EMTA-TBZ-1010, EMTA-TBZ-1011), the test products Emtricitabine/Tenofovir alafenamide Viatris film-coated tablets 200mg/25 mg and 200mg/10 mg (test products) compared to the reference products Descovy (emtricitabine and tenofovir alafenamide) film-coated tablets 200mg/25 mg and 200mg/10 mg manufactured by Gilead Sciences Ireland UC (reference products) meet the bioequivalence criteria in terms of rate and extent of absorption after administration of single doses as specified in the protocols. Bioequivalence of these formulations were demonstrated.

A benefit/risk ratio comparable to that of the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Emtricitabine/Tenofovir alafenamide Viatris is favourable in the following indication:

Emtricitabine/Tenofovir alafenamide Viatris is indicated in combination with other antiretroviral agents for the treatment of adults and adolescents (aged 12 years and older with body weight at least 35 kg) infected with human immunodeficiency virus type 1 (HIV-1) (see sections 4.2 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation 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).

Other 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.