21 May 2015
EMA/517796/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

EVOTAZ

International non-proprietary name: atazanavir / cobicistat

Procedure No. EMEA/H/C/003904/0000

Note

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

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List of abbreviations

AE	adverse event
ARV	antiretroviral
ATV	atazanavir; Reyataz
AUC	area under the concentration-time curve
AUC(INF)	area under the plasma concentration-time curve from time zero to infinite time
AUC(TAU)	area under the plasma concentration-time curve over 1 dosing interval
BID	twice daily
BCRP	breast cancer resistance protein
BMS	Bristol-Myers Squibb Company
C24	plasma concentration 24 hours post dose
CI	confidence interval
CK	creatine kinase
Ctau	minimum plasma concentration; plasma concentration at the end of the dosing interval
COBI	cobicistat; Tybost
Cmax	maximum concentration in plasma
CSR	clinical study report
CYP	cytochrome P-450
EC	European Commission
EC90	90% effective concentration
ECG	electrocardiogram
EDAC	1-ethyl-3-(3-dimethyl-aminopropyl
eGFRCG	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EU	European Union
FDC	fixed-dose combination
FCT	film-coated tablet
GC	Gas Chromatography
Gilead	Gilead Sciences, Inc.
HDPE	High density polyethylene
HIV-1	human immunodeficiency virus-type 1

HPLC	High Performance-Liquid Chromatography
ICH	International Conference on Harmonisation
IR	Infrared
ITT	intent-to-treat
LV	left ventricular
KF	Karl Fisher titration
MA	marked clinical laboratory abnormality
MAA	Marketing Authorization Application
NMR	Nuclear Magnetic Resonance
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic(s)
Ph. Eur.	European Pharmacopoeia
OATP	organic anion transporting polypeptide
QD	once daily
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	standard deviation
SmPC	Summary of Product Characteristics
TDF	tenofovir
TVD	Truvada
UGT	UDP glucuronosyltransferase 1
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 3 July 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for EVOTAZ, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 November 2013.

The applicant applied for the following indication:

"EVOTAZ is indicated for the treatment of HIV-1 infected adults aged 18 years and older in combination with other antiretroviral medicinal products.

Based on available virological and clinical data from adult patients, no benefit is expected in patients with strains resistant to multiple protease inhibitors (≥ 4 PI mutations) (see sections 4.4 and 5.1).

The choice of EVOTAZ in adult patients should be based on individual viral resistance testing and the patient's treatment history (see sections 4.4 and 5.1). "

The legal basis for this application refers to:

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

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0090/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0090/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

BRISTOL MYERS SQUIBB S.R.L.

LOC. FONTANA DEL CERASO, ANAGNI, 03012, Italy

1.3. Steps taken for the assessment of the product

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

Rapporteur: Bruno Sepodes

Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 4 July 2014.
- The procedure started on 23 July 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 1 October 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 6 November 2014.
- During the meeting on 20 November 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 November 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 January 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 6 March 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 March 2015.
- During the CHMP meeting on 26 March 2015, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 April 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 4 May 2015.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 7 May 2015.
- During the meeting on 21 May 2015, 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 EVOTAZ.

2. Scientific discussion

2.1. Introduction

The human immunodeficiency virus (HIV) is the virus that causes the Acquired Immune Deficiency Syndrome (AIDS). HIV infects and leads to a depletion of immune cells (CD4 + cells). As the CD4-positive cells are depleted, the host becomes increasingly susceptible to a variety of opportunistic pathogens and immune deficiency related diseases. In the absence of treatment, most infected individuals succumb to HIV-related disease. Many infected patients have been successfully treated with Highly Active Antiretroviral Therapy (HAART). The goal of HAART is to suppress HIV to undetectable levels so that immune function is preserved or restored. HIV infection in adults and children is a worldwide problem, both in developed and in developing countries. The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated the number of people living with HIV globally in 2012 was about 35.3 million. The number of people living with HIV has continued to increase as more patients are receiving antiretroviral therapy and living longer lives. While the number of people living with HIV has increased over the years, the number of new infections and deaths has decreased due to increased education and prevention efforts, increased access to antiretroviral therapy (ART), and effective prophylaxis and treatment of HIV-infected pregnant women and infected infants. In 2012, there were approximately 2.3 million new infections, a decrease of approximately 33% from 2001, and 1.6 million people died from AIDS-related illnesses, a decrease from 2.3 million in 2005. The use of antiretroviral agents for treatment and prophylaxis during pregnancy, delivery and breastfeeding has reduced the rate of HIV transmission from mother to child. The annual number of newly infected children in 2012 was approximately 260,000 in low- and middle-income countries, 35% lower than in 2009. One of the major factors related to the success of antiretroviral regimens is adherence. Drug adherence is directly related to clinical and virologic outcomes. High rates of drug adherence are associated with improved viral and clinical responses, durability of response and minimization of the emergence of drug resistance. There are many factors which negatively impact adherence in both the adult and paediatric populations. Among them are high pill burden, frequent dosing requirement, complexity of dosing regimens, dietary restriction and side effects.

Atazanavir (Reyataz; ATV) is an azapeptide human immunodeficiency virus-type 1 (HIV-1) protease inhibitor (PI). Atazanavir capsules (100, 150, 200, and 300 mg), in combination with low-dose ritonavir (RTV) as a pharmacoenhancer, has been approved for the treatment of HIV-1-infected adults and paediatric patients 6 to < 18 years of age in the European Union (EU) and many other countries globally.

Cobicistat (Tybost; COBI), an inhibitor of cytochrome P-450 (CYP) 3A enzymes, was developed by Gilead Sciences, Inc. (Gilead) for use as a pharmacoenhancer of 2 PIs, ATV and darunavir. Cobicistat is a new chemical entity that is a structural analogue of RTV. Cobicistat has no antiretroviral (ARV) activity, and in vitro, has been shown to be a more specific mechanism-based CYP3A inhibitor than RTV. To date, COBI as a single agent has been approved in the EU, Canada, Australia and USA.

This application concerns a fixed dose combination of atazanavir, 300 mg, and cobicistat, 150 mg. The current adult dosage form for commercialization is an oval bilayer film-coated tablet containing 300 mg ATV as the free base and 150 mg COBI to be taken orally with food.

Of note, cobicistat has already been the object of favourable assessment by the CHMP, either as a stan-alone procedure for the active principle (EMEA/H/C/002572) in which it has been approved for pharmacokinetic enhancement “of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults” or in

fixed dose combination with anti-retroviral compounds (EMA/200486/2013 and EMA/CHMP/578742/2014), for the treatment of HIV infection in infected subjects carrying susceptible viral strains.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing atazanavir sulphate corresponding to 300 mg of atazanavir and 150 mg of cobicistat as active substances.

Other ingredients for tablet core are: microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, crospovidone, stearic acid, magnesium stearate, hydroxypropyl cellulose and silicon dioxide.

Other ingredients for film-coating are: hypromellose (hydroxypropyl methyl cellulose, E464), titanium dioxide (E171), talc, triacetin, red iron oxide.

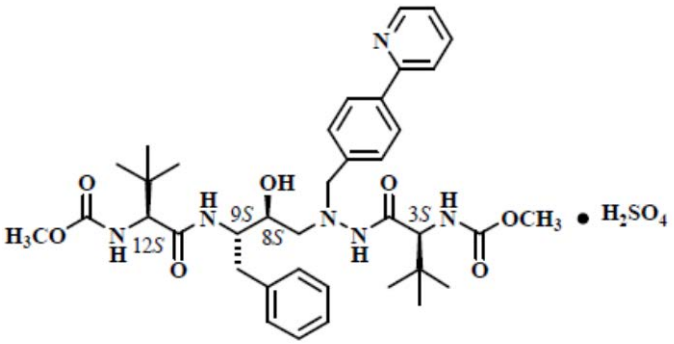
The product is available in high density polyethylene (HDPE) bottle with a child resistant polypropylene closure and a silica gel desiccant.

2.2.2. Active Substance

ATAZANAVIR SULPHATE

General information

The chemical name of atazanavir sulphate is dimethyl (3S,8S,9S,12S)-9-benzyl-3,12-di-tert-butyl-8-hydroxy-4,11-dioxo-6-[4-(2-pyridyl)benzyl]-2,5,6,10,13-pentaazatetradecanedioate, sulphate (1:1) and it has the following structure:



The active substance is a white to pale yellow powder, freely soluble in organic solvents and slightly soluble in water (4-5 mg/ml). The solubility of the substance is pH dependant (maximum solubility at pH 1.9).

The structure of atazanavir sulphate has been confirmed by elemental analysis, mass spectroscopy, ^{1}H and ^{13}C-NMR, IR, UV and single crystal X-ray analysis.

The substance contains four chiral centres however the manufacturing process leads, in a consistent way, to the single enantiomer S, S, S, S. The absolute configuration has been confirmed by single X-ray analysis on a triethanol solvate crystal. Enantiomeric purity is controlled routinely by specific optical rotation.

Atazanavir sulphate shows polymorphism. It has been demonstrated that the commercial process produces exclusively a non-solvated, highly crystalline form designed as form A.

The substance is not hygroscopic up to 75% relative humidity (RH), but undergoes solid-state modifications to a predominantly amorphous form in aqueous suspension and when exposed to 95% RH.

Manufacture, characterisation and process controls

Atazanavir sulphate is synthesized at two different manufacturing sites in two main steps using well defined starting materials 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.

Specification

The active substance specification includes tests for appearance, identity (IR and HPLC), assay (HPLC), impurity content (HPLC), optical rotation (USP), sulphuric acid, sulphated ash (Ph Eur), water content (KF), residual solvents (GC), heavy metals, particle size and EDAC content.

The formation of the desired enantiomer of atazanavir is ensured through the route of synthesis and adequate controls performed on the starting materials and the intermediate of appropriate isomeric purity. Therefore, the omission of a chiral assay in the specifications has been supported in this particular case.

Potential impurities have been well discussed. The suitability of the HPLC method for control of impurities including 4 significant stereoisomers has been demonstrated.

Considering the consistency of results obtained by X-ray diffraction for a great number of batches, control of polymorphism is not part of the specification of the active substance.

Specifications of the active substance are in adequacy with the route of synthesis and considered as appropriate.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data of the active substance (4 production batches for one manufacturing site and 3 production batches for the other manufacturing site) are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on six production batches of active substance from the proposed manufacturing sites stored in the intended commercial package for 36 months or 24 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

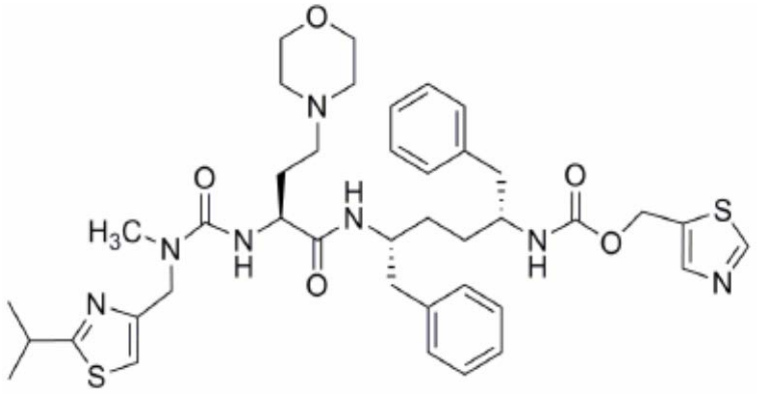
The following parameters were tested*:* description, assay, water, impurities*.* The analytical methods used were the same as for release and were stability indicating.

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

COBICISTAT

General information

The chemical name of cobicistat is 1,3-Thiazol-5-ylmethyl [(2R,5R)-5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate, corresponding to the structural formula below:



The structure has been confirmed by mass spectroscopy, ^{1}H and ^{13}C-NMR, IR, UV , X-raypower diffraction, DSC, DVS.

The molecular formula is $C_{40}H_{53}N_7O_5S_2$ and its relative molecular mass 776.0 g/mol. The active substance cobicistat is adsorbed on silicon dioxide. Cobicistat appears as a white to pale yellow, hygroscopic amorphous solid, soluble in 0.1N HCl pH 1.9, sparingly soluble at pH 4.5, practically insoluble in water and at pH 6.8-8.2, freely soluble in methanol. It shows three pKa; 1.8 (thiazole group), 2.5 (alkylthiazole group) and 6.4 (morpholino group). The partition coefficient LogP is 4.3 (at pH 8.5 buffer).

No crystal forms have been found. It has three chiral centres and is produced as a single isomer. The stereochemical configuration is defined through the synthetic process and the use of starting material with suitable chirality. Appropriate specifications for these starting materials ensure consistent quality during manufacture of cobicistat.

Cobicistat is an amorphous solid with a low glass transition temperature of 35 ºC. Because of the low glass transition temperature, cobicistat under ambient conditions undergoes moisture and temperature induced phase transition from a foam into a rubber-like material. To increase physical stability of cobicistat it is adsorbed on silicon dioxide. Cobicistat on silicon dioxide is a white to pale yellow amorphous powder and, as cobicistat, it is also hygroscopic, as determined by dynamic vapour sorption at room temperature. The relatively higher water uptake of cobicistat on silicon dioxide compared to cobicistat is due to the hygroscopic nature of the silicon dioxide carrier. Importantly however and contrary to cobicistat itself, moisture uptake of cobicistat on silicon dioxide is reversible and therefore cobicistat is isolated by adsorption on silicon dioxide to provide a stable solid form, which is suitable for further finished product manufacture.

Manufacture, characterisation and process controls

Four sites are involved in the manufacture of the active substance with three of them involved only in the manufacture of a synthesis intermediate. Cobicistat on silicon dioxide is manufactured in ten well defined steps using well defined starting materials with acceptable specifications. The route of synthesis has been described in sufficient detail and adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

Cobicistat on silicon dioxide specification includes tests and limits for appearance (visual), identification (cobicistat: IR, HPLC, UV, silicon dioxide: chemical reaction), water content (Ph. Eur.), assay (HPLC), enantiomeric purity (chiral HPLC), impurities (HPLC), residual solvents (GC) and heavy metals (Ph. Eur.).

No crystal forms have been identified and since the active substance is produced as an amorphous solid adsorbed onto silicon dioxide, a test for polymorphism is not required as per ICH Q6A.

Cobicistat genotoxic potential has been evaluated in accordance with the recommendations in ICH Q3A. All the identified impurities are of low concern for genotoxicity, and therefore no further qualification studies were considered necessary. The proposed test and limits are acceptable.

A microbial limit test for the active substance is not required in accordance with ICH Q6A because the latter steps of the active substance manufacturing process are non-aqueous and have been shown to limit microbial content. In addition data presented on several batches during development indicate that no significant bioburden is present.

All in-house analytical methods have been validated according to ICH Q2A principles.

Batch analysis data for 7 representative large scale batches have been provided. In addition data for other batches used during development were also provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

Two pilot scale batches packaged in a container simulating the proposed container were put on stability testing in accordance with the ICH Guideline under long-term conditions at 5 °C for up to 24 months for one batch and for up to 9 months for the other batch and accelerated at 25 °C/60% RH for up to 24 and 9 months. Additional stability results are provided for batches manufactured by another manufacturing site.

Appearance, water content, assay, impurities and chiral purity have been monitored. The analytical methods used are stability indicating.

All physicochemical attributes of cobicistat on silicon dioxide remained within the specification acceptance limits following long-term storage at 5 °C and no apparent trend has been observed. A statistical analysis performed for assay, total impurities and the major chiral impurity also demonstrate that there is little change over time. The physicochemical attributes of cobicistat on silicon dioxide remained also within the specification acceptance limits following 24 months of storage at 25 °C/60% RH.

Furthermore, one batch was also tested under 30 °C/75% RH for up to 6 months to evaluate the stability of cobicistat on silicon dioxide at elevated temperatures that may be encountered during shipping and handling. The duration of temperature and humidity excursions is limited to 3 months.

In addition, a photostability study was conducted on cobicistat on silicon dioxide according to ICH Q1B Guideline. The results showed no significant change in appearance, assay, and impurity content following exposure to light. The data indicate that cobicistat on silicon dioxide is not sensitive to light.

Based on the presented stability data, the proposed re-test period and storage when the active substance is packed in the proposed packaging materials is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The medicinal product has been developed to provide a fixed-dose combination (FDC) product containing the active pharmaceutical ingredient atazanavir and the pharmacoenhancer cobicistat on silicon dioxide in a single tablet.

Both active substances are approved in the EU as standalone medicinal products and cobicistat is also approved as a component of the medicinal product Stribild (cobicistat, elvitegravir, emtricitabine and tenofovir).

The pharmaceutical development of the finished product contains QbD elements The quality target product profile (QTPP) was defined as a fixed dose combination film coated tablet containing 300 mg of the active substance atazanavir (ATV) and 150 mg of the active substance cobicistat (COBI) with bioequivalent ATV PK profile to one Reyataz 300 mg capsule dosed with one COBI 150 mg tablet, meeting compendial and other relevant quality standards, and packaged in HDPE bottles with desiccants. The critical quality attributes identified were appearance, assay, impurities/degradation product content, content uniformity and dissolution.

The formulation has been developed based on prior formulation experience with other authorised medicinal products, initial screening studies, and design of experiment (DOE) studies. The film-coating system was chosen because it offers good chemical and physical compatibility with both ATV and cobicistat on silicon dioxide.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. and USP 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.

There is a polymorphic form change of ATV active substanceduring the granulation process.The development of the manufacturing process has focussed on optimisation to ensure integrity and sufficient strength of the bilayer interface and thus avoid delamination of the tablets on storage.

A bioequivalence study was conducted comparing the ATV/COBI FCT (1 x 300/150 mg) with the Reyataz capsule (1 x 300-mg) co-administered with a COBI tablet (1 x 150-mg). A detailed assessment of the bioequivalence study is presented in the clinical section. The results showed that the ATV/COBI FCT is bioequivalent to Reyataz capsules co-administered with COBI tablets when given with a light meal.

The composition, manufacturing process, size and shape of the ATV/COBI FCT used in the bioequivalence/ registration stability study is the same as that used for the proposed commercial tablets. One of the sites used for the manufacture of the bioequivalence batch is not the manufacturing site proposed for marketing however, the equipment is representative of that intended for commercial manufacture and the batches comply with the proposed specification.

The discriminatory power of the dissolution method has been demonstrated. However the dissolution method does not have the discriminating capability with regards to polymorphic form of atazanavir and to

active substances' particle size. Particle size distribution is controlled in the atazanavir specifications. The absence of particle size control in the cobicistat specifications was considered justified.

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

Manufacture of the product and process controls

The manufacturing process consists of five main steps: preparation of two separate blends, granulations, compression, tablet coating, packaging. The process is considered to be a standard manufacturing process. The critical steps are identified.

Major steps of the manufacturing process have been validated by a number of studies performed at all commercial manufacturing sites. Parametric controls performed ensure that consistent atazanavir polymorphic form conversion occurs during the manufacturing process.

Holding times for intermediates are validated.

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.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (IR, HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), impurities/degradants, dissolution, microbial limits.

The absence of water content control and atazanavir polymorphic form control in the specifications were considered justified.

The in-house analytical procedures are described and validated.

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

Batch analysis results are provided for 15 commercial scale batches manufactured at the proposed manufacturing sites confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 commercial scale batches of finished product stored under long term conditions for 18 months at 5°C, 25 ºC / 60% RH, 30°C/75%RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for assay and identification (HPLC), impurities and degradants, water content (KF), water activity, hardness, appearance, microbial limit test, content uniformity and dissolution.

The analytical procedures used are stability indicating.

Laboratory stability studies data were provided to demonstrate that there is no change in the polymorphic form from the initial time point up to 18 months at 30°C/75%RH conditions. The absence of identification

test for atazanavir polymorphic form in the shelf life specification of the finished product was therefore considered justified.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products and to stress conditions. The photostability study indicated that the finished product does not need to be protected from light. The freeze/thaw cycling and higher temperature stress data support shipping of the medicinal product through normal distribution channels.

Results from a 12-month open-dish stability study conducted at 25°C/60%RH were provided. The results demonstrate that the finished product remains stable when directly exposed to 25ºC/60%RH in an open dish for 12 months and justify the proposed in-use shelf-life.

Based on available stability data, the shelf-life is 2 years and the storage condition is "Do not store above 30°C". They are acceptable and included in the SmPC.

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The bilayer formulation has been selected considering the physicochemical stability of the two active substances. The formulation development was based on prior formulation experience with other approved medicinal products.The finished product manufacturing process is considered to be standard process and has been satisfactorily validated by appropriate process validation studies. 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

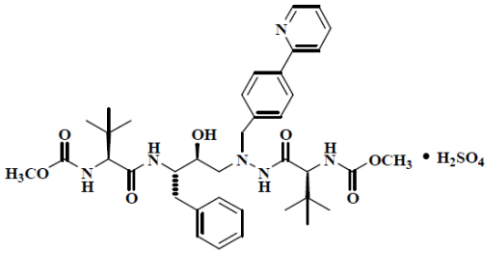
2.3.1. Introduction

2.3.2. Pharmacology

Atazanavir sulfate

The HIV-1 protease is a 99 amino acid aspartyl protease encoded in the N-terminal domain of the pol gene. This protein forms a homodimeric enzyme with 1 active site. ATV selectively inhibits the virus specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions. Due to the hydrophobic nature of the binding pocket of HIV protease, HIV PIs have reduced aqueous solubility and bind to serum proteins. Relative to other marketed HIV PIs, ATV retains superior antiviral activity in the presence of ≥40% human serum.

The structure of ATV is illustrated below

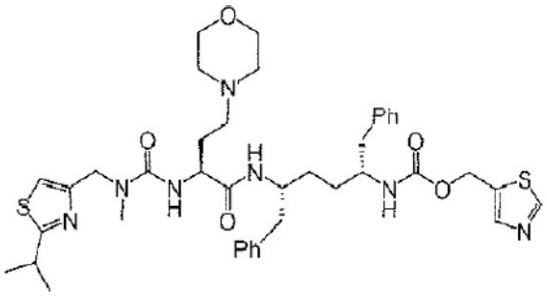


Cobicistat

Cobicistat (COBI) is a small molecule mechanism-based cytochrome P450 3A (CYP3A) inhibitor with micromolar potency and a CYP3A substrate. COBI is used as a pharmacoenhancer when bioavailability and half-life are reduced due to CYP3A-dependent metabolism.

COBI is a structural analogue of RTV and similarly boosts systemic exposure to ATV (CYP3A substrate). In vitro, COBI is a more specific, mechanism-based CYP3A inhibitor than RTV, indicating that COBI may have fewer adverse biochemical effects than RTV. Unlike RTV, which has modest activity against HIV, COBI has no antiviral activity against HIV-1, hepatitis B virus, or hepatitis C virus and does not antagonize the antiviral effects of HIV inhibitors.

The structure of COBI is illustrated below.



Complete nonclinical profiles of ATV and COBI were established in comprehensive investigational programs that included single-agent in vitro pharmacology studies, as well as in vitro and in vivo safety pharmacology, pharmacokinetic and metabolism, and toxicity (including toxicokinetics) studies. To support the combination of ATV + COBI, the Applicant conducted a combination toxicology study in rats. No new nonclinical pharmacology studies were conducted to support this application. Based on available data, no relevant adverse pharmacological or virological interactions are expected.

Safety pharmacology programme

In an ex vivo study of cardiac electrophysiology in rabbit hearts, ATV and COBI were infused in situ by retrograde perfusion of the aorta. Hearts were exposed for 15 minutes at concentrations of ATV, COBI, or

ATV/COBI. ATV (1.5, 4.5, 15, and 45 µM), COBI (0.15, 0.45, 1.5, and 4.5 µM), or ATV/COBI (1.5/0.045, 1.5/0.15, 1.5/0.45, 1.5/1.5 µM).

Criteria for evaluation included left ventricular (LV) function (reduced developed pressure, contractility, relaxation, and coronary perfusion pressure), heart rate, QT, QRS, and PR intervals, monophasic action potential duration at 30%, 50%, and 90% repolarization, action potential triangulation, and appearance of early after depolarizations on the monophasic action potential waveform. At each concentration of test article, mean values were compared to baseline.

Both single agents produced effects on LV contractility (≤50;≥15µM ATV, ≥15µM COBI) and PR prolongation(≤62%; ≥15 µM ATV, ≥4.5 µM COBI). The Applicant goes onto say that when administered in combination, it was concluded that these effects were not clearly additive. The no-observed effect levels (NOEL) for hemodynamic, electrophysiology, and electrocardiographic parameters of the single-agents and ATV + COBI in combination were 4.5 µM ATV, 0.45 µM COBI, and 1.5/0.45 µM ATV/COBI.

No additive or synergistic cardiovascular effects of ATV + COBI have been observed to date in clinical studies.

Atazanavir

In the in vitro Purkinje fibre assay, atazanavir was shown to increase action potential duration (13% increase at 30 µM which is four times the C_{max} and 17 times the C_{ss} in humans at a 400 mg dose). Furthermore, atazanavir-related effects on sodium, potassium, and calcium currents were evaluated in vitro. Atazanavir weakly inhibited sodium and HERG-encoded potassium currents (IC50>30 µM) while moderately inhibiting calcium currents (IC50 of 10.4 µM). Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were only observed in an initial 2-week oral toxicity study and not in subsequent 2-week and 9-month oral toxicity studies performed in dogs.

Cobicistat

In the isolated heart of the rabbit, shortening of the monophasic action potential duration (MAPD) was also observed at ≥ 1 µM. In addition, COBI was associated with a significant increase in coronary perfusion pressure (at ≥1.5 µM), decrease in ventricular function (at ≥1 µM; possibly secondary to interaction with cardiac calcium channels and/or the observed increase in perfusion pressure), decrease in the QT interval and increase in the PR and RR interval at ≥ 3 µM. In vivo, no significant effect on QT interval was observed in the dog, following single oral doses of up to 45 mg/kg. Increases in PR interval were noted at ≥15 mg/kg where the plasma levels were reported to be 3.2 to 4.9 fold higher than that observed clinically.

Combination atazanvir and cobicistat

No additional studies were performed with the combination of atazanavir and cobicistat. This was considered acceptable by the CHMP.

Pharmacodynamic drug interactions

No nonclinical drug interaction studies have been provided with the fixed dose combination product. The Applicant states that no drug-drug interaction studies have been performed using ATV/COBI FDC tablet formulations. The applicant stated that that PK drug-interaction studies with the individual components of

the FDC (either ATV or COBI) have been conducted, and based on these data, as well as the known impact of ATV or COBI on CYP enzymes and transporters, drug interactions are anticipated with the ATV/COBI FDC no specific drug-interaction studies have been conducted. This was considered acceptable by the CHMP.

The drug-drug interaction potential of ATV/COBI is discussed in the clinical section.

2.3.3. Pharmacokinetics

No new nonclinical pharmacokinetic studies were conducted to support the ATV/COBI FDC tablet, which was considered acceptable by the CHMP. Based on available data, a pharmacokinetic interaction between ATV and COBI is not expected. Both ATV and COBI have in general low propensity for clinically significant pharmacokinetic interactions with other co-administered drugs.

2.3.4. Toxicology

A 3-month oral combination toxicity study was conducted in rats (GS Study TX-216-2024) in which ATV and COBI were given daily, either alone or in combination (ATV/COBI: 0/0 (vehicle), 20/30, or 50/30 mg/kg/day) and 3-month qualification rat study (BMS Study DM13009) was carried out to evaluate degradation products of COBI observed in the ATV/COBI drug product. Cobicistat unspiked or spiked with degradants was given to animals by oral gavage at doses at 0 (vehicle) or 30 mg/kg/day (both sexes).

Apart from these studies no combination safety assessment studies have been conducted with ATV and COBI. An extensive number of nonclinical toxicity studies, previously conducted for each agent individually and submitted in support of this application, were reviewed.

In summary, the individual safety assessment programs supporting ATV and COBI clinical use included safety pharmacology studies, acute and repeated dose oral studies, developmental and reproductive toxicity studies, a battery of both in vitro and in vivo genotoxicity studies and rodent carcinogenicity studies. All pivotal nonclinical toxicity studies were conducted consistent with International Conference on Harmonisation (ICH) Nonclinical Testing Guidelines and in compliance with the Good Laboratory Practice (GLP) Regulations.

The rat and dog were chosen as the nonclinical toxicology species for both ATV and COBI development. Repeated dose toxicity studies with ATV and COBI were both conducted for up to 6 months in rats and 9 months in dogs. Developmental and reproductive toxicity was determined in rats and rabbits, and an assessment of carcinogenicity conducted in mice and rats. All pivotal studies were supported by toxicokinetic measurements.

Toxicokinetic data

90-Day Oral Gavage Bridging Study with GS-9350 and Atazanavir in Rats with a 1-Month Recovery Period (TX-216-2024)

ATV/COBI was given orally at doses of 0/0 (vehicle), 20/30, or 50/30 mg/kg/day to both sexes. ATV and COBI were administered alone at 20 or 50 mg/kg/day and 30 mg/kg/day, respectively. All doses were administered at 2 mL/kg. Survival, toxicokinetics, clinical observations, body weight, food consumption, ophthalmologic examinations, clinical pathology evaluations, organ weights, and gross and microscopic pathology were evaluated. Combined administration of ATV (AUC ≤ 45.1 µgh/mL) + COBI (AUC ≤ 6.22 µgh/mL) was well tolerated (in-life) at 20/30 or 50/30 (ATV/COBI) mg/kg/day.

Slight increases in cholesterol (≤ 1.7x control) were observed primarily in females given COBI and ATV alone and in combination at both doses. These increases were not considered adverse as they were low magnitude, not observed in males, and no microscopic correlate was present. Urine volume was slightly higher in males at 50 mg/kg/day ATV and 30 mg/kg/day COBI and in both sexes at 20/30 or 50/30 mg/kg/day ATV/COBI. Following the recovery period, cholesterol levels in females and urine volume were similar to control values, indicating reversibility.

Slight increases in absolute and relative (to body weight) mean liver weight values were noted at 30 mg/kg/day COBI, either alone or in combination with ATV. No organ-weight changes were observed in animals given ATV alone. This finding had no histomorphologic correlate and was considered likely a COBI-related induction of liver microsomal P450 enzyme.

Administration of ATV and COBI either alone or in combination resulted in no notable increase (≥2x) in protein yield, total cytochrome P450 content, or CYP1A, CYP2B, CYP2B/2C, CYP2E, CYP4A, and UDPGT activities. However, increases in CYP3A activity were observed in males and females at 30 mg/kg/day COBI (2.1 and 5.6x, respectively) and in females at 30/20 and 30/50 mg/kg/day COBI/ATV (3.5 and 2.6x, respectively).

Daily oral administration of ATV and COBI to rats for 3 months at doses ≤50 mg/kg/day for both ATV (Day 90 mean combined-sex AUC ≤ 45.1 µgh/mL) and COBI (Day 90 mean combined-sex AUC ≤ 7.89 µgh/mL) showed no toxicological interaction and COBI-induced increases of ATV systemic exposures were evident. All drug-related findings were minor and consistent with previous single-agent studies with these compounds.

For ATV dosed in combination with COBI, AUC values were ≤ 4x when compared to AUCs when ATV was dosed at the same dose (≤ 50 mg/kg/day) as a single agent in this study. Increases in ATV AUC values on Day 90 were less than dose proportional and AUC values were similar in males and females. Following repeated dosing, mean ATV AUC values were similar to Day 1, suggesting a low potential for accumulation.

For COBI dosed in combination with ATV, increases in COBI AUC values on Day 90 were less than dose proportional in males and approximately dose proportional in females; and AUC values were generally lower in males than in females (0.4 to 0.9x). Following repeated dosing, mean COBI AUC values were slightly higher (1.5 to 2.0x) than on Day 1, suggesting potential for accumulation. Day 90 COBI AUC values were lower (0.1 to 0.6x) when co-administered with ATV than when administered alone.

Table 1. Toxicokinetic data

Daily Dose (mg/kg):	0 (Control)		30 (COBI High)		20 (ATV Low)		50 (ATV High)		30/20 (COBI/ATV Low)		30/50 (COBI/ATV High)	
Sex: Number of Rats/Group:	M: 15	F: 15	M: 15	F: 15	M: 10	F: 10	M: 15	F: 15	M: 10	F: 10	M: 15	F: 15
Toxicokinetics - COBI:												
Cmax (µg/mL)												
Day 1	ND	ND	1.15	1.95	ND	ND	ND	ND	0.806	0.795	0.478	0.373
Day 90	ND	ND	2.99	2.59	ND	ND	ND	ND	0.862	2.11	1.23	1.66
AUC(0-T) (µg•h/mL)												
Day 1	ND	ND	6.92	12.9	ND	ND	ND	ND	4.16	6.41	2.58	3.75
Day 90	ND	ND	10.8	12.8	ND	ND	ND	ND	4.58	11.2	6.10	6.34
Toxicokinetics - ATV:												
Cmax (µg/mL)												
Day 1	ND	ND	ND	ND	1.13	0.990	2.46	3.17	4.06	2.53	5.79	3.58
Day 90	ND	ND	ND	ND	1.31	2.40	3.33	5.23	2.99	3.93	6.75	7.79
AUC(0-T) (µg•h/mL)												
Day 1	ND	ND	ND	ND	2.92	4.97	12.0	17.6	32.9	27.0	50.4	48.0
Day 90	ND	ND	ND	ND	7.94	11.7	15.4	31.6	30.8	30.6	44.3	45.9

Table 2. Summary of Mean Values for ATV and COBI in Rats Co-administered ATV + COBI for 3 Months

Analyte	Day	ATV/COBI 20/30 mg/kg/day		ATV/COBI 50/30 mg/kg/day	
		Males	Females	Males	Females
ATV AUC(0-T) (µg•h/mL)	1	32.9	27.0	50.4	48.0
	90	30.8	30.6	44.3	45.9
COBI[a] AUC(0-T) (µg•h/mL)	1	4.16	6.41	2.58	3.75
	90	4.58	11.2	6.10	6.34

[a] Day 90 Mean AUC values in male and female rats given COBI alone at 30 mg/kg/day were 10.8 and 12.8 µgh/mL, respectively

Data on individual active substances

Atazanavir

In safety pharmacology studies, there were no test article-related adverse effects on, respiratory, or central nervous system function in rats (≤ 1200 mg/kg/day) or dogs (≤ 360 mg/kg/day).

In the in vitro Purkinje fibre assay, atazanavir was shown to increase action potential duration (13% increase at 30 µM (4x Cmax and 17 x the Css in humans at a 400 mg). There were also effects on sodium, potassium, and calcium currents were evaluated in vitro. ATV weakly inhibited sodium and HERG-encoded potassium currents (IC50>30 µM) while moderately inhibiting calcium currents (IC50 of 10.4 µM). Electrocardiographic changes (sinus bradycardia, prolongation of PR interval, prolongation of QT interval, and prolongation of QRS complex) were observed in an initial 2-week oral toxicity study, however these effects were not seen in the subsequent 2-week and 9-month oral toxicity studies in dogs.

The metabolic pathways of atazanavir involve monooxygenation, dioxygenation, glucuronidation, N-dealkylation, hydrolysis and oxygenation with dehydrogenation. Several oxidative, but no conjugated metabolites of atazanavir were detected following incubation with mouse, rat, dog or human liver microsomes and cryopreserved hepatocytes. CYP3A4 is the major isozyme responsible for the metabolism of atazanavir in human liver microsomes.

Atazanavir shown to be a competitive inhibitor of CYP3A4, with a Ki value of 2.35 μM; in comparison, the Ki of ketoconazole for CYP3A4 in this system is < 0.1 μM. Atazanavir was also found to competitively inhibit CYP1A2 and CYP2C9, but the Ki values were appreciably higher (≥12.2 μM) than the steady state plasma concentrations of atazanavir observed in humans following 400 mg doses. In another study, atazanavir inhibited testosterone 6 β-hydroxylation (marker of CYP3A4 activity) by 61-92% in primary human hepatocytes and immortalised human hepatocytes transfected with CYP3A4. Atazanavir did not induce testosterone 6 β-hydroxylation in primary human hepatocytes, indicating that it is not an inducer of CYP3A4 in vitro.

Atazanavir was found to inhibit bilirubin glucuronidation in microsomal fractions of lymphoblast cellsheterologously expressing human uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) by a linear "mixed-type " mechanism, with Ki and α-Ki (measure of affinity of enzyme-substrate complexfor the inhibitor) values of 1.9 and 16.4 μM, respectively. However, the contribution of αKi to overall inhibition was small (< 10%) suggesting that competitive inhibition is predominant. Indinavir also exhibited inhibition of bilirubin glucuronidation by a similar mechanism, but had a higher Ki (47.9μM) and αKi (1317 μM) than atazanavir. The IC50 values for the inhibition of bilirubin glucuronidation in human liver microsomes and cDNA expressed UGT1A1 were similar for atazanavir (2.5 and 2.4 μM, respectively) and nelfinavir (2.7 and 8.4 μM, respectively) and saquinavir (5.0 and 7.3 μM, respectively), but were appreciably lower than the value for indinavir (68 and 87 μM, respectively). However, the IC50 values for these other drugs were > 13 fold above the respective unbound Cmax values at the therapeutic doses compared to ~ 2.4 fold above the unbound Cmax for atazanavir.

In repeat-dose toxicity studies, ATV was given to rats (up to 1200 mg/kg) in a two weeks study. Reduced food consumption and signs of dehydration were noted suggesting that this dose was close to the maximal tolerable level. The liver was the main target organ with hypertrophy, vacuolisation, increased weight and increased levels of bilirubin noted. No signs of cholestasis were seen. Cholesterol levels were increased at ⩾300 mg/kg. Haematological parameters were also slightly affected with a reduction in white blood cell noted at ›300 mg/kg. Glucose levels were increased at 1200 mg/kg. All these effects were mainly observed in females due to a higher exposure (1.2 to 3.2 fold compared to males).

In the three and six months studies ATV was administered at up to 900 mg/kg in rats. Again the liver was the main target organ with the same signs that were observed in the two weeks study. At six months animals showed an increase in water consumption and of urine volume suggesting that animals were dehydrated. The NOAEL was less than 100 mg/kg.

In repeat-dose toxicity studies in dogs, ATV was administered at up to 360 mg/kg in a two weeks study. Doses higher than 90 mg/kg were poorly tolerated. A second study of the same duration was then undertaken with doses up to 75 mg/kg. This dose was well tolerated with no effects observed.

In a 9-month pivotal study, dogs were given doses of up to 90 mg/kg. This doses was very well tolerated the 10 mg/kg dose was raised to 180 mg/kg, 3 months after the beginning of the study. Consequently, animals of the first group were treated for 3 months at 10 mg/kg and 6 months with 180 mg/kg. Results showed that increased levels of bilirubin, alkaline phosphatase and gamma glutamyltransferase. Not all the animals showed these effects. No signs of cholestasis were reported in this study.

Atazanavir was shown to be clastogenic in vitro. It was shown that ATV did not induce DNA damage in duodenum (UDS and comet assay), or unscheduled DNA repair in liver (UDS) at plasma and tissue concentrations exceeding those that were clastogenic in vitro. The increase in chromosome aberrations was reproducible in the second in vitro primary human lymphocyte assay, thus confirming that ATV is clastogenic in vitro. The mechanism for in vitro clastogenicity is not known. However given that ATV did not induce micronuclei, DNA damage (comets), or UDS in a variety of rodent tissues in vivo at plasma and

tissue concentrations exceeding those that were clastogenic in vitro, suggests that the mechanism of in vitro clastogenicity may not be biologically relevant in animals and humans.

In reproductive and developmental toxicity studies one study conducted in both sexes at doses up to 1400 mg/kg, showed a decreased in fertility rate at 1400 mg/kg and a significant reduction in the number of oestrus cycles at 375 mg/kg. Consequently, males from this study were placed in cohabitation with untreated females for 2 weeks. Mating and fertility were not affected in males at any dose. No effect on fertility was observed when treated females (1400 mg/kg) were mated with non-treated males. In the embryo-foetal development studies, AT produced no adverse embryonic or foetal effects at maternally toxic doses of up to 1920 mg/kg/day in rats and 60 mg/kg/day in rabbits. ATV induced a decrease in body weight at weaning at maternally toxic doses (1000 mg/kg).

The results obtained in the carcinogenicity studies showed that ATV induced hepatocellular adenoma in female mice at the highest dose tested (360 mg/kg/day). This observation is probably due to an epigenetic mechanism with hepatocyte hyperproliferation after cell necrosis (for which investigative studies were conducted), which is a well-known mechanism, observed in rodents. In this mouse study, liver carcinomas were not present, and in rats, all the results were negative. All together, these results suggest that atazanavir will not increase the carcinogenic risk in humans.

The nonclinical safety evaluation of ATV also demonstrated that this compound was generally well-tolerated.

Cobicistat

In an isolated heart of the rabbit safety pharmacology study, shortening of the monophasic action potential duration (MAPD) was also observed at ≥1 µM. In addition, COBI was associated with a significant increase in coronary perfusion pressure (at ≥1.5 µM), decrease in ventricular function (at ≥1 µM; possibly secondary to interaction with cardiac calcium channels and/or the observed increase in perfusion pressure), decrease in the QT interval and increase in the PR and RR interval at ≥3 µM. However, in vivo, no significant effect on QT interval was observed in the dog, following single oral doses of up to 45 mg/kg. Increases in PR interval were noted at ≥15 mg/kg where the plasma levels were reported to be 3.2 to 4.9 fold higher than that observed clinically.

The effects of COBI (0.45 to 1.5 µM)/ATV (1.5 µM) were evaluated in the rabbit isolated heart. The effects on HR and PR interval appeared to be more pronounced when ATV (1.5 µM) and COBI (1.5 µM) were administered in combination; however, the observed differences were not considered to be clinically significant. During this study, COBI alone had no effect on the QT interval or MAPD at up to 1.5 µM.

In vitro metabolism in all species yields 3 predominant primary oxidative metabolites [M21, M26, and M31 (GS-9612)]. Cobicistat is metabolised rapidly by hepatic microsomal fractions from non-clinical species, but exhibits self-limiting metabolism with human hepatic microsomal fractions, due to concurrent enzyme inactivation. CYP3A (major) and CYP2D6 (minor) enzymes appear to be responsible for the in vitro human metabolism of COBI.

There were no effects in rats and mice given single doses of up to 100 mg/kg/day and 500 mg/kg respectively.

The oral NOAEL of COBI in CD-1 mice for 13 weeks was 50 mg/kg/day and 5 mg/kg/day in males. The oral NOAEL was 30 mg/kg/day in rats for 26 weeks and the oral NOAEL was 10 mg/kg/day in dogs for 39 weeks.

The primary target organs were the liver (mouse, rat, and dog) and thyroid (rat only) in repeat dose toxicology studies. In the rat, the observed effects on the thyroid (increased thyroid weight and follicular

hyperplasia/hypertrophy), are considered rodent-specific, secondary to microsomal enzyme induction and thyroid hormone imbalance (decreased levels of T4 and thyroid-stimulating hormone), and it is unlikely that COBI presents a risk to the thyroid in man.

Hepatic changes in mice, rats, and dogs included microsomal enzyme induction [CYP2B (mouse only) and CYP3A (in mouse and rat only)], increased liver weights, and hepatocellular hypertrophy and/or vacuolation. All effects appeared to be completely reversible after a 1- or 3-month recovery period and/or are considered to be adaptive responses

No adverse effects were seen on male or female fertility and reproductive performance at up to 100 mg/kg/day, where the corresponding exposures (AUC) are at least 3 fold higher than that observed clinically. Increased post-implantation loss and skeletal variations (ossification changes in the spinal column and sternebra) along with decreased foetal weights (associated with significant decreases in maternal body weights) were observed at 125 mg/kg/day in the rat embryofoetal development study. The exposures at the no-effect level for embryo/fetal viability and growth and developmental toxicity were similar to that proposed clinically. In the rabbit, there were no test article-related effects on embryo/foetal viability and growth and no foetal anomalies at systemic exposures that were 6 fold higher than that proposed clinically.

The results from a bacterial reverse mutation test, mouse lymphoma assay and in vivo rat micronucleus assay all indicate that cobicistat does not pose a genotoxic risk to man.

COBI was not carcinogenic at exposures that were 7 to 16 fold higher than those observed clinically in the mouse (95 weeks (males) or 87 weeks (females)). In the rat at 10, 25, and 50 mg/kg/day (males) and 5, 15, and 30 mg/kg/day (females) for a minimum of 97 weeks, COBI caused an increased incidence of combined thyroid follicular cell adenoma and carcinomas at exposures (AUC) that were lower than that observed clinically. Thyroid and liver changes are considered adaptive changes, secondary to hepatic microsomal enzyme induction due to activation of PXR. Given that this extent of activation of PXR and CYP3A does not occur at clinically relevant concentrations in humans, COBI is not considered to pose a carcinogenic risk in man.

Qualification study

Based on identification of COBI-related degradants in a laboratory stability study of the ATV + COBI FDC tablet, a 3-month oral qualifying toxicity study in rat was conducted to compare the toxicity of a COBI-spiked batch (COBI-SP) with the toxicity profile of COBI not spiked (COBI-NS) with degradants. The spiked batch contained 4 degradation products (BMT-111068/BMT-111069, an isomeric mixture, BMT-089290, and BMT-115982). The results of this study were used to qualify batches of ATV + COBI drug product that potentially contain these degradants at approximately ≤1.5% each (total degradant level of approximately 4.6%). COBI-NS and COBI-SP was given to animals at 30 mg/kg/day. As COBI is an amorphous adsorbate on SiO2, the amount of SiO2 present in COBI formulations was added to the vehicle-control formulation. Survival, toxicokinetics of COBI in plasma, clinical observations, body weights, food consumption, physical and ophthalmologic examinations, clinical pathology, organ weights, and gross and microscopic pathology were assessed.

There were no deaths, and COBI-NS and COBI-SP were well tolerated (n-life) with no effects on body weight, food consumption, physical or ophthalmologic findings, or gross pathology. The following were observed (with generally similar onset, incidence, and/or severity) in both COBI groups: red-stained or wet fur of the muzzle/lower jaw, cranium and/or dorsal cervical, slight to moderate salivation, decreased red blood cells (0.93 to 0.94x control), haemoglobin (0.92 to 0.93x), and haematocrit (0.91 to 0.94x) in males, decreased prothrombin time (0.93 to 0.97x), decreased total bilirubin (0.43 to 0.59x), alkaline phosphatase (0.71 to 0.81x; males only), and aspartate aminotransferase (0.62 to 0.69x; females only)

activities and total cholesterol (0.82 to 0.88x; males only), increased globulins (1.12 to 1.19x) with corresponding increased total protein (1.05 to 1.07x) and decreased albumin to globulin ratio (0.85 to 0.91x) in females, decreased phosphorus (0.87 to 0.89x) in females, increased urine total protein concentration (1.81 to 2.71x) and urine total protein excretion (1.80 to 2.48x) in males, increased absolute and relative (to body and brain) liver weights (34% to 47%) with minimal to mild centrilobular hypertrophy in both sexes (2/10 males and 4/10 females), increased absolute and relative thyroid weights (9% to 16%) in females with a microscopic correlate of minimal follicular cell hypertrophy.

Changes in the liver and thyroid were consistent with hepatic induction of drug-metabolizing enzymes and an increased clearance of thyroid hormones, and were seen in previous rat studies with COBI.

The Applicant stated that additional non-adverse findings included increased platelets (1.32x control) in males and increased fibrinogen (1.26x) in females with COBI-NS; and decreased mean red cell volume (0.96x) with corresponding decreased mean cell haemoglobin (0.96x) and increased red cell distribution width (1.05x) in females with COBI-SP.

All COBI-NS or COBI-SP-related changes were considered non-adverse as they were generally minimal in severity and showed a low incidence.

In Week 13, COBI AUC (0-T) at 30 mg/kg/day of COBI-NS or COBI-SP were lower in males (0.3x) than in females. After repeat dosing, COBI AUC values were 1.4 to 3.1x those on Day 1, indicating slight to moderate accumulation. Overall, as spiked impurities had no impact on mean COBI AUC values, Week 13 AUC values were generally similar to those previously observed in rats following 3 months of COBI dosing at 30 mg/kg/day as a single agent.

Table 3. Toxicokinetic Summary - 3-month Oral Qualifying Toxicity Study in Rats

Parameter	Period	COBI-NS 30 mg/kg/day		COBI-SP 30 mg/kg/day	
		Males	Females	Males	Females
Mean AUC(0-T)[a] (µg•h/mL)	Day 1	2.94	10.4	5.73	9.63
	Week 13	9.10	32.4	8.07	29.4

a AUC determined at 0-8h or 0-24h

2.3.5. Ecotoxicity / environmental risk assessment

Atazanavir

The Phase I $PEC_{surfacewater}$ of atazanavir was calculated according the EMA guideline formula. It exceeds the action limit of 0.01 µg/L. A standard Phase II fate and effects assessment was performed by the applicant.

The studies reported comprised: a soil adsorption coefficient, a ready biodegradability test, a water/sediment study, chronic toxicity studies in aquatic organisms and an activated sludge respiration test.

The adsorption coefficient test resulted in a Koc≤10 000 L/Kg indicating that the adsorption potential is low. Atazanavir was not readily biodegradable and the reported results of the water / sediment study demonstrated that the substance shifts from the water phase to the sediment phase. Therefore, a further assessment of the sediment phase has been made in Phase II B with a chronic sediment toxicity study (chironomid test).

The Aerobic Transformation in Aquatic Sediment systems study has shown that atazanavir has the potential to be persistent in the environment.

PNECsurfacewater was based on the lowest NOEC determined in the algae reported study. The PNECmicroorganisms was based on the NOEC from the sludge respiration inhibition test and the PNEC groundwater based on the NOEC from the Daphnia chronic growth / reproduction test.

A refined PECsurfacewater was performed by the applicant based on prevalence of HIV-1 in Estonia. The calculated value was 2.6 µg/L. The threshold value was once more exceeded. A risk assessment was recalculated for the environmental compartments.

No risk has been identified for the surfacewater, groundwater, wastewater treatment plant and sediment compartments as the PEC/PNEC ratios were below the threshold values.

Summary of main study results

Substance (INN/Invented Name): atazanavir/ Evotaz			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log *K*ow	FDA Guideline 3.02	pH 5 = 3.47 pH 7 = 3.30 pH 9 = 3.23 (≤ 4.5)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log *K*ow	≥ 3	Potential B BCF not available Weight of evidence does not indicate a significant potential for bioaccumulation
Persistence	Ready biodegradability	Not readily biodegradable	P
Toxicity	NOEC	8.6 mg/L	T (N)
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$	2.0	µg/L	≥0.01 threshold
Refined $PEC_{surfacewater}$	2.6	µg/L	≥0.01 threshold Market Penetration based on the prevalence of HIV -1 in Estonia
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption 5 soils and 1 sludge	OECD 106	*Soils* K_{oc} = 537 - 4130 L/kg	Low adsorption

		Activated sludge K_{oc} = 279 L/kg	K_{oc}≤10 000 L/Kg
Ready Biodegradability Test	FDA 3.11	Not readily biodegradable	0.024% mineralization to CO2 over 43 days
Aerobic Transformation in Aquatic Sediment systems Two aquatic sediments HOCC=Higher Organic Carbonic Content LOCC= Lower Organic Carbonic Content	OECD 308	DT_{50} water = 14 -30 days % shifting to sediment >10% at or after 14 days Degradation products <10%	Potential P Risk to sediment dwelling organism

Phase IIa Effect studies

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test	OECD 201	NOEC, Growth rate	4.1	mg/L	*Pseudokirchneriella subcapitata* Concentrations used based on functional limit of solubility of active substance
Daphnia sp. Reproduction Test	OECD 211	NOEC (growth and reproduction	5.1	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC, Fish survival	8.6	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC 50 EC 10	≥1000 100	mg/L mg/L	A dose dependent inhibition was not observed.

Phase IIb Studies

Sediment dwelling organism	NOEC	100	mg/kg		*Chironomus riparius*

As a result of the above considerations atazanavir is not expected to pose a risk to the environment.

Cobicistat

The Phase I $PEC_{surfacewater}$ of cobicistat (0.75µg/L) was calculated according the EMA guideline formula. It exceeds the action limit of 0.01 µg/L. A standard Phase II fate and effects assessment was performed by the applicant.

The studies reported comprised: a soil adsorption coefficient study, a ready biodegradability test, a water/sediment study, toxicity studies in aquatic organisms and an activated sludge respiration test.

The adsorption coefficient test resulted in a Koc≤10 000 L/Kg indicating that the adsorption potential is low. Cobicistat was not readily biodegradable and the reported results of the water / sediment study demonstrated that the substance shifts significantly from the water phase to the sediment phase.

The Aerobic Transformation in Aquatic Sediment systems study has shown that cobicistat has the potential to be persistent in the environment.

PNECsurfacewater was based on the lowest NOEC determined in the early life-stage study for fish (the most sensitive aquatic organism). The PNECmicroorganisms was based on the NOEC from the sludge respiration inhibition test and the PNEC groundwater based on the NOEC from the Daphnia chronic reproduction test.

A refined PECsurfacewater was performed by the applicant based on prevalence of HIV-1 in Estonia. The calculated value was 0.975 µg/L, the threshold value was once more exceeded. A risk assessment was calculated for the environmental compartments.

No risk has been identified for the surfacewater, groundwater, wastewater treatment plant as the PEC/PNEC values were below the threshold values. However, the risk to the sediment compartment has not yet been investigated but the sediment dwelling organism study is planned for submission in the post-approval phase.

Substance (INN/Invented Name): cobicistat/ Evotaz			
CAS-number (if available):			
PBT screening	Method	Results	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 117	pH 5 = 3.05 pH 7 = 4.0 pH 9 = 4.10 (≤ 4.5)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioconcentration potential	log K_{ow}	≥ 3	B (N) BCF <2
Persistence	ready biodegradability	Not readily biodegradable	Potential P
Toxicity (fish)	NOEC	4.84 mg/L	T (N)
PBT-statement :	The compound is not considered as PBT or vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$	0.75	µg/L	≥0.01 threshold
Refined $PEC_{surfacewater}$	0.975	µg/L	≥0.01 threshold Market Penetration based on the prevalence of HIV -1 in Estonia
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption 3 soils and 2 sludges	OECD 106	*Soils* K_{oc} = 3624 - 9012L/kg Activated sludge K_{oc} = 1654 – 2664 L/kg	Low adsorption K_{oc}≤10 000 L/Kg
Ready Biodegradability Test	OCDE 301B	Not readily biodegradable	----------
Aerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50} total system = 241 days (HOCC) and 171 days (LOCC) % shifting to sediment >10%	**Potential P** Risk to Sediment Dwelling Organism

Two aquatic sediments HOCC=Higher Organic Carbonic Content LOCC= Lower Organic Carbonic Content		at or after 7 days Degradation products <10%			
Phase II-A Effect studies					
Study type	**Test protocol**	**End point**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition	OECD 201	EC_{10}	29.28	mg/L	*Pseudokirchneriella subcapitata* Acute toxicity study Highest dose tested
Daphnia sp. Reproduction Test	OECD 211	NOEC (growth and reproduction	17.48	mg/L	*Daphnia magna* Highest dose tested
Fish, Early Life Stage Toxicity	OECD 210	NOEC (mortality)	4.84	mg/L	*Pimephales promelas* Highest dose tested
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	mg/L	Highest dose tested
Phase II-B Studies					
Sediment Dwelling Organism	OCDE 218				*Chironomus riparius* Data not available yet

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

• The applicant committed to submit an updated environmental risk assessment which clarifies the effects of COBI on sediment dwelling organisms.

2.3.6. Discussion on non-clinical aspects

In an ex vivo Langendorff, isolated rabbit heart pharmacology study ATV and COBI exhibited effects on LV contractility and PR prolongation. When ATV + COBI were tested in combination, no clear additive or synergistic cardiovascular effects were observed.

A 3-month oral combination toxicity study in rats (GS Study TX-216-2024) in which ATV and COBI were given daily, either alone or in combination was conducted. ATV/COBI was given at 0/0 (vehicle), 20/30, or 50/30 mg/kg/day to both sexes. ATV and COBI were administered alone at 20 or 50 mg/kg/day and 30 mg/kg/day, respectively. All doses were administered at 2 mL/kg. No new or unexpected toxicities were noted this study. A 3-month oral qualifying toxicity study in rat was conducted to compare the toxicity of a COBI-spiked batch (COBI-SP) with the toxicity profile of COBI not spiked (COBI-NS) with degradants. This study showed that 4 potential COBI degradants did not alter the toxicological or toxicokinetic profile of COBI.

No other nonclinical pharmacology, pharmacokinetic or safety assessment studies have been conducted with the ATV/COBI FDC tablet, which was considered acceptable by the CHMP. Based on the nonclinical data presented of the individual agents, there appears to be no significant potential for adverse pharmacodynamic interactions between the two components. Pharmacokinetic interaction between ATV and COBI is also not expected and both ATV and COBI have in general low propensity for clinically significant pharmacokinetic interactions with other co-administered drugs.

An extensive number of nonclinical toxicity studies, previously conducted for each of the agents individually to support their respective original marketing applications. No significant toxicological finding was identified for either compound that would indicate a concern for ATV and COBI co-administration.

The applicant has conducted a full environmental risk assessment. The water-sediment-study (OECD 308) clearly shows that both active ingredients atazanavir and cobicistat are persistent in the total water-sediment system; with %shifting to sediment and DT50 exceeding the trigger value for "persistence". In addition, the CHMP note that the dataset are incomplete: As sediment shifting of the drug substance was demonstrated (sediment shifting > 10%), the CHMP recommended the Applicant to investigate the effects of cobicistat on sediment organisms and the data will be submitted post-authorisation.

2.3.7. Conclusion on the non-clinical aspects

There are no objections against the registration of the fixed dose combination of atazanvir and cobicistat from a non-clinical point of view. However, the applicant further committed to submit an updated environmental risk assessment which clarifies the effects of COBI on sediment dwelling organisms.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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.

2.4.2. Pharmacokinetics

The clinical pharmacology program for Atazanavir (ATV)/Cobicistat (COBI) FDC is based principally on demonstrating bioequivalence of ATV in ATV/COBI FDC compared to ATV capsule coadministered with a COBI tablet and PK bridging of ATV co-administered with COBI with ATV co-administered with low-dose ritonavir (rtv).

Bioavailability

The absolute bioavailability of the ATV/COBI FDC has not been investigated. The relative bioavailability of COBI and ATV when administered as part of a FDC tablet of ATV/COBI 300/150 mg were considered by the applicant to be similar to COBI/ATV administered as individual components under fasted conditions (see results of the bioequivalence Study AI424511). In addition; a Phase 1 randomised, open-label, single-centre, multiple-dose, 6-sequence, 3-period crossover study GS-US-216-0110 was conducted to evaluate the relative bioavailability and pharmacokinetics of Atazanavir co-administered with Cobicistat compared with Ritonavir.

The treatment groups were as follows:

- Treatment A: ATV 300 mg (1 × 300-mg capsule) + COBI (GS-9350)100 mg (1 × 100-mg tablet), coadministered orally QD in the morning for 10 consecutive days (ATV+COBI 300/100 mg)
- Treatment B: ATV 300 mg (1 × 300-mg capsule) + COBI 150 mg (1 × 150-mg tablet), coadministered orally QD in the morning for 10 consecutive days (ATV+COBI 300/150 mg)
- Treatment C: ATV 300 mg (1 × 300-mg capsule) + RTV 100 mg (1 × 100-mg capsule), coadministered orally QD in the morning for 10 consecutive days (ATV+RTV 300/100 mg).

A total of 42 healthy adult subjects were randomized and treated with study drug. A total of 33 subjects completed all study treatments; 9 subjects discontinued prematurely. Enrolled subjects were predominantly white (67%) and male (67%), with a mean age of 28 years (range: 18 to 45 years). Mean weight was 75.0 kg, mean height was 172 cm, mean body mass index was 25.3 kg/m2 (range: 20.3 to 30.6 kg/m2), and mean estimated creatine clearance was 127 mL/min.

Results

Atazanavir/COBI 300/150 mg and atazanavir/rtv 300/100 mg were found to be bioequivalent with regards to AUC_{tau}, C_{max}, and C_{tau}. In addition, atazanavir T_{max} and $T_{1/2}$ were comparable between these two treatments. Exposure of Atazanavir was lower with Atazanavir/COBI 300/100 mg dosing when compared with atazanavir/r 300/100 mg and there was a shorter $T_{1/2}$. Greater than dose-proportional increases in COBI exposures were observed at 150 mg relative to 100 mg (each when co-administered with atazanavir).

Statistical Comparison of Atazanavir Pharmacokinetic Parameters for Test versus Reference Treatments

Atazanavir PK Parameter	Geometric Least Squares Means		GMR (%) (90% CI)
	Test Treatment	Reference Treatment	
	Atazanavir/GS-9350 300/100 mg	**Atazanavir/r 300/100 mg**	
n	35	36	
AUC_{tau} (ng•h/mL)	42,835.83	52,772.91	81.17 (76.02, 86.67)
C_{max} (ng/mL)	4287.88	5094.52	84.17 (77.70, 91.17)
C_{tau} (ng/mL)	700.61	1220.18	57.42 (51.93, 63.49)
	Atazanavir/GS-9350 300/150 mg	**Atazanavir/r 300/100 mg**	
n	34	36	
AUC_{tau} (ng•h/mL)	53,272.76	52,772.91	100.95 (94.47, 107.87)
C_{max} (ng/mL)	4701.26	5094.52	92.28 (85.13, 100.03)
C_{tau} (ng/mL)	1190.42	1220.18	97.56 (88.14, 107.99)

CI = confidence interval, GMR = geometric least squares mean ratio

Study conclusions

The present study demonstrated that atazanavir exposures (AUC_{tau}, C_{max}, and C_{tau}) were bioequivalent following administration of atazanavir + GS-9350 300+150 mg versus atazanavir + ritonavir 300+100 mg. Furthermore, atazanavir t_{max} and $t_{1/2}$ were comparable between these two treatments.

Safety conclusions

With regard to safety and tolerability, results do not elicit new safety concerns with regard to both atazanavir and cobicistat, as there were no unexpected findings.

Bioequivalence

The relative bioavailability and PK of atazanavir when coadministered with cobicistat vs. coadministration with ritonavir (RTV) was assessed in study GS-US-216-0110. For the purpose of the ATV/COBI FDC application, only ATV pharmacokinetics/bioequivalence was assessed. Cobicistat and ritonavir PK results were considered as additional supportive information.

The relative bioavailability and PK of ATV in a FDC of ATV/COBI (300/150 mg) as compared to a 300 mg ATV capsule co-administered with a 150 mg COBI tablet when administered with a light meal was assessed in study AI424511.

Study AI424511

Study AI424511 was an open-label, single-dose, 5-period, 5-treatment, randomized crossover study in healthy subjects. Approximately 64 subjects were equally randomized to one of eight treatment sequences (ABCDE, ABDCE, BACDE, BADCE, ABCD, ABDC, BACD or BADC). Between period 1 and period 5, study was designed with a total duration of 31 days, according to the Figure 1:

Figure 1. Study scheme

Days -21 to -1	Period 1[a] and Period 2			Wash-out up to Day 14	Periods 3 and 4[b],			Wash-out up to Day 28	Period 5[c],	
	Day 1	Wash-out up to Day 7	Day 8		Day 15	Wash-out up to Day 21	Day 22		Day 29	Day 31
S & E[d]	Treatment A or B		Treatment B or A		Treatment C or D		Treatment D or C		Treatment E	Discharge

a Approximately 64 subjects will be randomized prior to Day 1 dosing
b Approximately 32 subjects will be discharged at the end of Period 4 (Day 24) based on the assigned treatment sequence
c Remaining approximately 32 subjects will be discharged at the end of Period 5 (Day 31) based on the assigned treatment sequence
d Screening and Enrollment

Treatments

Treatment A: atazanavir 300 mg (Capsule) + 150 mg cobicistat (Tablet) co-administered following a light meal

Treatment B: atazanavir 300 mg/150 mg cobicistat - Fixed Dose Combination (Tablet) administered following a light meal

Treatment C: atazanavir 300 mg (Capsule) + 150 mg cobicistat (Tablet) co-administered under fasted condition

Treatment D: atazanavir 300 mg/150 mg cobicistat - Fixed Dose Combination (Tablet) administered under fasted condition

Treatment E: atazanavir 300 mg/150 mg cobicistat - Fixed Dose Combination (Tablet) administered with a high fat meal

Subjects received Treatments A or B (following a light meal) according to the assigned treatment sequences on Day 1 and Day 8. On Day 15 and Day 22, subjects received Treatment C or D under fasted conditions according to the assigned treatment sequences. On Day 29, approximately half of the subjects, according to the assigned sequence, received Treatment E (following a high fat meal). Between all treatment periods there was a 7-day washout period.

Population

One hundred and forty nine (149) subjects were screened. From these, 64 subjects were enrolled and treated and 62 subjects completed all study treatments. Two subjects discontinued prior study completion.

Results

The results demonstrated that Atazanavir administered as a FDC tablet of ATV/COBI 300/150 mg is bioequivalent to ATV administered as an individual component, when given with a light meal. The 90% confidence intervals (CIs) of the model-based geometric mean ratios of ATV C_{max}, area under the concentration-time curve from time zero to time of the last quantifiable concentration [$AUC_{(0-T)}$], and area under the concentration-time curve from time zero to infinite time [$AUC_{(INF)}$] for the FDC versus co-administration of the individual component were completely contained within the (0.80, 1.25) range that was pre-specified to conclude bioequivalence.

Atazanavir

The bioavailability of ATV administered as a FDC tablet of ATV/COBI 300/150 mg (Treatment D) was similar to ATV + COBI administered as individual components when given under fasted conditions. The 90% CI of the ratios for $AUC_{(0-T)}$ and $AUC_{(INF)}$ were completely contained within the (0.80, 1.25) range. However, the upper range of the 90% CI for C_{max} and C24 for ATV were higher than 1.25 (1.292 and 1.3000 respectively.

Table 4. Results of the Statistical Analyses of ATV Following Administration of the Atazanavir/Cobicistat FDC and Coadministration of the Individual Components with a Light Meal

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean	AUC(0-T) (ng.h/mL) Adjusted Geometric Mean	AUC(INF) (ng.h/mL) Adjusted Geometric Mean
A (ATV 300 mg capsule + COBI 150 mg tablet with a light meal)	3821.89	32723.14	33474.57
B (ATV/COBI 300/150 mg FDC tablet with a light meal)	4101.02	34848.27	35622.54
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
B vs. A	1.073(1.012,1.137)	1.065(1.012,1.120)	1.064(1.011,1.120)

Table 5. Results of Statistical Analyses of ATV for Treatment C and Treatment D

TREATMENT AND COMPARISON	CMAX (ng/mL) Adj.GEO.MEAN[a]	AUC(0-T) (ng•h/mL) Adj.GEO.MEAN[a]	AUC(INF) (ng•h/mL) Adj.GEO.MEAN[a]	C24 (ng/mL) Adj.GEO.MEAN[a]
C	2587.993	25004.12	25531.53	294.310
D	2941.715	27841.20	28341.13	336.594
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
D vs C	1.137(1.000,1.292)	1.113(0.993,1.248)	1.110(0.991,1.244)	1.144(1.006,1.300)

Cobicistat

COBI administered as part of a FDC tablet of ATV/COBI 300/150 mg (Treatment B) was demonstrated to be bioequivalent to COBI administered as an individual component when given with a light meal. The geometric mean ratios of C_{max}, $AUC_{(INF)}$ and $AUC_{(0-T)}$ for COBI were close to 1.00 and the 90% CI of the ratios were completely contained within the (0.80, 1.25) bioequivalence range.

Table 6. Results of the Statistical Analyses of Cobicistat Following Administration of the FDC and Coadministration of the Individual Components with a Light Meal

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean	AUC(0-T) (ng.h/mL) Adjusted Geometric Mean	AUC(INF) (ng.h/mL) Adjusted Geometric Mean
A (ATV 300 mg capsule + COBI 150 mg tablet with a light meal)	1320.32	8745.30	9053.00
B (ATV/COBI 300/150 mg FDC tablet with a light meal)	1351.32	8912.26	9224.63
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
B vs. A	1.023(0.991,1.057)	1.019(0.983,1.057)	1.019(0.982,1.058)

The relative bioavailability of COBI administered as a FDC tablet of ATV/COBI 300/150 mg (Treatment D) was similar to COBI administered as an individual component under fasted conditions but the upper bound of the 90% CI for C_{max} and $AUC_{(0-T)}$ were 1.273 and 1.307, respectively. The 90% CI of the ratio of AUC (INF was contained within the (0.80, 1.25) bioequivalence range.

Table 7. Results of Statistical Analyses of COBI for Treatment C and Treatment D

TREATMENT AND COMPARISON	CMAX (ng/mL) Adj.GEO.MEAN[a]	AUC(0-T) (ng•h/mL) Adj.GEO.MEAN[a]	AUC(INF) (ng•h/mL) Adj.GEO.MEAN[a]
C	952.165	6533.615	7581.826
D	1032.980	7198.855	7398.160
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
D vs C	1.085(0.925,1.273)	1.102(0.929,1.307)	0.976(0.886,1.075)

Influence of food

Effect of food on Atazanavir

When the FDC tablet of ATV/COBI 300/150 mg was administered with a light meal compared to under fasted conditions, the AUCs of ATV were increased by approximately 28% and Cmax was increased by 42%; in addition, C_{24} was increased by 35%. However, the AUCs of ATV with high fat meal were not significantly affected compared to fasted conditions, but C_{max} decreased by 14% while C24 increased by 23%. C_{max} and AUCs after a high fat meal decreased 36% and 25% in comparison to a light meal respectively. However, ATV C_{24} was similar when FDC was administered with either a light meal or a high fat meal.

Table 8. Atazanavir Pharmacokinetic Parameters for Treatment B, Treatment D and Treatment E

	Treatment		
	B	D	E
Cmax (ng/mL)			
Geo.Mean [N]	4104 [62]	2941 [63]	2545 [30]
(%CV)	(32)	(44)	(43)
Tmax (h)			
Median [N]	2.50 [62]	2.00 [63]	3.54 [30]
(Min-Max)	(2.00 - 4.05)	(1.00-6.00)	(2.00-8.02)
AUC(0-T) (ng•h/mL)			
Geo. Mean [N]	34905 [62]	27875 [63]	25873 [30]
(%CV)	(31)	(41)	(40)
AUC(INF) (ng•h/mL)			
Geo. Mean [N]	35673 [62]	28378 [63]	26510 [30]
(%CV)	(32)	(42)	(40)
C24 (ng/mL)			
Geo. Mean [N]	449 [62]	337 [63]	398 [30]
(%CV)	(52)	(56)	(45)
T-HALF (h)			
Mean [N]	7.50 [62]	7.21 [63]	7.14 [30]
(SD)	(2.60)	(2.28)	(2.99)

Treatment: A = ATV 300mg cap+150mg COBI tab light meal, B = ATV 300mg/150mg COBI-FDC tab light meal, C = ATV 300mg cap+150mg COBI tab fasted, D = ATV 300mg/150mg COBI-FDC tab fasted, E = ATV 300mg/150mg COBI-FDC tab high fat meal.

Effect of food on Cobicistat

When a FDC tablet of ATV/COBI 300/150 mg was administered with a light meal, the AUCs of COBI were increased by approximately 24% and C_{max} was increased 30%, compared to fasted conditions. However, the exposures of COBI when administered as the FDC with a high fat meal showed no significant difference vs. the fasted condition (Treatment D); the 90% CIs of the geometric mean ratio for COBI C_{max}, $AUC_{(0-T)}$ and $AUC_{(INF)}$ were all contained within the 0.80-1.25 range. When comparing the FDC administered with the high fat meal (Treatment E) vs. a light meal (Treatment B), a 10% decrease of AUCs and 22% decrease in C_{max} were observed.

Table 9. Pharmacokinetic Parameters for Treatment B, Treatment D and Treatment E

	Treatment		
	B	**D**	**E**
Cmax (ng/mL) Geo.Mean [N] (%CV)	1348 [62] (29)	1033 [63] (38)	1060 [30] (32)
Tmax (h) Median [N] (Min-Max)	2.52 [62] (1.00 - 5.00)	2.00 [63] (1.00-5.00)	4.00 [30] (1.00-12.0)
AUC(0-T) (ng•h/mL) Geo. Mean [N] (%CV)	8866 [62] (38)	7204 [63] (44)	7916 [30] (39)
AUC(INF) (ng•h/mL) Geo. Mean [N] (%CV)	9178 [62] (41)	7408 [63] (46)	8298 [28] (39)
T-HALF (h) Mean [N] (SD)	4.33 [62] (1.42)	4.09 [63] (1.20)	4.27 [28] (1.39)

Treatment: A = ATV 300mg cap+150mg COBI tab light meal, B = ATV 300mg/150mg COBI-FDC tab light meal, C = ATV 300mg cap+150mg COBI tab fasted, D = ATV 300mg/150mg COBI-FDC tab fasted,
E = ATV 300mg/150mg COBI-FDC tab high fat meal

Distribution

It is expected that the distribution of the FDC tablet would be the same as after administration of the single components of ATV and COBI.

Cobicistat

The plasma protein binding of COBI in nonclinical species ranged from 90.9% to 97.7%, and was 97.3% in healthy human subjects this occurred in a concentration-independent manner.After an oral 150-mg dose of [14C]COBI in healthy subjects(based on equilibrium dialysis studies).

The blood-to-plasma ratio of 14C-radioactivity was time-independent and ~ 0.5, indicating that COBI and its metabolites are excluded from the cellular components of the blood.

The distribution of COBI into compartments other than plasma (eg, cerebrospinal fluid or genital tract secretions) was not clinically evaluated.

Atazanavir

Atazanavir is approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/ml. Atazanavir binds to both alpha 1 acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/ml).

Elimination

It is expected that the elimination pathway for the FDC tablet would be the same as after administration of the single components of ATV and COBI.

Cobicistat

The metabolism of COBI is mediated primarily via oxidative processes. Cobicistat is primarily metabolized via CYP3A- and/or CYP2D6-mediated oxidation, with no evidence of Phase 2 metabolism. The total combined mean (SD) recovery of 14C-radioactivity in faeces and urine was 94.4% (3.75%), with most of the radioactive dose recovered from the faeces (86.2% [3.95%]), consistent with the hepatobiliary excretion of COBI and primarily as parent drug or metabolites M21 (GS-9454, or E1) or M31 (GS-9612, or E3); 8.2% of the administered dose was recovered in urine, primarily as unchanged parent drug and with low levels of metabolites M21 and M31. The predominant species circulating in plasma was COBI, which accounted for 98.6% of the total 14C-radioactivity over 24 hours. Analysis by HPLC radiometry and LC/MS/MS showed that COBI was the major species in the faeces (27%), followed by known oxidative metabolites, E3 (14%), which results from hydroxylation of isopropyl thiazole; and E1 (5.5%), which results from carbamate cleavage.

All other metabolites detected in the feces were in trace amounts, with no values exceeding 3% of the administered radioactive dose.

Renal excretion of COBI was a minor pathway for elimination. In urine samples pooled for individual subjects by collection interval and analyzed by HPLC, a mean (SD) of 6.31% (1.15%) of the total radioactive dose was quantified and was comprised primarily of COBI. Known metabolites E1 (M21, GS-9454, GS-342006) and E3 (M31, GS-9612, GS-364751) were present in very low amounts (ie, < 10% of the administered dose was present in urine as parent drug plus metabolites).

Atazanavir

Studies in humans and in vitro studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma have been characterised.

Following a single 400 mg dose of [14C]atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily.

Dose proportionality

There is no discussion by the applicant regarding the dose proportionality of ATV alone or in combination with Cobi. It is noted from study GS-US-216-0110 that COBI exhibits non-linear increases in systemic exposure following and multiple-dose administration.

Intra- and inter-individual variability

Not discussed by the applicant however regarding inter-individual variability it does appear that CV% values are considerable for COBI after single and multiple dosing. In addition, in HIV-infected subjects the ATV CV% values were higher in the Phase 3 study GS-US-216-0114 (~50% for AUCtau and 40-50% for C_{max}) than in the Phase 2 study GS-US-216-0105. When ATV was boosted with COBI the CV% was comparable with that for ATV boosted with RTV in the Phase 3 study but lower with COBI than with RTV boosting in the Phase 2 study. However, the CV% for COBI C_{max} and AUC were lower in the Phase 3 study than in the Phase 2 study.

Pharmacokinetics in target population

Pharmacokinetic sub-studies analyses were conducted as part of two efficacy studies in HIV-1-infected subjects (GS-US-216-0105 and GS-US-216-0114).

Study GS-US-216-0105

A Phase 2, randomised, double-blind study comparing the safety and efficacy of COBI-boosted ATV compared to RTV-boosted ATV in combination with emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF] in HIV-1-infected, ARV treatment-naive adults in which a PK sub-study was performed at the Weeks 2, 4, or 8 visits in a subset of subjects in both treatment groups. The results are shown in Tables 10 and Table 11.

Table 10. Study GS-US-216-0105: Summary of ATV, COBI, and RTV Pharmacokinetic Parameters (PK Substudy Analysis Set)

	Cmax (ng/mL) Mean (%CV)	Tmax (h) Median (Q1, Q3)	Ctau (ng/mL) Mean (%CV)	AUCtau (ng•h/mL Mean (%CV)	T-HALF (h) Median (Q1, Q3)
ATV PK					
ATV+COBI+ FTC/TDF	3879.5 (36.3)	3.25 (2.84, 3.94)	644.0 (55.7)	41307.3 (33.1)	7.93 (5.72, 11.55)
ATV+RTV+ FTC/TDF	4386.1 (47.1)	3.25 (2.00, 5.00)	831.6 (60.4)	49845.2 (47.1)	8.08 (7.63, 16.50)
COBI PK					
ATV+COBI+ FTC/TDF	1124.8 (45.3)	3.00 (1.85, 4.19)	49.2 (78.5)	9034.0 (44.6)	3.95 (3.27, 5.17)
RTV PK					
ATV+RTV+ FTC/TDF	1576.5 (34.6)	4.18 (3.00, 6.00)	172.5 (231.5)	11547.2 (29.8)	3.95 (3.85, 4.21)

A single trough (pre-dose) PK blood sample was collected for all subjects 20 to 24 hours following an observed (in clinic) dose of study drugs at Weeks 8, 24, and 48.

Table 11. Study GS-US-216-0105: Summary of ATV Plasma Concentration Parameters for Trough PK Sample (PK Substudy Analysis Set)

	Visit[a]		
	Week 8	Week 24	Week 48
ATV/co+TVD	(N = 32)	(N = 42)	(N = 35)
ATV Concentration (ng/mL) Mean (%CV)	1073.8 (123.6)	1104.2 (107.9)	1039.0 (119.8)
ATV/r+TVD	(N = 19)	(N = 26)	(N = 25)
ATV Concentration (ng/mL) Mean (%CV)	928.3 (88.2)	962.8 (59.4)	895.0 (58.7)

[a] Only trough concentration data from Weeks 8,24 and 48 with sampling within range (20-24 hours after observed dosing time) were summarised.

Study GS-US-216-0114

A Phase 3, randomised, double-blind study of the safety and efficacy of COBI-boosted ATV vs. RTV-boosted ATV, each administered with FTC/TDF in HIV-1-infected, ARV treatment-naive adults. An intensive PK sub-study was performed between the Weeks 2 and 8 visits in a subset of subjects in both treatment groups. Pharmacokinetic parameters were determined for COBI, ATV, FTC, RTV, and TDF.

The PK sub-study analysis data set, comprising all randomized subjects who received at least 1 dose of study drug, participated in the PK sub-study, and for whom steady-state PK parameters of study drug analytes at the Weeks 2, 4, or 8 visits were calculable, was the primary analysis data set for the detailed PK analyses of COBI, ATV, FTC, RTV, and TDF.

Table 12. GS-US-216-0114: Summary of ATV, COBI, RTV, FTC, and TFV Pharmacokinetic Parameters (PK Substudy Analysis Set)

	C_{max} (ng/mL) Mean (%CV)	T_{max} (h) Median (Q1, Q3)	C_{tau} (ng/mL) Mean (%CV)	AUC_{tau} (ng·h/mL) Mean (%CV)	$t_{1/2}$ (h) Median (Q1, Q3)
ATV					
ATV/co+TVD	3911.5 (49.6)	3.51 (3.00, 4.50)	796.1 (90.3)	46131.6 (56.8)	7.41 (6.36, 11.03)
ATV/r+TVD	4761.2 (40.8)	3.23 (3.00, 3.53)	853.4 (84.7)	47594.2 (51.2)	8.92 (7.26, 12.56)
COBI					
ATV/co+TVD	1457.0 (31.4)	3.00 (2.00, 3.50)	53.7 (122.6)	11113.2 (40.5)	3.47 (3.16, 4.31)
RTV					
ATV/r+TVD	1422.2 (50.2)	3.51 (2.00, 4.02)	54.2 (70.7)	9937.9 (58.1)	4.97 (4.45, 5.72)
FTC					
ATV/co+TVD	2021.0 (18.0)	2.00 (2.00, 3.50)	108.6 (48.6)	12887.0 (27.1)	6.92 (6.61, 7.93)
ATV/r+TVD	1923.3 (24.0)	1.96 (1.00, 3.00)	87.0 (34.1)	10971.1 (23.1)	7.48 (6.94, 8.10)
TFV					
ATV/co+TVD	486.0 (23.8)	2.00 (1.00, 3.00)	99.7 (32.7)	4715.1 (27.5)	12.58 (11.54, 15.33)
ATV/r+TVD	392.6 (31.7)	1.01 (1.00, 2.00)	81.1 (28.7)	3944.0 (29.7)	11.76 (10.99, 13.34)

%CV = percentage coefficient of variation; Q1, Q3 = first and third interquartiles
For each subject in PK substudy, intensive PK was done at one time at Weeks 2, 4 or 8.

Impaired renal function

No studies have been conducted with the ATV/COBI FDC in patients with impaired renal function. However, both ATV and COBI as single components have been assessed in this population. Excretion by the kidney is a minor pathway of elimination for ATV and COBI with approximately 7% of administered ATV is eliminated renally and 8% of the administered dose of COBI is excreted in the urine.

Apparently in study AI424105, administration of ATV 400 mg QD in patients with severe renal impairment not undergoing haemodialysis resulted in ATV C_{max}, AUC, and C_{min} that were 9% lower, 19% higher, and 96% higher than in subjects with normal renal function who were matched in age, weight, and gender. However, when ATV was administered either prior to or immediately following haemodialysis, ATV C_{max}, AUC, and C_{min} were reduced 25% to 43% relative to subjects with normal renal function.

Apparently in subjects with severe renal impairment administered COBI, no clinically relevant impact on COBI systemic exposures was observed relative to subjects with normal renal function.

Impaired hepatic function

No studies have been conducted with the ATV/COBI FDC in patients with impaired hepatic function. Apparently in study AI424015, following administration of a single oral dose of ATV 400 mg to subjects with Child-Pugh class B hepatic impairment (N=12) or Child-Pugh class C hepatic impairment (N=2), ATV $AUC_{(INF)}$ was 42% higher and the $T_{1/2}$ of ATV was nearly 2-fold greater than that observed in subjects with normal hepatic function.

For COBI, relative to subjects with normal hepatic function, subjects with Child-Pugh class B hepatic impairment administered COBI did not display a clinically relevant change in COBI systemic exposures.

Interactions

No drug-interaction studies have been specifically conducted with the ATV/COBI FDC tablet or using ATV co-administered with COBI as separate agents. The drug interaction potential of ATV/COBI FDC has been evaluated on the basis of interactions observed with each of the single agents, the known impact of ATV/COBI on CYP enzymes and PK drug-interaction studies conducted with the individual components of the FDC (ATV/COBI) and the drug interaction potential of ATV when co-administered with rtv. This was considered acceptable by the CHMP.

Both ATV and COBI are metabolised by CYP3A4 and COBI is also metabolised by CYP2D6 to a lesser extent. Atazanavir is an inhibitor of CYP3A4 and UGT1A1 and a weak inhibitor of CYP2C8.

Cobicistat is a strong mechanism-based inhibitor of CYP3A. It is also an inhibitor of CYP2D6, as well as the transporters P-glycoprotein (P-gp), breast cancer resistant protein (BCRP), multidrug and toxin extrusion transporter (MATE1), organic anion transporting polypeptide (OATP) 1B1, and OATP1B3. However, COBI is not an inducer of CYP2C8, CYP2C9, CYP2C19 or UGT1A1.

Plasma concentrations of CYP3A4 substrates are expected to increase when coadministered with the ATV/COBI FDC. This is anticipated to be primarily driven by CYP3A4 inhibition by COBI; however, ATV is also an inhibitor of CYP3A4, and could be a contributor to overall CYP3A4 inhibition by the FDC, resulting in increased plasma concentrations of coadministered CYP3A4 substrates.

The inhibition of CYP2C8 by ATV is expected to result in increased plasma concentrations of CYP2C8 substrates if coadministered with the ATV/COBI FDC. Likewise, the inhibition of UGT1A1 by ATV is expected to increase plasma concentrations of UGT1A1 substrates if coadministered with the ATV/COBI FDC.

Co-administration of the ATV/COBI FDC with drugs that are substrates of CYP2D6, BCRP, MATE1, OATP1B1, and/or OATP1B3 could possibly increase plasma concentrations of those substrates due to inhibition of CYP2D6 and those transporters by COBI. Unlike RTV, COBI is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or UGT1A1. Therefore in some cases, extrapolation of drug interactions observed with ATV/RTV is anticipated to be different with the ATV/COBI FDC. Where data are available, drug interaction information with unboosted ATV (i.e., ATV without RTV) was taken into consideration when predicting the direction of impact on plasma concentrations of the coadministered drug when given with the ATV/COBI FDC, without the confounding effect of RTV.

A table summarising the theoretical drug-drug interactions for the ATV/COBI FDC as well as more detailed information on the background and extrapolation of drug-drug interactions is presented below.

Table 13. Potentially Significant and Theoretical Drug-Drug Interactions for ATV/COBI FDC

Medicinal products by therapeutic area	**Interaction**	**Recommendations concerning co-administration**
ANTI-RETROVIRALS		
Protease inhibitors: ATV/COBI FDC in combination with other protease inhibitors is not recommended because co-administration may not provide adequate protease inhibitor exposure.		
Indinavir	Indinavir is associated with indirect unconjugated hyperbilirubinaemia due to inhibition of UGT.	Co-administration of ATV/COBI FDC and indinavir is not recommended
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)		
Lamivudine 150 mg twice daily + zidovudine 300 mg twice daily (atazanavir 400 mg once daily)	No significant effect on lamivudine and zidovudine concentrations was observed when co-administered with atazanavir.	Based on these data and because cobicistat is not expected to have a significant impact on the pharmacokinetics of NRTIs, the co-administration of ATV/COBI FDC with these medicinal products is not expected to significantly alter the exposure of the co-administered medicinal products.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Didanosine (buffered tablets) 200 mg/stavudine 40 mg, both single dose (atazanavir 400 mg single dose)	Atazanavir, simultaneous administration with ddI+d4T (fasted) Atazanavir AUC ↓87% (↓92% ↓79%) Atazanavir C_{max} ↓89% (↓94% ↓82%) Atazanavir C_{min} ↓84% (↓90% ↓73%) Atazanavir, dosed 1 hr after ddI+d4T (fasted) Atazanavir AUC ↔3% (↓36% ↑67%) Atazanavir C_{max} ↑12% (↓33% ↑18%) Atazanavir C_{min} ↔3% (↓39% ↑73%) Atazanavir concentrations were greatly decreased when co-administered with didanosine (buffered tablets) and stavudine. The mechanism of interaction is a reduced solubility of atazanavir with increasing pH related to the presence of anti-acid agent in didanosine buffered tablets. No significant effect on didanosine and stavudine concentrations was observed.	Didanosine should be taken in the fasted state 2 hours after ATV/COBI FDC taken with food. The co-administration of ATV/COBI FDC with stavudine is not expected to significantly alter the exposure of stavudine.
Didanosine (enteric coated capsules) 400 mg single dose (atazanavir 400 mg once daily)	Didanosine (with food) Didanosine AUC ↓34% (↓40% ↓26%) Didanosine C_{max} ↓36% (↓45% ↓26%) Didanosine C_{min} ↑13% (↓9% ↑41%) No significant effect on atazanavir concentrations was observed when administered with enteric-coated didanosine, but administration with food decreased didanosine concentrations.	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Tenofovir disoproxil fumarate 300 mg once daily (atazanavir 400 mg once daily)	Atazanavir AUC ↓25% (↓30% ↓19%) Atazanavir C_{max} ↓21% (↓27% ↓14%) Atazanavir C_{min} ↓40% (↓48% ↓32%) Tenofovir: AUC: ↑24% (↑21% ↑28%) C_{max}: ↑14% (↑8% ↑20%) C_{min}: ↑22% (↑15% ↑30%) Co-administration of tenofovir disoproxil fumarate with cobicistat is expected to increase tenofovir plasma concentrations. Tenofovir: AUC: ↑23% C_{min}: ↑55% The mechanism of interaction between atazanavir and tenofovir is unknown.	Tenofovir may decrease the AUC and C_{min} of atazanavir. When co-administered with tenofovir, it is recommended that ATV/COBI FDC and tenofovir 300 mg be given together with food. Atazanavir increases tenofovir concentrations. Higher concentrations could potentiate tenofovir-associated adverse reactions, including renal disorders. Patients receiving tenofovir should be monitored for tenofovir-associated adverse reactions.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz 600 mg once daily (atazanavir 400 mg once daily)	Atazanavir Atazanavir AUC ↓74% (↓78% ↓68%) Atazanavir C_{max} ↓59% (↓77% ↓49%) Atazanavir C_{min} ↓93% (↓95% ↓90%)	ATV/COBI FDC is not recommended for co-administration with efavirenz. Efavirenz decreases atazanavir concentrations and is expected to decrease cobicistat plasma concentrations. This may result in loss of therapeutic effect of ATV/COBI FDC and development of resistance to atazanavir
Efavirenz 600 mg single dose (cobicistat 150 mg once daily)	Efavirenz: AUC: ↔7% (↓11% ↓3%) C_{max}: ↓13% (↓20% ↓6%) C_{min}: Not determined The mechanism of interaction between efavirenz and atazanavir, or efavirenz and cobicistat is CYP3A4 induction by efavirenz.	
Etravirine	Co-administration of etravirine and ATV/COBI FDC is expected to decrease atazanavir and cobicistat plasma concentrations. The mechanism of interaction is CYP3A4 induction by etravirine.	ATV/COBI FDC is not recommended for co-administration with etravirine because it may result in the loss of therapeutic effect and development of resistance to atazanavir.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Nevirapine 200 mg twice daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily) Study conducted in HIV infected patients	Nevirapine AUC ↑25% (↑17% ↑34%) Nevirapine C_{max} ↑17% (↑9% ↑25%) Nevirapine C_{min} ↑32% (↑22% ↑43%) Atazanavir AUC ↓42% (↓52% ↓29%) Atazanavir C_{max} ↓28% (↓40% ↓14%) Atazanavir C_{min} ↓72% (↓80% ↓60%) Co-administration of nevirapine and cobicistat is expected to decrease cobicistat plasma concentrations while nevirapine plasma concentrations may be increased. The mechanism of interaction is CYP3A4 induction by nevirapine and CYP3A4 inhibition by atazanavir and cobicistat.	Co-administration of ATV/COBI FDC and nevirapine is not recommended and may result in a loss of therapeutic effect of ATV/COBI FDC and development of resistance to atazanavir. Co-administration of nevirapine and ATV/COBI FDC is expected to increase nevirapine plasma concentrations which may increase the risk of nevirapine-associated toxicity
Rilpivirine	ATV/COBI FDC is expected to increase rilpivirine plasma concentrations. The mechanism of interaction is CYP3A inhibition.	Co-administration of ATV/COBI FDC and rilpivirine can be used without dose adjustments, as the expected increase in rilpivirine concentrations is not considered clinically relevant.
Integrase Inhibitors		
Dolutegravir	Co-administration with ATV/COBI FDC is expected to increase dolutegravir plasma concentrations. Dolutegravir is not expected to affect the pharmacokinetics of ATV/COBI FDC. The mechanism of interaction is inhibition of UGT1A1 by atazanavir.	ATV/COBI FDC and dolutegravir can be used without dose adjustments.
Raltegravir 400 mg twice daily (atazanavir 400 mg)	Raltegravir AUC ↑72% Raltegravir C_{max} ↑53% Raltegravir C_{12hr} ↑95% The mechanism is UGT1A1 inhibition by atazanavir.	No dose adjustment is required for raltegravir if co-administered with ATV/COBI FDC.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
CCR5 Antagonists		
Maraviroc	Maraviroc is a substrate of CYP3A and its plasma concentration increases when co-administered with potent CYP3A inhibitors. Maraviroc is not expected to have an impact on concentrations of atazanavir and cobicistat. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	When co-administering maraviroc and ATV/COBI FDC, patients should receive maraviroc 150 mg twice daily. For further details, consult the Summary of Product Characteristics for maraviroc.
HCV Protease Inhibitors		
Boceprevir 800 mg three times daily (atazanavir 300 mg/ritonavir 100 mg once daily)	boceprevir AUC ↔5% boceprevir C_{max} ↔7% boceprevir C_{min} ↔18% atazanavir AUC ↓35% atazanavir C_{max} ↓25% atazanavir C_{min} ↓49% Concomitant administration of boceprevir and atazanavir/ritonavir resulted in reduced exposures to atazanavir and ritonavir. The mechanism of interaction is unknown.	Co-administration of boceprevir and ATV/COBI FDC is not recommended.
Simeprevir	ATV/COBI FDC is expected to increase simeprevir plasma concentrations. Simeprevir may increase atazanavir and/or cobicistat plasma concentrations. The mechanism of interaction is CYP3A inhibition.	It is not recommended to co-administer ATV/COBI FDC with simeprevir.
Telaprevir 750 mg three times daily (atazanavir/ritonavir 300/100 mg once daily)	Telaprevir AUC ↓20% (↓24% ↓15%) Telaprevir C_{max} ↓21% (↓26% ↓16%) Telaprevir C_{min} ↓15% (↓25% ↓2%) Atazanavir AUC ↑17% (↓3% ↑43%) Atazanavir C_{max} ↓15% (↓27% ↓2%) Atazanavir C_{min} ↑85% (↑40% ↑144%)	No dose adjustment is required for telaprevir if co-administered with ATV/COBI FDC. Clinical and laboratory monitoring for hyperbilirubinaemia is recommended.
Telaprevir 750 mg three times daily (cobicistat 150 mg once daily in combination with elvitegravir)	Telaprevir AUC ↔ Telaprevir C_{max} ↔ Telaprevir C_{min} ↔ Cobicistat AUC ↔ Cobicistat C_{max} ↔ Cobicistat C_{min} ↑232%	

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ANTIBIOTICS		
Clarithromycin 500 mg twice daily (atazanavir 400 mg once daily)	Clarithromycin AUC ↑94% (↑75% ↑116%) Clarithromycin C_{max} ↑50% (↑32% ↑71%) Clarithromycin C_{min} ↑160% (↑135% ↑188%) 14-OH clarithromycin 14-OH clarithromycin AUC ↓70% (↓74% ↓66%) 14-OH clarithromycin C_{max} ↓72% (↓76% ↓67%) 14-OH clarithromycin C_{min} ↓62% (↓66% ↓58%) Atazanavir AUC ↑28% (↑16% ↑43%) Atazanavir C_{max} ↔6% (↓7% ↑20%) Atazanavir C_{min} ↑91% (↑66% ↑121%) Clarithromycin may increase concentrations of atazanavir and cobicistat. Exposure to clarithromycin is expected to increase if co-administered with ATV/COBI FDC. The mechanism of interaction is CYP3A4 inhibition by atazanavir and/or cobicistat and clarithromycin.	Alternative antibiotics should be considered.
ANTIDIABETICS		
Metformin	Cobicistat reversibly inhibits MATE1, and concentrations of metformin may be increased when co-administered with ATV/COBI FDC.	Careful patient monitoring and dose adjustment of metformin is recommended in patients who are taking ATV/COBI FDC.
ANTIFUNGALS		
Ketoconazole 200 mg once daily (atazanavir 400 mg once daily)	No significant effect on atazanavir concentrations was observed.	Caution is warranted. Specific dosing recommendations are not available for

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Itraconazole	Itraconazole, like ketoconazole, is a potent inhibitor as well as a substrate of CYP3A4. Concentrations of ketoconazole, itraconazole, and/or cobicistat may be increased with co-administration of ketoconazole or itraconazole with ATV/COBI FDC. The mechanism of interaction is CYP3A4 inhibition by atazanavir, cobicistat and ketoconazole or itraconazole.	co-administration of ATV/COBI FDC with either ketoconazole or itraconazole. If co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg.
Voriconazole	Effects unknown	Voriconazole should not be co-administered with ATV/COBI FDC unless the benefit/risk assessment justifies the use of voriconazole. Clinical monitoring may be needed upon co-administration with ATV/COBI FDC.
Fluconazole 200 mg once daily (atazanavir 300 mg and ritonavir 100 mg once daily)	Atazanavir and fluconazole concentrations were not significantly modified when atazanavir/ritonavir was co-administered with fluconazole. Concentration of fluconazole may be increased if co-administered with cobicistat.	Clinical monitoring is recommended upon co-administration with ATV/COBI FDC.
ANTIGOUT		
Colchicine	Colchicine plasma concentrations may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	ATV/COBI FDC must not be co-administered with colchicine to patients with renal or hepatic impairment. **Recommended dosage of colchicine when administered with ATV/COBI FDC in patients without renal or hepatic impairment:** a dose reduction in colchicine dosage or an interruption of colchicine treatment is recommended in patients with normal renal or hepatic function if treatment with ATV/COBI FDC is required.
ANTIMYCOBACTERIALS		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Rifabutin 150 mg twice weekly (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Rifabutin AUC ↑48% (↑19% ↑84%)* Rifabutin C_{max} ↑149% (↑103% ↑206%)* Rifabutin C_{min} ↑40% (↑5% ↑87%)* 25-O-desacetyl-rifabutin AUC ↑990% (↑714% ↑1361%)* 25-O-desacetyl-rifabutin C_{max} ↑677% (↑513% ↑883%)* 25-O-desacetyl-rifabutin C_{min} ↑1045% (↑715% ↑1510%)* *When compared to rifabutin 150 mg once daily alone. Total rifabutin and 25-O-desacetyl-rifabutin AUC ↑119% (↑78% ↑169%).	Co-administration of ATV/COBI FDC and rifabutin is not recommended. If the combination is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (for example Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dosage reduction of rifabutin to 150 mg twice weekly on set days is recommended for patients in whom the 150 mg dose 3 times per week is not tolerated. It should be kept in mind that the twice weekly dosage of 150 mg may not provide an optimal exposure to rifabutin thus leading to a risk of rifamycin resistance and a treatment failure. Consideration should be given to official guidance on the appropriate treatment of tuberculosis in HIV infected patients.
Rifabutin 150 mg every other day / elvitegravir 150 mg once daily / cobicistat 150 mg once daily	Cobicistat: AUC: ↔ C_{max}: ↔ C_{min}: ↓66% Rifabutin: AUC: ↔8% C_{max}: ↔9% C_{min}: ↔6% 25-O-desacetyl-rifabutin: AUC: ↑525% C_{max}: ↑384% C_{min}: ↑394% The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	
Rifampicin 600 mg once daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Rifampicin is a strong CYP3A4 inducer and has been shown to cause a 72% decrease in atazanavir AUC which can result in virological failure and resistance development. The mechanism of interaction is CYP3A4 induction by rifampicin.	Rifampicin substantially decreases plasma concentrations of atazanavir, which may result in loss of therapeutic effect of ATV/COBI FDC and development of resistance to atazanavir. The combination of rifampicin and ATV/COBI FDC is contraindicated

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
ACID REDUCING AGENTS		
H_2-Receptor antagonists		
Without Tenofovir		
Famotidine 20 mg twice daily (atazanavir 300 mg/ritonavir 100 mg once daily) in HIV-infected patients	Atazanavir AUC ↓18% (↓25% ↑1%) Atazanavir C_{max} ↓20% (↓32% ↓7%) Atazanavir C_{min} ↔1% (↓16% ↑18%)	**For patients not taking tenofovir,** ATV/COBI FDC once daily with food should be administered simultaneously with, and/or at least 10 hours after, a dose of the H_2-receptor antagonist. The dose of the H_2-receptor antagonist should not exceed a dose comparable to famotidine 20 mg twice daily.
With Tenofovir 300 mg once daily		
Famotidine 20 mg twice daily (atazanavir 300 mg/ritonavir 100 mg/tenofovir 300 mg once daily, simultaneous administration)	Atazanavir AUC ↓10% (↓18% ↓2%) Atazanavir C_{max} ↓9% (↓16% ↓1%) Atazanavir C_{min} ↓19% (↓31% ↓6%) The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with H_2 blockers.	**For patients who are taking tenofovir,** it is not recommended to co-administer ATV/COBI FDC with an H_2-receptor antagonist.
Proton pump inhibitors		
Omeprazole 40 mg once daily (atazanavir 400 mg once daily, 2 hours after omeprazole)	Atazanavir AUC ↓94% (↓95% ↓93%) Atazanavir C_{max} ↓96% (↓96% ↓95%) Atazanavir C_{min} ↓95% (↓97% ↓93%)	Co-administration of ATV/COBI FDC with proton pump inhibitors is not recommended.
Omeprazole 40 mg once daily (atazanavir 300 mg once daily with ritonavir 100 mg once daily, 2 hours after omeprazole)	Atazanavir AUC ↓76% (↓78% ↓73%) Atazanavir C_{max} ↓72% (↓76% ↓68%) Atazanavir C_{min} ↓78% (↓81% ↓74%)	
Omeprazole 20 mg once daily am (atazanavir 300 mg once daily with ritonavir 100 mg once daily pm, 12 hours after omeprazole)	Atazanavir AUC ↓42% (↓66% ↓25%) Atazanavir C_{max} ↓39% (↓64% ↓19%) Atazanavir C_{min} ↓46% (↓59% ↓29%) The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors.	
Antacids		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Antacids and medicinal products containing buffers	Reduced plasma concentrations of atazanavir may be the consequence of increased gastric pH if antacids, including buffered medicinal products, are administered with ATV/COBI FDC.	ATV/COBI FDC should be administered 2 hours before or 1 hour after antacids or buffered medicinal products.
ALPHA 1-ADRENORECEPTOR ANTAGONIST		
Alfuzosin	Potential for increased alfuzosin concentrations which can result in hypotension. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Co-administration of ATV/COBI FDC with alfuzosin is contraindicated
ANTICOAGULANTS		
Warfarin	Co-administration with ATV/COBI FDC has the potential to increase warfarin plasma concentrations. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Co-administration with ATV/COBI FDC has the potential to produce serious and/or life-threatening bleeding due to increased exposure to warfarin and has not been studied. It is recommended that the INR (International Normalized Ratio) be monitored.
Rivaroxaban	Co-administration of ATV/COBI FDC and rivaroxaban may result in increased exposure to rivaroxaban and may lead to increased bleeding. The mechanism of interaction is CYP3A4 and P-gp inhibition by cobicistat.	Avoid concomitant use of ATV/COBI FDC and rivaroxaban.
Dabigatran	Concentrations of dabigatran may be affected upon co-administration with ATV/COBI FDC. The mechanism of interaction is P-gp inhibition by atazanavir and cobicistat.	Clinical monitoring is recommended when dabigatran is co-administered with P-gp inhibitors. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.
Ticagrelor	Co- administration of ATV/COBI FDC and ticagrelor may increase concentrations of the anticoagulant. The mechanism of interaction is CYP3A and/or P-glycoprotein inhibition by atazanavir and cobicistat.	Concomitant administration of ATV/COBI FDC with ticagrelor is contraindicated. Use of other antiplatelets not affected by CYP inhibition or induction (e.g. prasugrel) is recommended
ANTIEPILEPTICS		
Carbamazepine **Phenobarbital** **Phenytoin**	These antiepileptics are expected to decrease atazanavir and/or cobicistat plasma concentrations. The mechanism of interaction is CYP3A induction by the antiepileptic.	Co-administration of ATV/COBI FDC and these antiepileptics is contraindicated
ANTIHISTAMINE AGENTS		
Astemizole **Terfenadine**	ATV/COBI FDC must not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration of ATV/COBI FDC with astemizole and terfenadine is contraindicated
ANTINEOPLASTICS AND IMMUNOSUPRESSANTS		
Antineoplastics		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Irinotecan	Atazanavir inhibits UGT and may interfere with the metabolism of irinotecan, resulting in increased irinotecan toxicities.	If ATV/COBI FDC is co-administered with irinotecan, patients should be closely monitored for adverse reactions related to irinotecan.
Dasatinib **Nilotinib** **Vinblastine** **Vincristine**	Concentrations of these medicinal products may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is CYP3A4 inhibition by cobicistat.	Concentrations of these medicinal products may be increased when co-administered with ATV/COBI FDC resulting in the potential for increased adverse events usually associated with these anticancer medicinal products.
Immunosuppressants		
Ciclosporin **Tacrolimus** **Sirolimus**	Concentrations of these immunosuppressants may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is inhibition of CYP3A4 by atazanavir and cobicistat.	More frequent therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with ATV/COBI FDC.
ANTIPSYCOTICS		
Pimozide **Quetiapine**	Concentrations of these medicinal products may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is CYP3A inhibition by atazanavir and cobicistat.	The combination of pimozide or quetiapine and ATV/COBI FDC is contraindicated
CARDIOVASCULAR AGENTS		
Antiarrhythmics		
Disopyramide **Flecainide** **Mexiletine** **Propafenone**	Concentrations of these antiarrhythmics may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is CYP3A inhibition by atazanavir and cobicistat.	Co-administration with ATV/COBI FDC has the potential to produce serious and/or life-threatening adverse reactions. Caution is warranted and therapeutic concentration monitoring of these medicinal products is recommended if they are used concomitantly with ATV/COBI FDC.
Amiodarone **Dronedarone** **Quinidine** **Systemic lidocaine**	Concentrations of these antiarrhythmics may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is CYP3A inhibition by atazanavir and cobicistat.	Amiodarone, dronedarone, quinidine and systemic lidocaine have a narrow therapeutic window and are contraindicated due to potential inhibition of CYP3A by ATV/COBI FDC

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Digoxin (0.5 mg single dose)/cobicistat (150 mg multiple doses)	Plasma concentrations of digoxin may be increased when co-administered with ATV/COBI FDC. Digoxin: AUC: ↔ C_{max}: ↑41% C_{min}: not determined The mechanism of interaction is inhibition of P-gp by cobicistat.	The peak concentration of digoxin is increased when co-administered with cobicistat. When co-administering with ATV/COBI FDC, titrate the digoxin dose and monitor digoxin concentrations. The lowest dose of digoxin should initially be prescribed.
Antihypertensives		
Metoprolol **Timolol**	Concentrations of beta-blockers may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is inhibition of CYP2D6 by cobicistat.	Clinical monitoring is recommended when co-administered with ATV/COBI FDC and a dose reduction of the beta-blocker may be necessary.
Calcium channel blockers		
Bepridil	ATV/COBI FDC must not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration with bepridil is contraindicated
Diltiazem 180 mg once daily (atazanavir 400 mg once daily)	Diltiazem AUC ↑125% (↑109% ↑141%) Diltiazem C_{max} ↑98% (↑78% ↑119%) Diltiazem C_{min} ↑142% (↑114% ↑173%) Desacetyl-diltiazem AUC ↑165% (↑145% ↑187%) Desacetyl-diltiazem C_{max} ↑172% (↑144% ↑203%) Desacetyl-diltiazem C_{min} ↑121% (↑102% ↑142%) No significant effect on atazanavir concentrations was observed. There was an increase in the maximum PR interval compared to atazanavir alone. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Exposure to diltiazem and a metabolite, desacetyl-diltiazem, is increased when diltiazem is co-administered with atazanavir, a component of ATV/COBI FDC. An initial dose reduction of diltiazem by 50% should be considered, and electrocardiogram monitoring is recommended.
Amlodipine **Felodipine** **Nicardipine** **Nifedipine** **Verapamil**	Concentrations of these calcium channel blockers may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is inhibition of CYP3A4 by atazanavir and cobicistat.	Caution is warranted. Dose titration of the calcium channel blockers should be considered. Electrocardiogram monitoring is recommended. Clinical monitoring of therapeutic effect and adverse events is recommended when these medicinal products are co-administered with ATV/COBI FDC.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Endothelin Receptor Antagonists		
Bosentan	Co-administration of bosentan with cobicistat may lead to decreased cobicistat plasma concentrations. The mechanism of interaction is induction of CYP3A4 by bosentan.	Atazanavir plasma concentrations may decrease as a consequence of a reduction in cobicistat plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Co-administration is not recommended.
CORTICOSTEROIDS		
Fluticasone propionate	Concomitant use of inhaled or nasal fluticasone and ATV/COBI FDC may increase plasma concentrations of fluticasone, resulting in reduced serum cortisol concentrations. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Concomitant use of ATV/COBI FDC and fluticasone propionate or other inhaled or nasal corticosteroids is not recommended unless the potential benefit of treatment outweighs the risks of systemic corticosteroid effects. Consider alternatives particularly for long-term use.
ANTIDEPRESSANTS		
Other antidepressants:		
Trazodone	Plasma concentrations of trazodone may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	If trazodone is co-administered with ATV/COBI FDC, the combination should be used with caution and a lower dose of trazodone should be considered.
ERECTILE DYSFUNCTION		
PDE5 Inhibitors		
Sildenafil **Tadalafil** **Vardenafil** **Avanafil**	Sildenafil, tadalafil, and vardenafil are metabolised by CYP3A4. Co-administration with ATV/COBI FDC may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5-associated adverse events, including hypotension, visual changes, and priapism. The mechanism of this interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Patients should be warned about these possible side effects when using PDE5 inhibitors for erectile dysfunction with ATV/COBI FDC. For the treatment of erectile dysfunction, it is recommended that when co-administered with ATV/COBI FDC, sildenafil should be used with caution at reduced doses of 25 mg every 48 hours; tadalafil should be used with caution at reduced doses of 10 mg every 72 hours; vardenafil should be used with caution at reduced doses of no more than 2.5 mg every 72 hours. Increase monitoring for adverse reactions. The combination of avanafil and ATV/COBI FDC is contraindicated. Also see PULMONARY ATERIAL HYPERTENSION in this table for further information regarding co-administration of ATV/COBI FDC with sildenafil.
HERBAL PRODUCTS		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
St. John's wort (*Hypericum perforatum*)	Concomitant use of St. John's wort with ATV/COBI FDC may be expected to result in significant reduction in plasma levels of cobicistat and atazanavir. This effect may be due to an induction of CYP3A4. There is a risk of loss of therapeutic effect and development of resistance to atazanavir (see section 4.3).	Co-administration of ATV/COBI FDC with products containing St. John's wort is contraindicated.
HORMONAL CONTRACEPTIVES		
Progestin/estrogen	Concentrations of ethinyl estradiol and norethindrone are increased when a combined oral contraceptive containing those agents is co-administered with atazanavir. The mechanism of interaction is inhibition of metabolism by atazanavir. Effects of co-administration of ATV/COBI FDC on progestin and estrogen are unknown.	Co-administration of ATV/COBI FDC and hormonal contraceptives should be avoided. An alternate (non-hormonal) reliable method of contraception is recommended.
LIPID LOWERING AGENTS		
HMG-CoA reductase inhibitors		
Simvastatin **Lovastatin**	Simvastatin and lovastatin are highly dependent on CYP3A4 for their metabolism and co-administration with ATV/COBI FDC may result in increased concentrations.	Co-administration of simvastatin or lovastatin with ATV/COBI FDC is contraindicated due to an increased risk of myopathy including rhabdomyolysis.
Atorvastatin	The risk of myopathy including rhabdomyolysis may also be increased with atorvastatin, which is also metabolised by CYP3A4.	Co-administration of atorvastatin with ATV/COBI FDC is not recommended. If the use of atorvastatin is considered strictly necessary, the lowest possible dose of atorvastatin should be administered with careful safety monitoring
Pravastatin **Fluvastatin** **Pitavastatin**	Although not studied, there is a potential for an increase in pravastatin or fluvastatin exposure when co-administered with protease inhibitors. Pravastatin is not metabolised by CYP3A4. Fluvastatin is partially metabolised by CYP2C9. Plasma concentrations of pitavastatin may be increased if co-administered with ATV/COBI FDC.	Caution should be exercised.
Rosuvastatin (10 mg single dose)/Elvitegravir (150 mg once daily)/Cobicistat (150 mg once daily)	Rosuvastatin: AUC: ↑38% C_{max}: ↑89% C_{min}: ↑43% Cobicistat: AUC: ↔ C_{max}: ↔ C_{min}: ↔ The mechanism of interaction is potential inhibition of the transporter OATP1B1 by cobicistat.	Rosuvastatin dose should not exceed 10 mg/day. The risk of myopathy, including rhabdomyolysis, may be increased.
INHALED BETA AGONISTS		

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
Salmeterol	Co-administration with ATV/COBI FDC may result in increased concentrations of salmeterol and an increase in salmeterol-associated adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	Co-administration of salmeterol with ATV/COBI FDC is not recommended.
ERGOT DERIVATES		
Dihydroergotamine **Ergometrine** **Ergotamine** **Methylergonovine**	ATV/COBI FDC must not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration of ATV/COBI FDC and these ergot derivates is contraindicated.
NEUROLEPTICS		
Perphenazine **Risperidone** **Thioridazine**	Co-administration of neuroleptics with ATV/COBI FDC may result in increased plasma concentrations of neuroleptics. The mechanism of interaction is inhibition of CYP3A4 and/or CYP2D6 by atazanavir and/or cobicistat.	A decrease in the dose of neuroleptics metabolized by CYP3A or CYP2D6 may be required when co-administered with ATV/COBI FDC.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
OPIOIDS		
Buprenorphine, once daily, stable maintenance dose (atazanavir 300 mg once daily with ritonavir 100 mg once daily)	Buprenorphine AUC ↑67% Buprenorphine C_{max} ↑37% Buprenorphine C_{min} ↑69% Norbuprenorphine AUC ↑105% Norbuprenorphine C_{max} ↑61% Norbuprenorphine C_{min} ↑101% The mechanism of interaction is CYP3A4 and UGT1A1 inhibition by atazanavir. Concentrations of atazanavir were not significantly affected.	Co-administration warrants clinical monitoring for sedation and cognitive effects. A dose reduction of buprenorphine may be considered.
Buprenorphine/naloxone in combination with cobicistat	Buprenorphine AUC: ↑35% Buprenorphine C_{max}: ↑66% Buprenorphine C_{min}: ↑12% Naloxone AUC: ↓28% Naloxone C_{max}: ↓28% The mechanism of interaction is CYP3A4 inhibition by cobicistat.	
Methadone, stable maintenance dose (atazanavir 400 mg once daily)	No significant effect on methadone concentrations was observed when co-administered with atazanavir. Given that cobicistat has been shown to have no significant effect on methadone concentrations, no interaction is expected if methadone is co-administered with ATV/COBI FDC.	No dosage adjustment is necessary if methadone is co-administered with ATV/COBI FDC.
PULMONARY ARTERIAL HYPERTENSION		
PDE5 Inhibitors		
Sildenafil	Co-administration with ATV/COBI FDC may result in increased concentrations of the PDE5 inhibitor and an increase in PDE5 inhibitor-associated adverse events. The mechanism of interaction is CYP3A4 inhibition by atazanavir and cobicistat.	A safe and effective dose in combination with ATV/COBI FDC has not been established for sildenafil when used to treat pulmonary arterial hypertension. Sildenafil, when used for the treatment of pulmonary arterial hypertension, is contraindicated.

Medicinal products by therapeutic area	Interaction	Recommendations concerning co-administration
SEDATIVES/HYPNOTICS		
Midazolam **Triazolam**	Midazolam and triazolam are extensively metabolized by CYP3A4. Co-administration with ATV/COBI FDC may cause a large increase in the concentration of these benzodiazepines. Based on data for other CYP3A4 inhibitors, plasma concentrations of midazolam are expected to be significantly higher when midazolam is given orally. Data from concomitant use of parenteral midazolam with other protease inhibitors suggest a possible 3-4 fold increase in midazolam plasma levels.	ATV/COBI FDC should not be co-administered with triazolam or orally administered midazolam, whereas caution should be used with co-administration of ATV/COBI FDC and parenteral midazolam. If ATV/COBI FDC is co-administered with parenteral midazolam, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage adjustment for midazolam should be considered, especially if more than a single dose of midazolam is administered.
Buspirone **Clorazepate** **Diazepam** **Estazolam** **Flurazepam** **Zolpidem**	Concentrations of these sedatives/hypnotics may be increased when co-administered with ATV/COBI FDC. The mechanism of interaction is inhibition of CYP3A4 by cobicistat.	For these sedatives/hypnotics, dose reduction may be necessary and concentration monitoring is recommended.
GASTROINTESTINAL MOTILITY AGENTS		
Cisapride	ATV/COBI FDC must not be used in combination with medicinal products that are substrates of CYP3A4 and have a narrow therapeutic index.	Co-administration of ATV/COBI FDC and cisapride is contraindicated.

2.4.3. Pharmacodynamics

Mechanism of action

Atazanavir

Reyataz, atazanavir (ATV) is a human immunodeficiency virus (HIV) protease inhibitor. It is an azapeptide that blocks the processing of viral gag-pol proteins in HIV-1 infected cells, thus preventing formation of mature virions.

Cobicistat

Tybost, cobicistat, COBI has been shown to inhibit the activity of human CYP3A enzymes (IC50 values 0.03 to 0.15 µM) and enzyme kinetic studies have demonstrated that it is an efficient inactivator of human CYP3A activity. The potency of the observed inhibition and inactivation was comparable to that observed with RTV and hence, the applicant has identified COBI as a mechanism-based inhibitor. The Applicant has provided evidence that the inhibition of CYP3A is time, NADPH and concentration dependent, which suggests that cobicistat is capable of mechanism-based inhibition. However, the Applicant states that the precise molecular mechanism of inhibition is not completely understood and that overall, the mechanism may be mixed.

2.4.4. Discussion on clinical pharmacology

The applicant has not conducted a comprehensive investigation of the PK of ATV/COBI and relies on demonstrating bioequivalence of ATV in ATV/COBI FDC compared to ATV capsule coadministered with a COBI tablet. In addition PK data bridging ATV co-administered with COBI with ATV co-administered with low-dose ritonavir (RTV) is provided. This approach is considered acceptable in principle as the pharmacokinetics of the single agents have previously been characterised.

The results of the study (AI424511) demonstrated that ATV and COBI contained in the FDC are bioequivalent to the individual components following a light meal therefore the primary objective of the study was fulfilled. In the fasted state however, Cmax and C24 for ATV and the AUC(0-t) and Cmax for COBI contained in the FDC were found to be increased as compared to the individual component and were not bioequivalent. In addition, there was a decrease in ATV and COBI Cmax, exposure (AUCs) and delay in Tmax following a high fat meal in comparison to a light meal. Differences on PK behaviour between light fat and high fat meals are not totally understood, but might be due to solubility and gastric emptying issues. Moreover, the obtained results are in accordance with Reyataz SmPC (ATV) and in accordance with cobicistat pharmacokinetic properties described on Stribild SmPC (Gilead), as a four-drug (elvitegravir/cobicistat/emtricitabine/tenofovir), fixed-dose combination drug product developed by Gilead for HIV treatment. Nevertheless, it was requested that differences be clearly stated in section 5.2 of the SmPC.

PK sub-studies were also conducted as part of the efficacy studies (GS-US-216-0114 and GS-US-216-0105). The results of study GS-US-216-0105 showed that the plasma concentrations of ATV were slightly lower on boosting with COBI when compared with RTV. The trough concentration levels were higher with ATV boosted with COBI as compared with RTV and in study GS-US-216-0114 the results showed that FTC and TFV plasma concentration levels were higher with COBI however ATV plasma levels were lower on co-administration with COBI. In addition, the CV% values are quite high in both studies, especially for Cmax and AUC of ATV when given with either COBI or RTV, which was concluded by the applicant to be of no clinically relevance.

No drug-drug interaction studies have been performed using ATV/COBI FDC tablet formulations or ATV co-administered with COBI as separate agents and the applicant bases the drug interaction potential on the interactions observed with each single agent which is considered adequate. The pharmacodynamic section has been completely omitted as the applicant considers that the ATV and COBI have previously been characterised in procedures EMEA/H/C/000494 (ATV) and EMEA/H/C/002572 (COBI). This has been accepted and the lack of information will not be pursued further.

Overall, there are no major concerns regarding the PK of this FDC and all points for clarification have been resolved.

2.4.5. Conclusions on clinical pharmacology

The applicant has not conducted a comprehensive investigation of the PK of ATV/COBI and relies on demonstrating bioequivalence of ATV in ATV/COBI FDC compared to ATV capsule coadministered with a COBI tablet. In addition PK data bridging ATV co-administered with COBI with ATV co-administered with low-dose ritonavir (RTV) is provided. This approach is considered acceptable as the pharmacokinetics of the single agents have previously been characterised.

Overall, there are no major concerns regarding the PK of this FDC and all points for clarification have been resolved.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

No dose response study was conducted. The clinical programme of ATV/COBI is primarily based on a pharmacokinetic bridging clinical programme based on demonstrating the bioequivalence of ATV when co-administered with COBI either as the FDC (formulation G006) or the single agents under fed conditions. Two studies have been conducted in which ATV and COBI were administered as part of the regimen; GS-US-216-0105 and GS-US-216-0114.

Study GS-US-216-0114

Title of Study: A Phase 3, randomised, double-blind study to evaluate the safety and efficacy of GS-9350 (COBI)-boosted Atazanavir compared with ritonavir-boosted Atazanavir administered with Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 infected, antiretroviral treatment-naive adults

Study participants

During the randomized, blinded phase of the study through Week 48, continuing to Week 96, the following study drugs were administered orally, once daily, with food, at approximately the same time each day:

Treatment Group 1:

COBI (1 x 150-mg tablet) + ATV (1 x 300-mg capsule) + TVD (FTC/TDF 200/300 mg; 1 x tablet) + RTV placebo (1 x 100 mg tablet)

Treatment Group 2:

RTV (1 x 100-mg tablet) + ATV (1 x 300-mg capsule) + TVD (FTC/TDF 200/300 mg; 1 x tablet) + COBI placebo (1 x 150-mg tablet)

Objectives

The primary objective of this study was to evaluate the efficacy of a regimen containing ATV/co versus ATV/r, each administered with TVD, in HIV-1 infected, antiretroviral treatment-naive adult subjects as determined by the achievement of HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 48 . The primary efficacy endpoint was evaluated in the Week 48 interim analysis and evaluated in the Weeks 96 and 144 interim analyses.

The secondary objective of this study (evaluated beyond Week 48) was to evaluate the efficacy, safety, and tolerability of the 2 treatment regimens through 192 weeks of treatment

Outcomes/endpoints

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot analysis algorithm.

Secondary efficacy endpoints were as follows:

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 192, as defined by the snapshot algorithm
- The achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48 and 192, as defined by the time to loss of virologic response (TLOVR) algorithm

Sample size

A total sample size of 700 HIV-1 infected subjects randomized in a 1:1 ratio to 2 treatment groups (350 subjects per group) was considered to have at least 95% power to establish non-inferiority with respect to the response rate of HIV-1 < 50 copies/mL at Week 48 between the 2 treatment groups, as defined by the Food and Drug Administration (FDA) snapshot analysis. For sample size and power computations it was assumed that both treatment groups would have a response rate of 0.795 (based on Gilead Study GS-01-934), that the non-inferiority margin was 0.12, and that the significance level of the test was at a 1-sided, 0.025 level. Calculations were made using the software package Query Advisor, Version 6.0.

Randomisation

Subjects were randomized in a 1:1 ratio to Treatment Group 1 or Treatment Group 2. Randomization was stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening.

Blinding (masking)

The IVRS/IWRS assigned blinded study drug bottle numbers at each study visit (except Week 2). Study drug (COBI/RTV and matching placebos) was dispensed to subjects in a blinded fashion.

Statistical methods

Analysis populations for efficacy analyses were defined as follows:

Randomised Analysis Set

Included all randomised subjects (as statistical analysis plan).

Intent-to-Treat Analysis Set

For efficacy analyses using the ITT analysis set subjects were grouped by randomised treatment. The ITT analysis set included all randomised who received at least 1 dose of study drug. This was the primary analysis set for efficacy analyses.

Per Protocol Analysis Set

For efficacy analyses using the per protocol (PP) analysis set subjects were grouped by actual treatment received. The PP analysis set included all randomised who received at least 1 dose of study drug and had no major protocol violation (including violation of major entry criteria). For the PP analysis set, efficacy data were summarised up to the last dose date of blinded study drug. The PP analysis set was the secondary analysis set for the primary endpoint. Subjects meeting any of the following criteria were excluded from the PP analysis set:

Discontinued study drug prior to/on the upper bound of the Week 48 analysis window due to reasons other than lack of efficacy and the assessments of HIV-1 RNA on randomised treatment were not available in the Week 48 analysis window. Lack of efficacy was defined as having the check-box for “Lack of Efficacy” marked as the reason for study drug discontinuation on the study drug completion electronic Case Report Form (eCRF) page.

- Did not discontinue study drug prior to/on the upper bound of the Week 48 analysis window but assessments of HIV-1 RNA on randomised treatment were not available in the Week 48 analysis window
- Did not have documented sensitivity to FTC, TDF and ATV in a screening genotype report

- Received ongoing therapy with any of the forbidden medications
- Had an adherence rate for active study drug below the 2.5th percentile
- Took antiretroviral medication other than randomised study drug consecutively for ≥ 4 weeks prior to the Week 48 HIV-1 RNA assessment
- Interrupted study drug for ≥ 4 consecutive weeks prior to the Week 48 HIV-1 RNA assessment
- Had missing HIV-1 RNA assessments in 3 consecutive scheduled visits prior to the Week 48 HIV-1 RNA assessment

Interim analyses

The first interim analysis took place after the first 350 subjects either completed the Week 12 visit or prematurely discontinued study drugs.

The Week 24 IDMC analysis was conducted after the last subject either completed the Week 24 visit or prematurely discontinued study drugs.

Primary Analysis

The currently reported Week 48 interim analysis was conducted after all randomised subjects either completed their Week 48 study visit or prematurely discontinued study drugs before their Week 48 visit. The last subject completed the Week 48 visit on 31 October 2011. The database was finalised on 01 December 2011 and included all data through Week 48 and available data collected after the Week 48 visit. The Week 48 analysis data cut included all eCRF data collected up to 31 October 2011 and all laboratory, virology and PK data through 01 December 2011. Further interim analyses were provided during the evaluation and are presented later in this section.

The non-inferiority evaluation of proportions that achieved HIV-1 RNA < 50 copies/mL at Week 48 (FDA-defined snapshot approach) was the pre-specified primary comparison.

In light of the interim IDMC analyses at Weeks 12 and 24, the alpha level for the Week 48 analysis was adjusted to 0.048. The sponsor did not have a prior intent to ask the IDMC to consider early termination of the study even if there was early evidence of favourable efficacy. Since there was no intent to stop the study early, the Haybittle procedure was used as a stopping rule.

An alpha penalty of 0.001 was applied for each interim analysis performed by the IDMC. Therefore, for the primary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.

A Week 48 it was intended that the IDMC analysis would be performed at the same time as the primary efficacy endpoint was analysed and on this basis no alpha penalty was applied as the same data were used for this and for the primary analysis.

Snapshot Analysis Algorithm

In the snapshot analysis for the Week 48 virological outcome, the analysis window was defined from Days 309 to 378 inclusive. All the HIV-1 RNA data collected on treatment (prior to or on the last dose date of study drug) were used in the snapshot analysis. Virological outcome was defined as:

Virological Success: last available HIV-1 RNA < 50 copies/mL in the Week 48 analysis window

Virological Failure: last available HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window OR did not have on-treatment HIV-1 RNA data in the Week 48 analysis window due to either of:

1) discontinuation of study drug for lack of efficacy

2) discontinuation of study drug for reasons other than an AE, death or lack of efficacy AND last available HIV-1 RNA value on treatment was ≥ 50 copies/mL

No Virological Data in the Week 48 analysis window: no on-treatment HIV-1 RNA data in the Week 48 analysis window because:

1) study drug was discontinued due to AE or death (regardless of last available HIV-1 RNA)

2) study drug was discontinued due to reasons other than AE/death and lack of efficacy and the last available HIV-1 RNA value on treatment was < 50 copies/mL

3) missing data during the window but remained on study drug

The baseline HIV-1 RNA stratum (≤ 100,000 copies/mL or > 100,000 copies/mL)-weighted difference in the response rate (P1 – P2) and its 95% CI were calculated based on stratum-adjusted Mantel-Haenszel (MH) proportion.

Non-inferiority margin

It was concluded that ATV/COBI + TVD was non-inferior to the comparative regimen if the lower bound of the 2-sided 95% CI of the difference in the response rate (ATV/COBI – ATV/RTV group) was > −12%. If non-inferiority was established, the same 95% CI used to evaluate non-inferiority was used to evaluate superiority using the ITT analysis set. The superiority of ATV/COBI over comparator was established if the lower bound of the 95% CI was greater than 0. The baseline HIV-1 RNA stratum (≤ 100,000 copies/mL or > 100,000 copies/mL)-weighted, 2-sided CMH test was also used to assess superiority as a supportive analysis.

Secondary and Sensitivity Analyses for the Primary Efficacy Endpoint

A secondary analysis based on the PP analysis set was to evaluate the robustness of the primary analysis of the primary endpoint. Subjects excluded from the PP analysis set were determined before database lock.

In addition, a series of sensitivity analyses were performed using the ITT analysis set to evaluate the robustness of the primary analysis of the primary endpoint:

- For the first sensitivity analysis, subjects who had no HIV-1 RNA data in the Week 48 analysis window due to study drug discontinuation for reasons other than lack of efficacy, AEs or death and whose last available on-treatment HIV-1 RNA value was < 50 copies/mL were excluded from the numerator and denominator in the response rate computation. Additionally, for late discontinuation (i.e. discontinuation of study drug due to reasons other than death in the Week 48 analysis window) all the HIV-1 RNA data in the Week 48 analysis window including data collected after the last dose of study drug were included in the evaluation of virological response per the FDA-defined snapshot algorithm.
- As a second sensitivity analysis, subjects who had no HIV-1 RNA data in the Week 48 analysis window due to study drug discontinuation for reasons other than lack of efficacy, AEs, or death and whose last available on-treatment HIV-1 RNA value was < 50 copies/mL were counted in the virological success category. HIV-1 RNA data collected after the last dose of study drug for late discontinuation were handled in the same way as in the first sensitivity analysis.
- The last sensitivity analysis was to assess whether the treatment effect was confounded by region and baseline plasma HIV-1 RNA level. The following analyses were performed for the primary endpoint: (1) stratifying by region and (2) without any stratification factors. The results were

compared with the primary analysis (i.e. stratified by baseline HIV-1 RNA level). The stratified CMH analyses were used to estimate the odds ratio, the corresponding 95% CI and to obtain p-values. A region was defined as multiple sites combined based on sites from the neighbouring counties states in the US.

TLOVR Algorithm

The outcome variable for the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Week 48 (responder) was derived using all available HIV-1 RNA data (including unscheduled data, post-Week 48 data and 30-day follow-up data) based on the FDA-defined TLOVR algorithm.

Table 14. GS-US-216-0114: Disposition of Subjects (All Screened Subjects)

Subject Disposition[a, b, c]	ATV/co+TVD	ATV/r+TVD	Total
Subjects Screened			867
Screen Failure Subjects Who Were Not Randomized			169
Subjects Randomized	349	349	698
Rescreened	4	0	4
Screen Failures	1	0	1
Subjects Randomized but Never Treated	5	1	6
Subjects in Safety Analysis Set	344	348	692
Subjects in Intent-to-Treat (ITT) Analysis Set	344	348	692
Subjects Still on Study Treatment up to the Week 48 Analysis Data Cut Date	294 (85.5%)	309 (88.8%)	603 (87.1%)
Subjects Prematurely Discontinuing Study Treatment prior to the Week 48 Analysis Data Cut Date	50 (14.5%)	39 (11.2%)	89 (12.9%)
Reasons for Prematurely Discontinuing Study Treatment			
Adverse Event	25 (7.3%)	25 (7.2%)	50 (7.2%)
Death	0	0	0
Pregnancy	1 (0.3%)	3 (0.9%)	4 (0.6%)
Lack of Efficacy	2 (0.6%)	0	2 (0.3%)
Investigator's Discretion	3 (0.9%)	1 (0.3%)	4 (0.6%)
Withdrew Consent	4 (1.2%)	2 (0.6%)	6 (0.9%)
Lost to Follow-Up	11 (3.2%)	4 (1.1%)	15 (2.2%)
Subject Non-Compliance	4 (1.2%)	3 (0.9%)	7 (1.0%)
Protocol Violation	0	1 (0.3%)	1 (0.1%)
Study Discontinued by Sponsor	0	0	0
Subjects Still on Study up to the Week 48 Analysis Data Cut Date	310 (90.1%)	327 (94.0%)	637 (92.1%)
Subjects Prematurely Discontinuing from Study prior to the Week 48 Analysis Data Cut Date	34 (9.9%)	21 (6.0%)	55 (7.9%)
Reasons for Prematurely Discontinuing from Study			
Adverse Event	13 (3.8%)	9 (2.6%)	22 (3.2%)
Death	0	0	0
Pregnancy	0	2 (0.6%)	2 (0.3%)
Lack of Efficacy	1 (0.3%)	0	1 (0.1%)
Investigator's Discretion	2 (0.6%)	1 (0.3%)	3 (0.4%)
Withdrew Consent	3 (0.9%)	3 (0.9%)	6 (0.9%)
Lost to Follow-Up	13 (3.8%)	4 (1.1%)	17 (2.5%)
Subject Non-Compliance	2 (0.6%)	2 (0.6%)	4 (0.6%)
Protocol Violation	0	0	0
Study Discontinued by Sponsor	0	0	0

a The denominator for percentages is based on the number of subjects in the safety analysis set.
b The number of screen failures is counted by unique subject based on the date of birth, race, ethnicity, and initials.
c CRF data collected up to 31OCT2011 (except for Subject 5131-8564, CRF data collected up to 28NOV2011) were included in the Week 48 analysis data cut, including data collected after the Week 48 visit.

Conduct of the study

There were three protocol amendments after study initiation and four administrative letters were issued. These occurred before unblinding the week 48 dataset. Two of these amendments were specific to study sites in France and concerned:

- Details of the management of subjects with virological failure made in response to a request from the French Ethics Committee. These details were not applied to the original protocol outside France.
- The first exclusion criterion was revised to clarify that subjects with an AIDS-defining diagnosis of a CD4-positive T lymphocyte count < 200/ìL or a CD4-positive T lymphocyte count < 14% of the total lymphocyte count were not excluded from participation in the study.

The documentation does not provide details of the third amendment mentioned in the study report.

Baseline data

The majority of subjects in the safety analysis set were male (82.9%), with a mean age of 37 years (range, 19 to 70 years); most were white (59.7%) or black (18.5%), and non-Hispanic/Latino (71.8%). The mean value for BMI at baseline was 25.1 kg/m2.

The mean (SD) baseline HIV-1 RNA value was 4.83 (0.589) log10 copies/mL, CD4 count was 352 (172.9) cells/ìL, and CD4% was 20.6% (8.57). Overall, 60.3% of subjects had baseline HIV-1 RNA ≤ 100,000 copies/mL. The most common HIV risk factor category was homosexual sex (65.5% of subjects). The majority of subjects (83.4%) had asymptomatic HIV-1 infection, 9.1% of subjects had symptomatic HIV-1 infection, and 7.5% of subjects had been diagnosed with AIDS. A small percentage of subjects were HBsAg positive (3.6%) or HCV seropositive (5.3%). Overall, the mean (SD) baseline eGFR was 117.2 (30.08) mL/min using the CG method, 102.4 (18.73) mL/min/1.73m2 using the MDRD method, and 100.8 (21.11) mL/min/1.73m2 using the CysC method. There were no significant differences between treatment groups in baseline eGFR using CG, MDRD, or CysC methods.

Numbers analysed

Of the 698 subjects who were randomized, 692 were included in the safety and ITT analysis sets and 599 were included in the PP analysis set. Of the 99 subjects excluded from the PP analysis set, 81 discontinued study drugs prior to the Week 48 analysis window for reasons other than lack of efficacy. Other reasons for exclusion from the PP analysis set are summarised in Table 15.

A total of 48 subjects were included in the analysis set for the intensive PK sub-study (22 in the ATV/co+TVD group and 26 in the ATV/r+TVD group).

There were 106 important protocol deviations in 88 subjects of which 73 had a single important deviation, 12 had two and 3 subjects had 3 deviations.

Protocol deviations were proportionally distributed between treatment groups and study centres and the majority were due to non-adherence (< 70% adherence at any visit based on pill count). Overall 24 subjects violated a single eligibility criterion of which most were due to CD4 counts < 200 cells/ìL at the screening visit that were identified after treatment had commenced; these subjects did not have any other AIDS-defining condition and were not discontinued.

Outcomes and estimation

Virologic Outcome at Week 48 Using Snapshot Analysis and HIV-1 RNA < 50 copies/mL

Virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis in the ITT analysis set

At Week 48, 85.2% of subjects (293 of 344) in the ATV/co+TVD group and 87.4 % of subjects (304 of 348) in the ATV/r+TVD group had virologic success (ITT analysis set). The difference in the percentages of subjects with virologic success was −2.2% (95% CI: −7.4% to 3.0%). Since the lower bound of the 2-sided 95% CI of the baseline HIV-1 RNA stratum weighted difference in response rates (ATV/co+TVD – ATV/r+TVD) was greater than the pre-specified –12% non-inferiority margin, ATV/co+TVD was demonstrated to be non-inferior to ATV/co+TVD.

At Week 48, 5.8% of subjects (20 of 344) in the ATV/co+TVD group and 4.0% of subjects (14 of 348) in the ATV/r+TVD group had virologic failure; 9.0% of subjects (31 of 344) in the ATV/co+TVD group and 8.6% of subjects (30 of 348) in the ATV/r+TVD group had no virologic data in the Week 48 analysis window. Reasons for virologic failure and lack of virologic data in the Week 48 analysis window were balanced between the treatment groups.

Table 15. GS-US-216-0114: Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis, ITT Analysis Set)

			ATV/co+TVD vs. ATV/r+TVD	
Time Point HIV-1 RNA Category	ATV/co+TVD (N=344)	ATV/r+TVD (N=348)	p-value[a]	Difference in Percentages (95.2% CI)[b]
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	293 (85.2%)	304 (87.4%)	0.40	-2.2% (-7.4% to 3.0%)
Virologic Failure at Week 48	20 (5.8%)	14 (4.0%)		
HIV-1 RNA >= 50 copies/mL	6 (1.7%)	7 (2.0%)		
Discontinued Study Drug Due to Lack of Efficacy	1 (0.3%)	0		
Discontinued Study Drug Due to Other Reasons[c] and Last Available HIV-1 RNA >= 50 copies/mL	13 (3.8%)	7 (2.0%)		
No Virologic Data in Week 48 Window[d]	31 (9.0%)	30 (8.6%)		
Discontinued Study Drug Due to AE/Death	22 (6.4%)	23 (6.6%)		
Discontinued Study Drug Due to Other Reasons[c] and Last Available HIV-1 RNA < 50 copies/mL	9 (2.6%)	7 (2.0%)		
Missing Data during Window but on Study Drug	0	0		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum.
b Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.
d Week 48 window is between Day 309 and 378 (inclusive).

Non-inferiority was also demonstrated in the PP analysis set although actual success rates were higher. At Week 48, 98.0% of subjects (289 of 295) in the ATV/co+TVD group and 98.0% of subjects (298 of 304) in the ATV/r+TVD group had virologic success. The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success was −0.1% (95% CI: −2.5% to 2.3%)

Table 16. Virologic Outcome at Week 48 (HIV-1 RNA Cut-off at 50 copies/mL, Snapshot analysis) PP Analysis Set

			ATV/co +TVD vs ATV/r + TVD	
	ATV/co + TVD (N=295)	ATV/r + TVD (N=304)	p-value	Difference in percentages (95.2% CI)
Virologic success at Week 48 HIV-1 RNA < 50 cp/mL	289 (98.0%)	298 (90.0%)	0.95	-0.1% (-2.5% to 2.3%)
Virologic failure at Week 48 HIV-1 RNA ≥ 50 cp/mL Discontinued due lack of efficacy Discontinued due to other reasons and last available HIV-RNA ≥ 50 cp/mL	6 (2.0%) 5 (1.7%) 1 (0.34%) 0	6 (2.0%) 6 (2.0%) 0 0		
No virologic data in Week 48 window Discontinued study due to AE/death Discontinued due to other reasons and last available HIV-RNA > 50 cp/mL Missing data during window while on study drug	0 0 0 0	0 0 0 0		

Sensitivity analysis of the primary endpoint demonstrated the following:

- After excluding study drug discontinuations not related to virologic response and included all HIV-1 RNA data for late discontinuation (ITT analysis set). At Week 48, 87.5% of subjects (294 of 344) in the ATV/co+TVD group and 89.4% of subjects (305 of 348) in the ATV/r+TVD group had virologic success. The HIV-1 RNA stratum-weighted difference in the percentage of subjects with virologic success was −2.0% (95% CI: −6.9% to 2.8%).
- Including study drug discontinuations not related to virologic response as virologic successes and included all HIV-1 RNA data for late discontinuation (ITT analysis set). At Week 48, 87.8% of subjects (302 of 344) in the ATV/co+TVD group and 89.7% of subjects (312 of 348) in the ATV/r+TVD group had virologic success. The difference in the percentages of subjects with virologic success was −1.9% (95% CI: −6.7% to 2.8%)
- After evaluating the impact of stratification factors (baseline HIV-1 RNA level and region) on the treatment effect at Week 48 (ITT analysis set) The baseline HIV-1 RNA level-adjusted odds ratio (ATV/co+TVD vs ATV/r+TVD) for achieving HIV-1 RNA < 50 copies/mL was 0.83 (95% CI: 0.54 to 1.28) and the region-adjusted odds ratio was 0.81 (95% CI: 0.52 to 1.26), both of which were similar to the unadjusted odds ratio of 0.83 (95% CI: 0.54 to 1.28)

Achievement and Maintenance of HIV-1 RNA < 50 copies/mL Through Week 48

Virologic Outcome, TLOVR Analysis

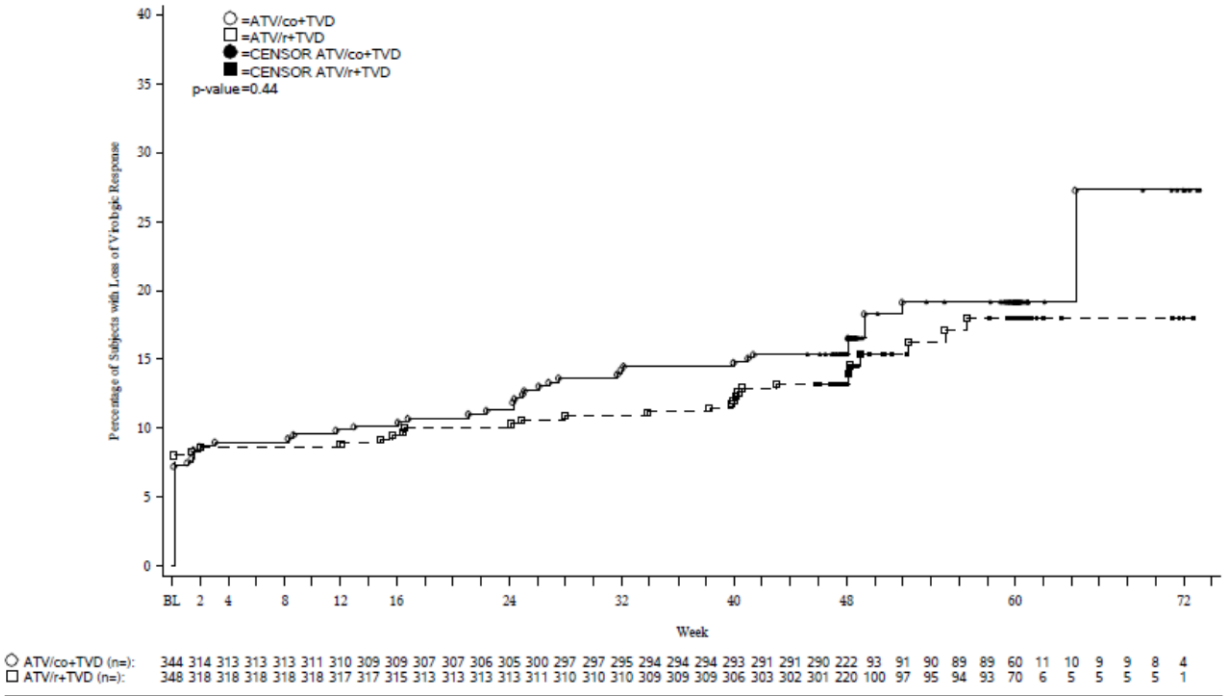
A total of 82.8% of subjects (285 of 344) in the ATV/co+TVD group and 85.3% of subjects (297 of 348) in the ATV/r+TVD group achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48 and were considered responders. The HIV-1 RNA stratum-weighted difference in the percentage of responders at Week 48 was −2.6% (95% CI: −8.1% to 2.8%), indicating that ATV/co+TVD was non-inferior to ATV/r+TVD using the TLOVR algorithm.

Percentages of non-responders were similar between the 2 treatment groups . At Week 48, 3.5% of subjects (12 of 344) in the ATV/co+TVD group and 4.0% of subjects (14 of 348) in the ATV/r+TVD group had confirmed viral rebound or never achieved viral suppression through Week 48 and were considered non-responders. Similar percentages of subjects in each treatment group were considered non-responders due to death or study drug discontinuation.

Time to Loss of Virologic Response

In the Kaplan Meier analysis of TLOVR, the percentage of subjects with loss of virologic response was similar between treatment groups. At Week 48, 19% of subjects in the ATV/COBI +TVD group and 16% of subjects in the ATV/rtv +TVD group had loss of virologic response (overall p-value = 0.44).

Figure 2. GS-US-216-0114: Time to Loss of Virologic Response with HIV-1 RNA Cut-off at 50 copies/mL (Kaplan-Meier Estimate) (ITT Analysis Set)



Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48

In the M = F analysis, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL was similar in the ATV/co + TVD group and the ATV/r + TVD group from Week 2 through Week 48. At Week 48, the percentage of subjects with plasma HIV-1 RNA levels < 50 copies/mL was 89.0% (306 of 344 subjects) in the ATV/co + TVD group and 89.7% (312 of 348 subjects) in the ATV/r + TVD group. The stratum-weighted difference in response rate between treatment groups (ATV/co +TVD − ATV/r + TVD) was −0.7% (95% CI: −5.4% to 3.9%), indicating that ATV/co + TVD was non-inferior to ATV/r +T VD using the M = F method.

In the M = E analysis, the percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 was 97.1% (306 of 315 subjects) in the ATV/co+TVD group and 96.0% (312 of 325 subjects) in the ATV/r+TVD group. The stratum-weighted difference in the response rate between treatment groups (ATV/co+TVD − ATV/r+TVD) was 1.1% (95% CI: −1.8% to 4.1%), indicating that ATV/co+TVD was non-inferior to ATV/r+TVD using the M = E method.

Change from Baseline in Plasma HIV-1 RNA

Mean (SD) baseline HIV-1 RNA levels were 4.81 (0.585) $\log_{10}$ copies/mL in the ATV/co+TVD group and 4.84 (0.594) $\log_{10}$ copies/mL in the ATV/r+TVD group. HIV-1 RNA levels decreased following administration of study drug, and the mean decreases were similar in the ATV/co+TVD group and the ATV/r+TVD group at all time-points (Week 2 through Week 48). At Week 48, the mean (SD) decreases from baseline in HIV-1 RNA were −3.08 (0.658) $\log_{10}$ copies/mL in the ATV/co+TVD group and −3.09 (0.731) log10 copies/mL in the ATV/r+TVD group. The difference in least-squares means (LSM) was −0.01 (95% CI: −0.09 to 0.07).

Change from Baseline in CD4 Cell Count at Week 48

Mean (SD) baseline CD4 cell counts were 353 (170.5) cells/ìL in the ATV/co+TVD group and 351 (175.5) cells/ìL in the ATV/r+TVD group. CD4 counts increased following administration of study drug, and the mean increases were similar between the ATV/co+TVD and ATV/r+TVD groups at all time-points through Week 48. At Week 48, the mean (SD) increases from baseline in CD4 cell count were 213 (151.0) cells/ìL in the ATV/co+TVD group and 219 (150.4) cells/ìL in the ATV/r+TVD group. The difference in LSM from an ANOVA model was −5 (95% CI: −28 to 18).

Change from Baseline in CD4 Percentage at Week 48

In the ITT analysis set, mean (SD) baseline CD4% was 20.4% (8.72) in the ATV/co+TVD group and 20.8% (8.42) in the ATV/r+TVD group. CD4% increased following administration of study drug, and the mean increases were similar between the 2 groups. At Week 48, the mean (SD) increases from baseline in CD4% were 9.7% (4.79) in the ATV/co+TVD group and 9.8% (5.27) in the ATV/r+TVD group. The difference in LSM was 0.0 (95% CI: −0.8 to 0.8).

Additional Efficacy data provided during the evaluation

Study GS-US-216-0114 is an ongoing, Phase 3, randomized, double-blind, multicenter, active controlled study evaluating the efficacy and safety of COBI-boosted ATV versus ritonavir- boosted ATV in antiretroviral treatment-naive adult subjects with HIV-1 infection. A total of 698 subjects were randomized to receive ATV/co+TVD or ATV+RTV+TVD (349 subjects in each group) for 192 weeks. The intent-to-treat (ITT) analysis set included a total of 692 subjects who received at least one dose of study drug (ATV/co+TVD 344 subjects, ATV+RTV+TVD 348 subjects).

The primary efficacy endpoint was the percentage of subjects with virologic success (HIV RNA < 50 copies/mL) at Week 48 using the US Food and Drug Administration (FDA) defined snapshot analysis algorithm. The primary efficacy endpoint was evaluated in the Week 48 interim analysis and evaluated again in the Weeks 96 and 144 interim analyses. The interim Week 144 efficacy results are summarized in this section.

Percentage of Subjects with HIV-1 RNA Cutoff at 50 copies/mL at Week 144

High rates of virologic success were seen in both treatment groups at Week 144 in Study GS-US-216-0114 using the FDA-defined snapshot analysis algorithm with HIV 1 RNA < 50 copies/mL for the ITT analysis set (ATV/co+TVD 72.1%, 248 of 344 subjects; ATV+RTV+TVD 74.1%, 258 of 348 subjects). The difference in the percentages of subjects with virologic success was –2.1% (95% confidence interval [CI]: -8.7% to 4.5%).

Subgroup analyses at Week 144 based on the FDA-defined snapshot analysis algorithm revealed high and generally comparable rates of virologic success between treatment groups within subgroups according to age, sex, race, baseline HIV 1 RNA level, baseline CD4 cell count, and study drug adherence rate.

Table 17. GS-US-216-0114: Virologic Outcome at Week 144 (HIV 1 RNA Cutoff at 50 copies/mL, Snapshot Analysis Algorithm, ITT Analysis Set, Week 144 Dataset)

	Number of Subjects (%)			
HIV-1 RNA Category	ATV/co+TVD (N=344)	ATV+RTV +TVD (N=348)	ATV/co+TVD vs. ATV+RTV +TVD p-value[a]	Difference in Percentages (95% CI)[b]
Virologic Success at Week 144				
HIV-1 RNA < 50 copies/mL	248 (72.1)	258 (74.1)	0.53	-2.1 (-8.7 to 4.5)
Virologic Failure at Week 144	28 (8.1)	17 (4.9)	--	--
HIV-1 RNA >= 50 copies/mL	10 (2.9)	6 (1.7)	--	--
Discontinued Study Drug Due to Lack of Efficacy	3 (0.9)	0	--	--
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[c]	15 (4.4)	11 (3.2)	--	--
No Virologic Data in Week 144 Window[d]	68 (19.8)	73 (21.0)	--	--
Discontinued Study Drug Due to AE/Death	38 (11.0)	38 (10.9)	--	--
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	29 (8.4)	34 (9.8)	--	--
Missing Data during Window but on Study Drug	1 (0.3)	1 (0.3)	--	--

aP-value for the superiority test comparing the percentages of virologic success was from the Cochran-Mantel- Haenszel (CMH) test stratified by baseline HIV-1 RNA stratum.
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion
c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy
d Week 144 window is between Day 967 and Day 1050 (inclusive)

Percentage of Subjects with HIV-RNA < 50 copies/mL at Week 144

Using the missing = failure (M=F) method, the percentage of subjects in Study GS-US-216-0114 with HIV-1 RNA levels < 50 copies/mL was similar in each treatment group through Week 144 (Week 144: ATV/co+TVD 77.3%, 266 of 344 subjects; ATV+RTV+TVD 80.2%, 279 of 348 subjects). The stratum-weighted difference in response rate between treatment groups at Week 144 (ATV/co+TVD – ATV+RTV+TVD) was –2.9% (95% CI: –9.0% to 3.2%). While using the missing = excluded (M=E) method, the percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 144 was similar in the 2 treatment groups (ATV/co+TVD 96.0%, 266 of 277 subjects; ATV+RTV+TVD 96.9%, 279 of 288 subjects). The stratum-weighted difference in the response rate between treatment groups (ATV/co+TVD – ATV+RTV+TVD) was –0.8% (95% CI: –4.0% to 2.4%)

Change from Baseline in CD4 Cell Count

CD4 cell counts increased following initiation of study drug, and the mean increases were generally similar in the 2 treatment groups through Week 144 of Study GS-US-216-0114. The mean (SD) increases from baseline using the M=E method were 310 (188.0) cells/µL for ATV/co+TVD and 332 (199.9) cells/µL for ATV+RTV+TVD.

Similar increases were observed when using the last observation carried forward (LOCF) imputation method (ATV/co+TVD 281 [199.0] cells/µL; ATV+RTV+TVD 297 [208.1] cells/µL). The CD4 cell counts continued to increase with increased duration of exposure to study drug.

Summary of Clinical Resistance Findings

Of the 692 randomized and treated subjects in Study GS-US-216-0114, 40 subjects (5.9%) with either suboptimal virologic response or virologic rebound were analyzed for resistance development through Week 144 (ATV/co+TVD 21 of 344, 6.1%; ATV+RTV+TVD 19 of 348, 5.5%).

Resistance development to 1 or more components of ATV/co+TVD or ATV+RTV+TVD occurred infrequently in this study. Three subjects (3 of 344, 0.9%) in the ATV/co+TVD group developed a resistance mutation to emtricitabine (FTC). Two subjects developed M184V and phenotypic resistance to FTC. One subject developed M184V as a mixture with wild-type with no phenotypic resistance to FTC. One subject (1 of 348, 0.3%) in the ATV+RTV+TVD group developed M184V and phenotypic resistance to FTC. No subject developed K65R or K70E in the reverse transcriptase gene and/or phenotypic resistance to TDF in either treatment group. There was no development of primary protease inhibitor resistance (PI-R) mutations within either treatment group.

Summary of main efficacy study

Table 18 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 18. Summary of efficacy for trial

Title: A Phase 3, randomised, double-blind study to evaluate the safety and efficacy of GS-9350 (COBI)-boosted Atazanavir compared with ritonavir-boosted Atazanavir administered with Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 infected, antiretroviral treatment-naive adults		
Study identifier	**Study GS-US-216-0114**	
Design	Phase 3, randomised, double-blind study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks not applicable 192 weeks
Hypothesis	Non-inferiority	
Treatments groups	Treatment Group 1:	COBI (1 x 150-mg tablet) + ATV (1 x 300-mg capsule) + TVD (FTC/TDF 200/300 mg; 1 x tablet) + RTV placebo (1 x 100 mg tablet) number randomized:
	Treatment Group 2:	RTV (1 x 100-mg tablet) + ATV (1 x 300-mg capsule) + TVD (FTC/TDF 200/300 mg; 1 x tablet) + COBI placebo (1 x 150-mg tablet) <number randomized>

Endpoints and definitions	Primary endpoint	percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot analysis algorithm
	Secondary endpoint	The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 192, as defined by the snapshot algorithm
	Secondary endpoint	The achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48 and 192, as defined by the time to loss of virologic response (TLOVR) algorithm (described below)

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Treatment Group 1:	Treatment Group 2:
	Number of subjects	344	349
	Percentage virologic success at week 48 HIV-1 RNA<50 copies/ml	293 (85.2%)	304 (87.4%)
	Achievement and Maintenance of HIV-1 RNA < 50 copies/mL Through Week 48	285 (82.8%)	297 (85.3%)
	The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 144, as defined by the snapshot algorithm	248 (72,1%)	258 (74,1%)

Supportive study

Study GS-US-216-0105

A Phase 2, randomised, double-blinded study conducted to assess the safety and efficacy of GS-9350 (COBI)-boosted Atazanavir (ATV/GS-9350) compared to ritonavir-boosted Atazanavir (ATV/r) in Combination with Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF) in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults.

Subjects enrolled in this study were HIV-1 infected, antiretroviral treatment-naive subjects who met the following criteria:

- Plasma HIV-1 RNA levels ≥ 5000 copies/mL at screening
- Cluster determinant 4 (CD4) cell count > 50 cells/ìL
- No prior use of any approved or experimental anti-HIV drug
- No nucleoside or nucleotide reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI) or primary protease inhibitor (PI) resistance mutations (by current International Antiviral Society-United States of America [IAS-USA] guidelines [December 2008]) in a screening genotype report

Treatments

Treatment Group 1: COBI 150 mg once daily + RTV placebo once daily + ATV 300 mg once daily + TVD (single-tablet FTC/TDF 200/300 mg) once daily (n = 50)

Treatment Group 2: RTV 100 mg once daily + COBI placebo once daily + ATV 300 mg once daily + TVD (single-tablet FTC/TDF 200/300 mg) once daily (n = 25)

Objectives

The primary objective of this study was as follows:

- To evaluate the efficacy of a regimen containing COBI-boosted ATV (ATV/co)+TVD versus RTV-boosted ATV (ATV/r)+TVD in HIV-1 infected, antiretroviral treatment naive adult subjects as determined by the achievement of HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 24

The secondary objectives of this study were as follows:

- To evaluate the efficacy of a regimen containing ATV/co+TVD versus ATV/r+TVD in HIV-1 infected, antiretroviral treatment-naive adult subjects as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48
- To evaluate the safety and tolerability of the 2 treatment regimens through 48 weeks of treatment

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24.

The secondary efficacy endpoints included:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48

- The change from baseline in $\log_{10}$ HIV-1 RNA and in CD4 cell count at Weeks 24 and 48 Subjects who experienced either suboptimal virologic response or virologic rebound were considered to have virologic failure, and had their HIV-1 genotype/phenotype analysed using PhenoSense GT Assay.

Pharmacokinetics

An intensive PK sub-study was performed at the Week 2, 4, or 8 visit in a subset of subjects (target n = 24 evaluable) at selected study sites. A single trough (pre-dose) PK blood sample was collected for all subjects 20 to 24 hours following an observed (in clinic) dose of study drugs at Weeks 8, 24, and 48. In addition, a single PK blood sample was collected at Weeks 2, 4, 12, 16, 32, and 40 for non-sub-study subjects. The PK of ATV, COBI, COBI metabolites, FTC, TFV, and RTV were explored.

Sample size

A sample size of 50 subjects in the COBI group (Treatment Group 1) was chosen to estimate the response rate of HIV-1 RNA < 50 copies/mL at Week 24 for the regimen to allow for the planning of Phase 3 studies. A total sample size of 75 subjects has 26% power to evaluate non-inferiority with respect to the response rate of HIV-1 RNA < 50 copies/mL at Week 24 if a response rate of 84% for both groups and a non-inferiority margin of 0.12 are assumed. A total of 85 subjects were actually enrolled in the study, with 79 subjects dosed, 4 subjects more than the sample size planned (75 subjects).

Randomisation

Subjects were randomized in a 2:1 ratio to Treatment Group 1 or Treatment Group 2. Randomization was stratified by HIV-1 RNA level (≤100,000 copies/mL or > 100,000 copies/mL) at screening. A block size of 6 subjects was used for randomisation.

Statistical methods

The primary analysis of efficacy was based on the ITT analysis set for randomized treatment groups. The secondary analysis of efficacy was based on the PP analysis set. The primary efficacy endpoint, the number and percentage of subjects with HIV-1 RNA < 50 copies/mL was summarized at Week 24.

The primary analysis for the primary efficacy endpoint was analysed using the missing equals failure (M=F) method, all missing data were considered as failure (HIV-1 RNA ≥ 50 copies/mL), and included in the denominator for calculating the percentage of subjects with HIV-1 RNA < 50 copies/mL.

The secondary analyses for the primary efficacy endpoint was analysed using missing or ART switch equals failure (M/S=F) method, in which all missing data and the HIV-1 RNA assessment data after the ART switch were considered as failure (HIV-1 RNA ≥ 50 copies/mL), and included in the denominator for calculating the percentage of subjects with HIV-1 RNA < 50 copies/mL.

In the above M=F analysis and M/S=F analysis for all ATV/co+TVD efficacy analysis set, the denominator is the number of all ATV/co+TVD efficacy analysis set. Using the missing equals excluded (M=E) method, all missing data was excluded from the percentage calculation, ie, all missing data was excluded from both the numerator and the denominator.

The primary efficacy endpoint was assessed for non-inferiority of treatment with ATV/co+TVD relative to treatment with ATV/r+TVD. Non-inferiority was assessed using a conventional 95% confidence interval (CI) approach, with a delta of 0.12

Baseline data

Table 19. GS-US-216-0105: Demographics and baseline Characteristics (Safety Analysis Set)

Characteristic[a,b]	ATV/co+TVD (N=50)	ATV/r+TVD (N=29)	Total (N=79)	ATV/co+TVD vs. ATV/r+TVD ---------- p-value
Age (years)[c]				
N	50	29	79	0.15
Mean (SD)	37 (9.6)	34 (10.1)	36 (9.8)	
Median	37	34	35	
Q1, Q3	31, 43	27, 43	28, 43	
Min, Max	19, 57	19, 55	19, 57	
Sex				
Male	47 (94.0%)	25 (86.2%)	72 (91.1%)	0.41
Female	3 (6.0%)	4 (13.8%)	7 (8.9%)	
Race				
Asian	0	2 (6.9%)	2 (2.5%)	0.20
Black	18 (36.0%)	9 (31.0%)	27 (34.2%)	
White	31 (62.0%)	16 (55.2%)	47 (59.5%)	
Other	1 (2.0%)	2 (6.9%)	3 (3.8%)	
Ethnicity				
Hispanic/Latino	7 (14.0%)	5 (17.2%)	12 (15.2%)	0.75
Non-Hispanic/Latino	43 (86.0%)	24 (82.8%)	67 (84.8%)	
Weight (kg)				
N	50	29	79	0.12
Mean (SD)	78.6 (14.34)	73.7 (12.20)	76.8 (13.72)	
Median	75.3	72.1	73.9	
Q1, Q3	65.9, 90.2	63.0, 81.6	65.3, 88.0	
Min, Max	51.7, 117.9	55.3, 109.9	51.7, 117.9	
Height (cm)				
N	50	29	79	0.68
Mean (SD)	175.5 (7.86)	174.3 (8.49)	175.0 (8.06)	
Median	175.3	175.3	175.3	
Q1, Q3	170.2, 180.3	167.6, 180.3	170.2, 180.3	
Min, Max	154.9, 195.6	154.9, 188.0	154.9, 195.6	
Body Mass Index (kg/m^2)				
N	50	29	79	0.12
Mean (SD)	25.5 (4.07)	24.5 (5.44)	25.1 (4.61)	
Median	25.4	23.6	24.5	
Q1, Q3	22.7, 27.8	21.0, 25.8	21.9, 27.0	
Min, Max	17.3, 35.3	18.5, 45.8	17.3, 45.8	

a Denominator for percentages was the number of subjects in the safety analysis set.
b For categorical data, p-values were from the Fisher exact test; for continuous data, p-values were from the Wilcoxon rank sum test.
c Age was calculated at first dose date of study drug.

Table 20. GS-US-216-0105: Baseline Disease Characteristics (Safety Analysis Set)

Disease Characteristic[a]	ATV/co+TVD (N=50)	ATV/r+TVD (N=29)	Total (N=79)	ATV/co+TVD vs. ATV/r+TVD p-value[b]
HIV-1 RNA (log10 copies/mL)				
N	50	29	79	0.28
Mean (SD)	4.56 (0.657)	4.69 (0.530)	4.61 (0.614)	
Median	4.51	4.61	4.58	
Min, Max	2.98, 6.02	3.48, 5.73	2.98, 6.02	
HIV-1 RNA Category (copies/mL)				
<= 100,000 copies/mL	38 (76.0%)	18 (62.1%)	56 (70.9%)	0.19
> 100,000 copies/mL	12 (24.0%)	11 (37.9%)	23 (29.1%)	
CD4 Cell Count (/uL)				
N	50	29	79	0.91
Mean (SD)	365 (201.3)	343 (178.1)	357 (192.2)	
Median	341	367	345	
Min, Max	32, 1022	49, 743	32, 1022	
CD4 Cell Count (/uL) Category				
<= 50	1 (2.0%)	1 (3.4%)	2 (2.5%)	0.93
51 - <= 200	9 (18.0%)	6 (20.7%)	15 (19.0%)	
201 - <= 350	16 (32.0%)	7 (24.1%)	23 (29.1%)	
351 - <= 500	17 (34.0%)	11 (37.9%)	28 (35.4%)	
> 500	7 (14.0%)	4 (13.8%)	11 (13.9%)	
CD4 Percentage (%)				
N	50	29	79	0.93
Mean (SD)	22.1 (8.96)	22.0 (9.25)	22.0 (9.01)	
Median	22.2	23.4	22.3	
Min, Max	4.6, 43.1	7.1, 40.6	4.6, 43.1	
HIV Risk Factors[c]				
Heterosexual Sex	10 (20.0%)	5 (17.2%)	15 (19.0%)	
Homosexual Sex	39 (78.0%)	24 (82.8%)	63 (79.7%)	
IV Drug Use	1 (2.0%)	0	1 (1.3%)	
Transfusion	0	0	0	
Vertical Transmission	0	0	0	
Unknown	1 (2.0%)	0	1 (1.3%)	
Other	0	0	0	
HIV Disease Status				
Asymptomatic	41 (82.0%)	25 (86.2%)	66 (83.5%)	0.55
Symptomatic HIV Infections	1 (2.0%)	1 (3.4%)	2 (2.5%)	
AIDS	8 (16.0%)	3 (10.3%)	11 (13.9%)	

Chronic HBV Infection Status[d]				
Negative	50 (100.0%)	29 (100.0%)	79 (100.0%)	
Chronic HCV Infection Status[d]				
Negative	50 (100.0%)	29 (100.0%)	79 (100.0%)	
Estimated Glomerular Filtration Rate by Cockcroft-Gault (CG) Formula (mL/min)				
N	50	29	79	0.62
Mean (SD)	117.1 (27.13)	121.7 (35.18)	118.8 (30.19)	
Median	109.7	113.1	112.4	
Min, Max	80.1, 216.3	56.4, 223.5	56.4, 223.5	
Estimated Glomerular Filtration Rate by Modification of Diet in Renal Disease (MDRD) Formula (mL/min/1.73 m^2)				
N	50	29	79	0.17
Mean (SD)	101.9 (18.14)	109.5 (23.88)	104.7 (20.62)	
Median	102.8	106.5	103.9	
Min, Max	70.3, 138.0	58.7, 162.8	58.7, 162.8	

a Denominator for percentages was the number of subjects in the safety analysis set.
b For ordinal data, p-values were from CMH row mean score test; for continuous data, p-values were from Wilcoxon rank sum test.
c A subject may fit more than one category of HIV Risk Factors, therefore percentages may add to more than 100.
d HBV and HCV infection statuses were determined by serology test.

Numbers analysed

Of the 85 subjects who were randomized, 79 were included in the safety and ITT analysis sets (6 subjects were randomized but were not dosed with study drug). Nine subjects were excluded from the PP analysis set due to either discontinuation of study drug prior to Week 48 (n = 8) or non-adherence to study drug (n = 1)

Outcomes and estimation

The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 (ITT, M=F) was 84.0% (42/50) in the ATV/co+TVD group and 89.7% (26/29) in the ATV/r+TVD group. The baseline HIV-1 RNA stratum-weighted difference in the response rate between the 2 treatment groups was −7.4% (95% CI: −24.6% to 9.9%; p = 0.37). Using the M/S=F method, in which 1 additional subject was considered to be a failure, the percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 was 84.0% (42/50) in the ATV/co+TVD group and 86.2% (25/29) in the ATV/r+TVD group. The baseline HIV-1 RNA stratum-weighted difference in the response rate between the 2 treatment groups was −4.4% (95% CI: −22.5% to 13.6%; p = 0.60). Using the M=E method, the percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 was 91.3% (42/46) in the ATV/co+ TVD group and 96.3% (26/27) in the ATV/r+ TVD group. The baseline HIV-1 RNA stratum-weighted difference in the response rate between the 2 treatment groups was −7.3% (95% CI: −22.3% to 7.8%; p = 0.26).

Table 21. GS-US-216-0105: Percentage of Subjects with Plasma HIV-1 RNA < 50 cp/mL at Week 24 (ITT Analysis Set)

Week 24[a, b]	ATV/co+TVD (N =50)	ATV/r+TVD (N =29)	ATV/co+TVD vs. ATV/r+TVD[c]	
			p-value[c]	Difference in Percentages (95% CI)
Missing = Failure[d]				
< 50 copies/mL	42/50 (84.0%)	26/29 (89.7%)	0.37	−7.4% (−24.6% to 9.9%)
95% CI	70.9% to 92.8%	72.6% to 97.8%		
Missing/ART Switch = Failure[e]				
< 50 copies/mL	42/50 (84.0%)	25/29 (86.2%)	0.60	−4.4% (−22.5% to 13.6%)
95% CI	70.9% to 92.8%	68.3% to 96.1%		
Missing = Excluded[f]				
< 50 copies/mL	42/46 (91.3%)	26/27 (96.3%)	0.26	−7.3% (−22.3% to 7.8%)
95% CI	79.2% to 97.6%	81.0% to 99.9%		

a HIV-1 RNA results were from HIV Cobas Amplicor version 1.5 assay only.
b The 95% CI for proportion estimate of HIV-1 RNA < 50 copies/mL for each treatment was obtained using Exact method.
c P-values were from the CMH tests stratified by baseline HIV-1 RNA category (<= 100,000 or > 100,000 copies/mL). Difference in percentages of success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted Mantel-Haenszel (MH) proportion.
d For missing = failure: Denominator for percentage was the number of subjects in ITT analysis set. P-value and percentage difference (95% CI) were based on a binary response: success (HIV RNA <50 c/mL) and failure (HIV RNA >=50 copies/mL or missing).
e For missing/ART switch: Denominator for percentage was the number of subjects in the ITT analysis set. P-value and percentage difference (95% CI) were based on a binary response: success (HIV-1 RNA<50) and failure (HIV-1 RNA>=50, missing, ART switch). Subjects who discontinued study drug and had no follow-up information on new ART were treated as having an ART switch. The commercial ATR switch for subjects who were randomized to and treated in ATR group was not considered an ART switch.
f For missing = excluded: Denominator for percentage was the number of subjects in the ITT analysis set with non-missing HIV-1 RNA value at each visit. P-value, percentage difference, and its 95% CI were based on a binary response: success (HIV-1 RNA < 50 copies/mL) and failure (HIV-1 RNA >= 50 copies/mL).

Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 48

The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL (ITT, M=F) at Week 48 was 82.0% in the ATV/co+TVD group and 89.7% in the ATV/r+TVD group. At Week 48, the baseline HIV-1 RNA stratum-weighted difference in the response rate between the 2 treatment groups was −8.3% (95% CI: −25.9% to 9.4%; p = 0.34). Similar results were obtained using the M/S=F method in which 1 additional subject was considered to be a failure.

Using the M=E method, the percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 48 was 89.1% (41/46) in the ATV/co+TVD group and 96.3% (26/27) in the ATV/r+TVD group. At Week 48, the baseline HIV-1 RNA stratum-weighted difference in the response rate between the 2 treatment groups was −7.8% (95% CI: −23.0% to 7.4%; p = 0.26).

Table 22. GS-US-216-0105: Percentage of Subjects with Plasma HIV-1 RNA < 50 cp/mL at Week 48 (ITT Analysis Set)

Week 48[a,b]	ATV/co+TVD (N =50)	ATV/r+TVD (N =29)	ATV/co+TVD vs. ATV/r+TVD[c]	
			P-value	Difference in Percentages (95% CI)
Missing = Failure[d]				
< 50 copies/mL	41/50 (82.0%)	26/29 (89.7%)	0.34	−8.3% (−25.9% to 9.4%)
95% CI	68.6% to 91.4%	72.6% to 97.8%		
Missing/ART Switch = Failure[e]				
< 50 copies/mL	41/50 (82.0%)	25/29 (86.2%)	0.55	−5.4% (−23.8% to 13.1%)
95% CI	68.6% to 91.4%	68.3% to 96.1%		
Missing = Excluded[f]				
< 50 copies/mL	41/46 (89.1%)	26/27 (96.3%)	0.26	−7.8% (−23.0% to 7.4%)
95% CI	76.4% to 96.4%	81.0% to 99.9%		

a HIV-1 RNA results were from HIV Cobas Amplicor version 1.5 assay only.
b The 95% CI for proportion estimate of HIV-1 RNA < 50 copies/mL for each treatment was obtained using Exact method.
c P-values were from the CMH tests stratified by baseline HIV-1 RNA category (<= 100,000 or > 100,000 copies/mL). Difference in percentages of success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
d For missing = failure: Denominator for percentage was the number of subjects in the ITT analysis set. P-value and percentage difference (95% CI) were based on a binary response: success (HIV-1 RNA < 50 copies/mL) and failure (HIV-1 RNA >= 50 copies/mL or missing).
e For missing/ART switch: Denominator for percentage was the number of subjects in the ITT analysis set. P-value and percentage difference (95% CI) were based on a binary response: success (HIV-1 RNA<50) and failure (HIV-1 RNA>=50, missing, ART switch). Subjects who discontinued study drug and had no follow-up information on new ART were treated as having an ART switch.
f For missing = excluded: Denominator for percentage was the number of subjects in the ITT analysis set with non-missing HIV-1 RNA value at each visit. P-value, percentage difference, and its 95% CI were based on a binary response: success (HIV-1 RNA < 50 copies/mL) and failure (HIV-1 RNA >= 50 copies/mL).

Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using Snapshot Analysis

At Week 24, 84.0% of subjects in the ATV/co+TVD group and 86.2% of subjects in the ATV/r+TVD group had virologic success (ITT). The difference in the percentage of subjects with virologic success was −4.4% (95% CI: −22.5% to 13.6%). At Week 48, 82.0% (41/50) of subjects in the ATV/co+TVD group and 86.2% (25/29) of subjects in the ATV/r+TVD group had virologic success (ITT). The difference in the percentage of subjects with virologic success was −5.4% (95% CI: −23.8% to 13.1%).

Table 23. GS-US-216-0105: Virologic outcome at Week 24 and 48 using the Snapshot analysis and HIV-1 RNA < 50 cp/mL at (ITT Analysis Set)

Time Point HIV-1 RNA Category	ATV/co+TVD (N=50)	ATV/r+TVD (N=29)	ATV/co+TVD vs ATV/r+TVD	
			p-value[a]	Difference in Percentages (95% CI)[b]
Snapshot Analysis				
Virologic Success at Week 24				
HIV-1 RNA < 50 copies/mL	42 (84.0%)	25 (86.2%)	0.60	-4.4% (-22.5% to 13.6%)
Virologic Failure at Week 24	5 (10.0%)	3 (10.3%)		
HIV-1 RNA ≥ 50 copies/mL	4 (8.0%)	1 (3.4%)		
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[c]	1 (2.0%)	2 (6.9%)		
No Virologic Data in Week 24 Window[d]				
Discontinued Study Drug Due to AE/Death	2 (4.0%)	1 (3.4%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	1 (2.0%)	0		
Missing Data during Window but on Study Drug	0	0		
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	41 (82.0%)	25 (86.2%)	0.55	-5.4% (-23.8% to 13.1%)
Virologic Failure at Week 48	5 (10.0%)	3 (10.3%)		
HIV-1 RNA≥ 50 copies/mL	4 (8.0%)	1 (3.4%)		
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[c]	1 (2.0%)	2 (6.9%)		
No Virologic Data in Week 48 Window[e]				
Discontinued Study Drug Due to AE/Death	2 (4.0%)	1 (3.4%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	2 (4.0%)	0		
Missing Data during Window but on Study Drug	0	0		

a p-value was from the CMH test stratified by baseline HIV-1 RNA category (<=100,000 or >100,000 copies/mL).
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum adjusted MH proportion.
c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject non-compliance, and protocol violation.
d Week 24 window is between Day 141 and 196 (inclusive)
e Week 48 window is between Day 309 and 378 (inclusive)

Change from Baseline in HIV-1 RNA (log_{10} copies/mL) at Weeks 24 and 48

The mean (SD) change at Week 24 was −2.80 (0.619) log10 copies/mL in the ATV/co+TVD group (n = 46) and −2.97 (0.707) log10 copies/mL in the ATV/r+TVD group (n = 27) (p = 0.87, ITT analysis set and at Week 48, the mean (SD) change at was −2.79 (0.678) log10 copies/mL in the ATV/co+TVD group (n = 46) and −2.96 (0.765) log10 copies/mL in the ATV/r+TVD group (n = 27) (p = 0.82, ITT analysis set.

2.5.2. Discussion on clinical efficacy

The clinical efficacy of ATV/COBI FDC is primarily focused on a pharmacokinetic bridging clinical programme based on demonstrating the bioequivalence of ATV when co-administered with COBI either as the FDC (formulation G006) or the single agents under fed conditions. This approach is considered acceptable because this FDC is proposed as a 'substitution indication' of an already approved regimen (Cobicistat is already approved for use as a pharmacokinetic-enhancer of ATV).

Design and conduct of clinical studies

Two studies have been conducted in which ATV and COBI were used as part of the regimen to support this proposed substitution indication; an ongoing phase 2 study, GS-US-216-0105 and a phase 3 study, GS-US-216-0114 (these studies were part of the registration dossier for COBI).

GS-US-216-0114

The primary objective of this double blind study was to evaluate the efficacy of a regimen containing ATV/COBI versus ATV/rtv, each administered with TVD through 48 weeks of treatment and secondarily to assess the efficacy of the regimen in terms of virologic response (plasma viral load <50 copies/mL) at 24 and 48 weeks using a snap-shot analysis and secondarily to evaluate the efficacy, safety, and tolerability of the 2 treatment regimens through 192 weeks of treatment. The study population consisted of a treatment-naïve population with HIV demonstrated to be susceptible to ATV, FTC and TDF. The baseline characteristics of the study population were comparable with those reported from many other studies in the ART-naïve.

The pre-defined non-inferiority margin was -12% and may be considered to be slightly wide but this is not considered to be an issue because the results demonstrates that the lower bound of the 95% CI fall within 10% for both the primary and sensitivity analyses. It was also apparent that ATV/COBI provided rates for < 50 copies/mL that were comparable with ATV/RTV in the subsets with HIV RNA > 100,000 copies/mL at baseline and CD4 < 350 cells/mm-3. Additional analyses were performed for subjects with baseline HIV-1 RNA $\leqslant$ 100,000, > 100,000 to $\leqslant$ 400,000, and > 400,000 and for subjects with baseline CD4 count $\leqslant$ 200 cells/μL, > 200 to $\leqslant$ 350 cells/μL and > 350 cells/µL. These results indictaed that the efficacy of ATV/COBI+TVD was generally consistent and comparable within each subgroup analyzedThe rationale for including planned interim analyses by the IDMC was not considered that these threatened the integrity of the primary analysis.

GS-US-216-0105

This supportive study was conducted to evaluate the efficacy of a regimen containing COBI-boosted ATV (ATV/co +TVD versus RTV-boosted ATV (ATV/r) +TVD in HIV-1 infected, antiretroviral treatment naive adult subjects as determined by the achievement of HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 24. The design, non-inferiority margin, study population and baseline characteristics were comparable with those of the phase 3 study.

The results from this Phase 2 study suggested that ATV/COBI was numerically inferior to ATV/RTV. This is however not considered to be an issue as the pivotal Phase 3 study provided primary and sensitivity analyses that demonstrated non-inferiority for ATV/COBI vs. RTV/COBI although small numerical differences were also apparent.

Efficacy data and additional analyses

ATV/COBI in combination TVD is non-inferior to ATV/RTV + TVD through to 48 weeks and the additional sensitivity analyses conducted support this finding. Week 144 efficacy results confirmed the efficacy

observed over 48 weeks. Resistance development to 1 or more components of ATV/co+TVD or ATV+RTV+TVD occurred infrequently in Study GS-US-216-0114.

2.5.3. Conclusions on the clinical efficacy

The efficacy data from the studies support the use of COBI as a pharmacokinetic-enhancer of ATV and since the ATV/COBI FDC tablet has been demonstrated to be bioequivalent to the single components, it is considered that these results can be extrapolated to the FDC. Additional efficacy studies were provided, as well as supportive studies on the individual components.

2.6. Clinical safety

Patient exposure

Study AI424511 was conducted by the Applicant in order to demonstrate the bioequivalence of the FDC and will be assessed in terms of the safety results. This is the only study in which the safety of the FDC has been specifically evaluated, whereas not at the long-term pattern of exposure expected in clinical use.

No other studies have been specifically conducted to evaluate the efficacy and safety of the FDC combination. However studies with the individual components contained in the FDC were submitted in support of this application.

The data submitted derived from studies 216-105 and 216-0114 which have been described for the supportive efficacy data.

Study AI424511

Study AI424511 was an open-label, single-dose, 5-period, 5-treatment, randomized crossover study in healthy subjects. Subjects were equally randomized to 1 of 8 treatment sequences. Subjects received a 300 mg ATV capsule coadministered with a 150 mg COBI tablet or FDC tablet of ATV/COBI (300/150 mg) following a light meal (Treatments A or B, respectively) according to the assigned treatment sequences on Days 1 and 8. On Days 15 and 22, subjects received a 300 mg ATV capsule coadministered with a 150 mg COBI tablet or FDC tablet of ATV/COBI (300/150 mg) under fasted conditions (Treatments C or D, respectively) according to the assigned treatment sequences. On Day 29, approximately half of the subjects, according to the assigned sequence, received FDC tablet of ATV/COBI (300/150 mg) following a high fat meal (Treatment E). There was a 7-day washout period between all treatments. Approximately half of the subjects, according to assigned sequences, were to be discharged from the study at the end of Period 4 (Day 24) and the remaining subjects continued to Period 5 and were to be discharged at the end of Period 5 (Day 31).

A total of 149 subjects were enrolled, and 64 subjects were randomized to receive treatment with ATV/COBI. Only 2 subjects discontinued prior to study completion. Sixty-four subjects received study medication based on 1 of the 8 treatment sequences, of which 32 subjects were to receive treatments through Period 4 (a total of 4 treatments) and the remaining 32 subjects were to receive treatments through Period 5 (a total of 5 treatments).

Two subjects discontinued study medication. All 64 subjects receiving study medication were included in the safety dataset. At baseline, the mean age was 33 years (range: 18 - 48 years), the majority of subjects were male, and 52% of the subjects were Black. All subjects were healthy with no history of significant disease.

Table 24. Subject Disposition (Study AI424511)

	No. of Subjects
No. of Subjects Enrolled	149
No. of Subjects Treated	64
No. of Subjects Discontinued	2
Poor/noncompliance	1
Withdrew consent	1
No. of Subjects Completing the Study	62

Pooled studies 216-105 and 216-0114

Overall, 394 subjects received ATV+COBI+TVD in these 2 studies, and 377 subjects received ATV+RTV+TVD. The median duration of exposure to study drug was 48.4 weeks in the ATV+COBI+TVD group and 48.3 weeks in the ATV+RTV+TVD group.

At baseline, the overall mean (standard deviation [SD]) HIV-1 ribonucleic acid (RNA) was 4.81 (0.595) log10 copies/mL, mean (SD) CD4 count was 353 (174.8) cells/µL, and mean CD4 percentage was 21% (8.62%). Overall, 62% of subjects had baseline HIV-1 RNA ≤ 100,000 copies/mL. The majority of subjects (83%) had asymptomatic HIV-1 infection. Eight percent of subjects were diagnosed with acquired immunodeficiency syndrome.

Adverse events
Study AI424511

Twenty subjects (31%) had AEs. The most common AE was dizziness (6%). All AEs resolved by study completion. All AEs were mild to moderate intensity. The most common AEs (≥ 2 subjects) are summarized in Table 25.

Table 25. Most common Adverse Events (at Least 2 Subjects) (Study AI424511)

Preferred term %	**N=64**
Total subjects with an event	30 (31.1)
Dizziness	4 (6.3)
Abdominal discomfort	3 (4.7)
Musculoskeletal chest pain	3 (4.7)
Nasopharyngitis	3 (4.7)
Headache	2 (3.1)
Nausea	2 (3.1)
Pre-syncope	2 (3.1)
Vomiting	2 (3.1)

Six subjects (9%) had AEs considered related to the study drug by the investigator. Related AEs were dizziness (3 subjects [5%]), headache and vomiting (2 subjects [3%] each), and abdominal discomfort, nausea, and vision blurred (1 subject [2%] each).

Pooled studies 216-105 and 216-0114

Ten percent of subjects in the ATV+COBI+TVD group and 7% of subjects in the ATV+RTV+TVD group had serious adverse events (SAEs). The incidence of treatment-emergent AEs was similar in both groups (92%).The most frequently reported treatment-emergent AEs in the ATV+COBI+TVD group were jaundice, ocular icterus, and nausea, and the most frequently reported treatment-emergent AEs in the ATV+RTV+TVD group were diarrhoea, ocular icterus, and nausea.

The most frequent treatment-emergent AEs reported in ≥ 5% of subjects in either group are summarized in Table 27.

Table 26. Overall Summary of Adverse Events (pooled Safety Analysis)

Event	ATV+COBI+TVD (N=394) N (%)	ATV+RTV+TVD (N=377) N (%)
Any Treatment-emergent Adverse Event	361 (91.6)	347 (92.0)
Grade 2 - 4 Treatment-emergent Adverse Event	236 (59.9)	213 (56.5)
Grade 3 - 4 Treatment-emergent Adverse Event	70 (17.8)	50 (13.3)
Treatment-emergent Related Adverse Event	224 (56.9)	216 (57.3)
Death	0	0
Treatment-emergent Serious Adverse Event	38 (9.6)	25 (6.6)
Treatment-emergent Adverse Event Leading to Discontinuation of Study Drug	27 (6.9)	27 (7.2)

Serious adverse event / deaths / other significant events

Study AI424511

No deaths, SAEs, or discontinuations due to AEs were reported.

Pooled studies 216-105 and 216-0114

No deaths were reported during the two studies. The incidence of Grade 3 -4 treatment-emergent AEs were 18% and 13% in the ATV+COBI+TVD and ATV+RTV+TVD groups, respectively. Grade 3 - 4 treatment-emergent AEs were reported in 18% and 13% of subjects in the ATV+COBI+TVD and ATV+RTV+TVD groups, respectively. The difference was driven by Grade 3 events, as Grade 4 AEs were balanced and reported for 2 subjects in the ATV+COBI+TVD group and 3 subjects in the ATV+RTV+TVD group. Most Grade 3 - 4 treatment-emergent AEs were not considered related to the study drug by the investigators.

No pattern was apparent in specific types of AEs of higher incidence in the ATV+COBI+TVD group, with the exception of AEs associated with bilirubin elevations (i.e., ocular icterus, hyperbilirubinemia, jaundice, blood bilirubin increased), which are events reported in the ATV prescribing information as related to ATV use. The only other Grade 3 - 4 treatment-emergent AE reported in ± 1% of subjects in either treatment group was acute renal failure, which was reported for 0 subjects in the ATV+COBI+TVD group and 4 subjects (1%) in the ATV+RTV+TVD group.

Table 27. Treatment emergent Adverse Events Reported for at least 5% of Subjects in Either Treatment Group (Pooled Safety Analysis)

MedDRA System Organ Class Preferred Term	ATV+COBI+TVD (N=394) N (%)	ATV+RTV+TVD (N=377) N (%)
Any Treatment-emergent Adverse Event	361 (91.6)	347 (92.0)
Blood and Lymphatic System Disorders	32 (8.1)	37 (9.8)
Lymphadenopathy	14 (3.6)	20 (5.3)
Eye Disorders	79 (20.1)	83 (22.0)
Ocular Icterus	68 (17.3)	68 (18.0)
Gastrointestinal Disorders	184 (46.7)	180 (47.7)
Diarrhea	59 (15.0)	80 (21.2)
Nausea	66 (16.8)	59 (15.6)
Vomiting	27 (6.9)	17 (4.5)
Flatulence	25 (6.3)	15 (4.0)

General Disorders & Administration Site Conditions	88 (22.3)	84 (22.3)
Fatigue	30 (7.6)	29 (7.7)
Pyrexia	21 (5.3)	25 (6.6)
Hepatobiliary Disorders	99 (25.1)	77 (20.4)
Jaundice	74 (18,8)	55 (14.6)
Hyperbilirubinemia	43 (10.9)	34 (9.0)
Infections & Infestations	227 (57.6)	237 (62.9)
Nasopharyngitis	37 (9.4)	56 (14.9)
Upper Respiratory Tract Infection	40 (10.2)	30 (8.0)
Sinusitis	23 (5.8)	18 (4.8)
Bronchitis	20 (5.1)	20 (5.3)
Urinary Tract Infection	14 (3.6)	20 (5.3)
Musculoskeletal& Connective Tissue Disorders	65 (16.5)	55 (14.6)
Back Pain	17 (4.3)	26 (6.9)
Nervous System Disorders	95 (24.1)	83 (22.0)
Headache	41 (10.4)	54 (14.3)
Dizziness	27 (6.9)	22 (5.8)
Psychiatric Disorders	68 (17.3)	60 (15.9)
Depression	21 (5.3)	20 (5.3)
Respiratory Tract & Mediastinal Disorders	76 (19.3)	80 (21.2)
Cough	26 (6.6)	23 (6.1)
Skin & Subcutaneous Tissue Disorders	115 (29.2)	105 (27.9)
Rash	24 (6.1)	23 (6.1)

Related Treatment-emergent Adverse Events

Treatment-emergent AEs considered related to the study drug were reported in 57% of subjects in each group. The most frequently reported AEs considered related to the study drug by the investigators in the ATV+COBI+TVD and ATV+RTV+TVD groups, respectively, were ocular icterus (15% vs. 17%), nausea (12% vs. 11%), and jaundice (14% vs. 11%).

Laboratory findings
Study AI424511

The overall incidence of laboratory abnormalities was low. The most frequently occurring laboratory abnormalities were high total bilirubin and high white blood cells in the urine. None of the laboratory abnormalities was considered clinically significant, and none was reported as an AE.

Haematology

Hematologic laboratory abnormalities were low leukocytes (4 subjects [6%]) and low absolute neutrophils (5 subjects [8%]). These laboratory abnormalities were within normal limits at end of study.

Serum Chemistries

Nine subjects had a total of 12 serum chemistry Mas. Serum chemistry laboratory abnormalities were high total bilirubin (6 subjects [9%]), high CK and high direct bilirubin (2 subjects [3%] each), and high aspartate aminotransferase and high dehydrogenase (1 subject [2%] each). None of the subjects met the criteria for potential drug-induced liver injury (i.e., alanine aminotransferase > 3 x upper limit of normal [ULN] and total bilirubin > 2 x ULN).

Urinalysis

Urinalysis laboratory abnormalities were high white blood cells in the urine (7 subjects [11%]), high blood in the urine (3 subjects [5%]), and high red blood cells in the urine (2 subjects [3%]). Laboratory abnormalities were within normal limits at end of study.

Physical findings and cardiologic evaluation

There was no evidence of any clinically relevant effect of the administration of ATV/COBI 300 mg/150 mg on vital signs. No subject had a QT interval > 500 msec and 1 subject had a QTcF interval (453 msec) > 450 msec on 1 ECG that was not considered clinically significant by the investigator. Three subjects had investigator-identified ECG abnormalities that were not present prior to study drug administration: 2 subjects had sinus bradycardia and 1 subject had a QRS duration abnormality. None of the abnormalities was reported as an AE or considered clinically significant by the investigator

Pooled studies 216-105 and 216-0114

The majority of subjects had at least 1 treatment-emergent laboratory abnormality reported. Among subjects with post-baseline laboratory assessments, 99% of subjects in both groups had laboratory abnormalities (Grade 1 - 4).

Treatment-emergent Grade 3 or 4 abnormalities were reported in 75% and 64% of subjects in the ATV+COBI+TVD and ATV+RTV+TVD groups, respectively. The difference between groups was driven predominantly by abnormalities of total bilirubin.

The most frequently reported Grade 3 or 4 abnormalities were as follows:

- ATV+COBI+TVD group — total bilirubin (49% Grade 3, 16% Grade 4, n = 255), lipase (7% Grade 3, 2% Grade 4, n = 4 of 44 subjects assessed), and creatinine kinase (CK) (3% Grade 3, 3% Grade 4, n = 21).
- ATV+RTV+TVD group — total bilirubin (45% Grade 3, 11% Grade 4, n = 211), lipase (6% Grade 3, 0 subjects Grade 4, n = 2 of 34 subjects assessed), and CK (2% Grade 3, 4% Grade 4, n = 22).

Renal Laboratory Parameters

Increases from baseline in median serum creatinine in the ATV+COBI+TVD group were noted as early as Week 2 (median change from baseline at Week 2 was 0.11 mg/dL), after which it generally stabilized through Week 48 (median change from baseline at Week 48 was 0.13 mg/dL). The pattern of change in serum creatinine in the ATV+RTV+TVD group was similar (median change from baseline at Week 2 was 0.05 mg/dL; median change from baseline at Week 48 was 0.09 mg/dL).

Modest decreases in median estimated glomerular filtration rate calculated using the Cockcroft-Gault equation (eGFRCG) were observed post-baseline in the ATV+COBI+TVD group (baseline median 111.2 mL/min and median change from baseline at Week 48 of –12.9 mL/min) and ATV+RTV+TVD group (baseline median 114.5 mL/min and median change from baseline at Week 48 of –9.3 mL/min). Decreases in eGFRCG were seen as early as Week 2, with only minimal additional decreases after that time point; median values remained within the normal range.

Other Observations Related to Safety

In Study GS-US-216-0114, 2 subjects in each group with normal electrocardiograms (ECGs) at baseline developed clinically significant abnormal ECGs by Week 48. In Study GS-US-216-0105, 1 subject in the ATV+COBI+TVD group and 2 subjects in the ATV+RTV+TVD group had clinically significant ECG findings reported.

Safety in special populations
Not evaluated.

Immunological events
Rash was reported in 6.1% of each of the two comparative treatment groups in studies 216-105 and 216-0114 and no other hypersensitivity related events are discussed. This frequency is in line with the current information for the product and with the proposed frequency in section 4.8 of the SmPC.

Discontinuation due to adverse events
In study AI424511, no discontinuations due to AEs were reported.

In the pooled studies 216-115 and 216-0104, 7% of subjects in both groups had treatment-emergent AEs that led to discontinuation of the study drug. Events associated with hyperbilirubinemia, such as jaundice (2% in both groups) and ocular icterus (2% in the ATV+COBI+TVD group and 1% in the ATV+RTV+TVD group) were the only AEs that led to discontinuation of study drug in > 1% of subjects in either group.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

About 400 subjects have been treated with ATV/COBI in combination with TVD with a median duration of exposure of 48 weeks and 64 healthy subjects have been treated with ATV/COBI FDC.

In studies GS-US-216-0105 and GS-US-216-0114 the incidence of grade 3 -4 treatment-emergent AEs was slightly higher in the ATV+COBI+TVD (18%) compared with ATV/COBI + TVD (13%).

In terms of adverse events and taking into consideration the known adverse event profile for both ATV and COBI, the following is noted; there was no excess of renal AEs or renal laboratory anomalies in the COBI Phase 2 and 3 studies except for the recognised effect on serum creatinine and higher rates of hypophosphataemia and of Grade 3 glycosuria and haematuria.

Adverse events associated with bilirubin elevations which relate to ATV use were noted to be higher in the ATV+COBI+TVD group.

ATV/COBI was associated with higher rates of elevated AST and ALT although the frequency of occurrence of these events at 3 x ULN or more in conjunction with elevated bilirubin was comparable with the ATV/RTV group.

Even though the number of subjects reporting any SAE was higher in the ATV/COBI group (38 vs. 25; 9.6% vs. 6.6%) there was no apparent clustering of SAEs of any one SOC or PT that can explain this overall difference.

In study GS-US216-0114, the median (first quartile [Q1] – third quartile [Q3]) duration of exposure to study drug was 146.3 weeks (143.0–155.6) in the ATV/co+TVD group and 145.1 weeks (142.8–155.5) in the ATV+RTV+TVD group. The majority of subjects in each treatment group received study drug for ≥

144 weeks (ATV/co+TVD 72.7%, 250 subjects; TV+RTV+TVD 70.7%, 246 subjects). As observed for week 48, higher percentages of subjects in the ATV/co+TVD group reported any Grade 3 or 4 AE (ATV/co+TVD 27.0%, 93 subjects; ATV+RTV+TVD 21.0%, 73 subjects) or any serious AEs (SAEs) (ATV/co+TVD 17.7%, 61 subjects; ATV+RTV+TVD 12.9%, 45 subjects). However, similar percentages of subjects in each group reported Grade 3 or 4 AEs considered related to study drug (ATV/co+TVD 8.1%, 28 subjects; ATV+RTV+TVD 6.6%, 23 subjects) or SAEs considered related to study drug (ATV/co+TVD 1.7%, 6 subjects; ATV+RTV+TVD 2.9%, 10 subjects).

Common AEs were consistent with those expected in the subject population and the known safety profiles of the study drugs.

One non-treatment-emergent death occurred during Study GS-US-216-0114 in a subject in the ATV+RTV+TVD group. Death was due to left parieto-occipital intra-parenchymal hemorrhage on Day 604, while no deaths were reported for the ATV/co+TVD group.

Discontinuation of study drug due to AEs occurred in similar percentages of subjects in the 2 treatment groups (ATV/co+TVD 11.0%, 38 subjects; ATV+RTV+TVD 11.2%, 39 subjects).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the data suggest that ATV/COBI is generally well tolerated. No particular concern has been identified with this fixed dose combination or ATV/cobi given as single agents to date.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Assessment report on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable. The PRAC advice an overview is attached.

The CHMP endorsed this without changes.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

Summary of Ongoing Safety Concerns

Important identified risks	• PR interval prolongation (both paediatric and adult populations) • Hyperbilirubinemia • Nephrolithiasis • Severe skin reactions • Cholelithiasis
Important potential risks	• QT prolongation • Kernicterus • Acute renal failure (adults) • Angioedema • Interstitial nephritis • Immune reconstitution inflammatory syndrome (IRIS) • Concurrent use of drugs whose coadministration with COBI is contraindicated • Medication error leading to overdose in case of concurrent use of ATV/COBI with any components, including ATV, COBI, or with FDC products that contain COBI
Missing information	• Long term safety of ATV/COBI FDC • Hepatic impairment (ATV and COBI) • Pregnancy (ATV and COBI) • Pediatric population ATV and COBI • Geriatrics (ATV and COBI) • Lactation (ATV and COBI) • Renal impairment (COBI) • Cardiac conduction disorders (COBI) • Drug-drug interactions (ATV and COBI)

Pharmacovigilance plan

On-Going and Planned Additional PhV Studies / Activities in the Pharmacovigilance Plan

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned, Actual)
GS-US-216-0105: A Phase 2, randomized, double-blinded study of the safety and efficacy of GS-9350-boosted atazanavir (ATV/GS-9350) compared to ritonavir-boosted atazanavir (ATV/r) in combination with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in HIV-1 infected, antiretroviral treatment-naïve adults	To evaluate the efficacy, safety and tolerability of ATV/COBI+TVD versus ATV/RTV+TVD	Missing information Long-term safety of ATV/COBI in HIV-1 infected patients	Ongoing	Final report (Week 192) Q1 2016
GS-US-216-0114: A Phase 3, randomized, double-blind study to evaluate the safety and efficacy of GS-9350-boosted atazanavir versus ritonavir-boosted atazanavir each administered with emtricitabine/tenofovir disoproxil fumarate in HIV-1 infected, antiretroviral treatment-naïve adults	To evaluate the efficacy, safety and tolerability of ATV/COBI+TVD versus ATV/RTV+TVD	Missing information Long-term safety of ATV/COBI in HIV-1 infected patients	Ongoing	Final report (Week 192) Q1 2016
Antiretroviral Pregnancy Registry: (to detect any major teratogenic effects involving any of the Registry drugs, including ATV/COBI, to which pregnant women are exposed)	To detect any major teratogenic effects involving any of the Registry drugs, including ATV/COBI, to which pregnant women are exposed)	Missing information Pregnancy (ATV and COBI)	Ongoing	Interim reports are issued by the APR in June and December each year and the most current data available are included in PSUR/PBRER submissions

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

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

Risk minimisation measures

Risk Minimization Measures by Safety Concern	
Safety Concern: PR Interval Prolongation	
Objective(s) of the risk minimization measure	Early detection with early intervention..
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable

Risk Minimization Measures by Safety Concern	
Impact of risk minimization	Not applicable
Safety Concern: Hyperbilirubinemia	
Objective(s) of the risk minimization measure	Early detection with early intervention..
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Nephrolithiasis	
Objective(s) of the risk minimization measure	Early detection with early intervention.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Severe Skin Reactions	
Objective(s) of the risk minimization measures	Early detection with early intervention.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Cholelithiasis	
Objective(s) of the risk minimization measure	Early detection with early intervention.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: QT prolongation	
Objective(s) of the risk minimization measure	Early detection with early intervention.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the	Evaluation of frequency and severity of cases received.

Risk Minimization Measures by Safety Concern	
proposed risk minimization measures	
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Kernicterus	
Objective(s) of the risk minimization measure	Early detection with early intervention.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Acute Renal Failure	
Objective(s) of the risk minimization measures	Early detection with early intervention..
Routine risk minimization measures	Label
Additional risk minimization measure(s):	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Angioedema	
Objective(s) of the risk minimization measures	Early detection with early intervention.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Interstitial Nephritis	
Objective(s) of the risk minimization measure	Evaluation of frequency and severity of cases received.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Immune Reconstitution Inflammatory Syndrome (IRIS)	
Objective(s) of the risk minimization measures	Early detection with early intervention..
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization	Monitoring through ongoing routine PV activites. Assessment and

Risk Minimization Measures by Safety Concern	
measures for the safety concern will be measured	reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Concurrent Use of Drugs Whose Coadministration with COBI is Contraindicated	
Objective(s) of the risk minimization measures	To prevent coadministration of contra-indicated drugs.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Medication Error Leading to Overdose in Case of Concurrent Use of ATV/COBI with Any Components Including ATV, COBI, or with FDC Prodcts That Contain COBI	
Objective(s) of the risk minimization measures	To warn of the potential for overdose from medication errors from concurrent use of ATV/COBI with any components includingATV, COBI or with FDC products that contain COBI.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Long-term Safety of ATV/COBI in Adults with HIV-1 Infection	
Objective(s) of the risk minimization measures	To characterize the long-term safety of ATV/COBI
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Safety in Children	
Objective(s) of the risk minimization measures	To advise on the lack of data in this population.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable

Risk Minimization Measures by Safety Concern	
Safety Concern: Safety in Elderly Patients	
Objective(s) of the risk minimization measures	To advise on the lack of data in this population.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Safety in Pregnancy	
Objective(s) of the risk minimization measures	To advise on the lack of data in this population.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	Antiretroviral Pregnancy Registry
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Safety in Lactation	
Objective(s) of the risk minimization measures	To advise on the lack of data in this population.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Safety in Patients with Severe Hepatic Impairment (Child-Pugh Class C)	
Objective(s) of the risk minimization measures	To advise on the lack of data in this population.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Safety in Patients with Renal Impairment	
Objective(s) of the risk minimization measures	To advise on the lack of data in this population.
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.

Risk Minimization Measures by Safety Concern	
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Safety in Patients with Cardiac Conduction Disorders	
Objective(s) of the risk minimization measures	To advise of the risk of arrythmia in this population
Routine risk minimization measures	Routine
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable
Safety Concern: Drug-drug Interactions	
Objective(s) of the risk minimization measures	To warn of the potential for drug-drug interactions
Routine risk minimization measures	Label
Additional risk minimization measure(s)	None
Effectiveness of Risk Minimization Measures	
How effectiveness of risk minimization measures for the safety concern will be measured	Monitoring through ongoing routine PV activites. Assessment and reporting in the PBRER and DSUR.
Criteria for judging the success of the proposed risk minimization measures	Evaluation of frequency and severity of cases received.
Planned date of assessment	Ongoing
Results of effectiveness measurement	Not applicable
Impact of risk minimization	Not applicable

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

2.9. Significance of paediatric studies

Not applicable.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Atazanavir is a well-established compound for use in the treatment of HIV-infection, with adequate antiviral activity and the possibility of once-daily dosing.

Cobicistat has previously demonstrated to be an acceptable pharmacokinetic enhancer of atazanavir, with

boosting activity comparable to that of the widely used compound ritonavir.

The combination may provide for the simplification of treatment regimen, since there is currently no co-formulation of atazanavir with a pharmacokinetic enhancer available for clinical use.

Uncertainty in the knowledge about the beneficial effects

The clinical program for ATV/COBI FDC is primarily based on a pharmacokinetic bridging clinical programme based on demonstrating the bioequivalence of ATV when co-administered with COBI either as the FDC (formulation G006) or the single agents under fed conditions. The ATV/COBI FDC is proposed as a 'substitution indication' of an already approved regimen. The efficacy data provided therefore consists only of studies conducted with the single components i.e. ATV and COBI (ATV/COBI)with a bioequivalence study conducted in the fed state to bridge the data from the single components to the proposed FDC; no efficacy study has been conducted using the FDC.

Cobicistat has shown a trend towards a slightly lower response at 48 weeks relative to the use of ritonavir boosted atazanavir, while the results of the two supportive studies in which the compounds were used separately are within the non-inferiority range and there were no notable differences in terms of the emergence of resistant strains. This trend was maintained at the week 144 interim analysis, while still within the non-inferiority margin. Virologic failure rates at week 144 were higher for the EVOTAZ group (8.1% versus 4.9%) with 3 discontinuations due to lack of efficacy in the EVOTAZ group and none in the ATV/RTV group.

Risks

Unfavourable effects

The safety of the FDC tablet is supported by the safety of the individual components (i.e. safety data from GS-US-216-0105 and GS-US-216-0114) and the safety of the individual components given in combination and the FDC in the bioequivalence study (AI424511). About 400 subjects have been treated with ATV/COBI in combination with TVD with a median duration of exposure of 142 weeks and 64 healthy subjects have been treated with ATV/COBI FDC in the bioequivalence study AI 424511.

In studies GS-US-216-0105 and GS-US-216-0114, the most frequently reported treatment-emergent AEs in the ATV+COBI+TVD group were jaundice, ocular icterus, and nausea. In study AI424511, the most common AE was dizziness (6%).

Uncertainty in the knowledge about the unfavourable effects

There are no clinical studies evaluating the safety of ATV/COBI FDC tablet in patients. In studies GS-US-216-0105 and GS-US-216-0114, the incidence of grade 3 -4 treatment-emergent AEs was slightly higher in the ATV+COBI+TVD (18%) compared with ATV/COBI + TVD (13%).

There was no excess of renal AEs or renal laboratory anomalies in the COBI Phase 2 and 3 studies except for the recognised effect on serum creatinine and higher rates of hypophosphataemia and of Grade 3 glycosuria and haematuria.

Adverse events associated with bilirubin elevations which relate to ATV use were noted to be higher in the ATV+COBI+TVD group.

ATV/COBI was associated with higher rates of elevated AST and ALT although the frequency of occurrence of these events at 3 x ULN or more in conjunction with elevated bilirubin was comparable with the ATV/RTV group.

It is considered that there are a few gaps regarding the safety of ATV/COBI given as a FDC in terms of the duration of exposure.

No drug-drug interaction studies have been performed using ATV/Cobi FDC tablet formulations or ATV co-administered with Cobi as separate agents and the applicant bases the drug interaction potential on the interactions observed with each single agent and ATV when co-administered with rtv.

Benefit-risk balance

Importance of favourable and unfavourable effects

COBI is a useful alternative to RTV as a pharmacokinetic-enhancer of specific antiretroviral agents that are substrates of CYP3A4. There are no identified safety concerns and it is actually already approved for use with ATV, Darunavir and other ART. Therefore the FDC is potentially useful as a substitution indication for ATV/rtv. The FDC has been demonstrated to be bioequivalent to the individual components in the fed state which is considered adequate as the efficacy studies were also conducted in the fed state and food is known to improve the bioavailability of ATV and reduce variability.

Even though the number of subjects reporting any SAE was higher in the ATV/COBI group (38 vs. 25; 9.6% vs. 6.6%) there was no apparent clustering of SAEs of any one SOC or PT that can explain this overall difference.

Discussion on the benefit-risk balance

Considering the already demonstrated efficacy and safety profiles of the two compounds in the FDC and the potential for dosing simplification and the fact that it is not expected to be countered by the potential risks, the balance is currently considered positive.

Antiretroviral efficacy was demonstrated in 344 treatment-naïve subjects, which appeared in line with that known for ATV/rtv.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Evotaz in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults without known mutations associated with resistance to atazanavir (see sections 4.4 and 5.1) is favourable and 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).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.