25 July 2013
EMA/CHMP/609914/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tybost

International non-proprietary name: cobicistat

Procedure No. EMEA/H/C/002572/0000

Note

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

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GLOSSARY OF ABBREVIATIONS and definition of terms

3TC	lamivudine
ADR	adverse drug reaction
ADV	adefovir
AE	adverse event
aGFR	actual glomerular filtration rate
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
CD4	cluster determinant 4
CI	confidence interval
CL_{cr}	creatinine clearance
CMH	Cochran-Mantel-Haenszel
/co	boosted with cobicistat
COBI	cobicistat
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450 enzyme(s)
DRV	darunavir
EC_{xx}	concentration of a compound inhibiting virus replication by xx%
ECG	electrocardiogram
ECHO	echocardiogram
EFV	efavirenz
EU	European Union
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
EMA	European Medicines Agency
EU	European Union
EVG	elvitegravir
FDA	(United States) Food and Drug Administration
FTC	emtricitabine (Emtriva®)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV, HIV-1, HIV-2	human immunodeficiency virus, type 1, type 2
IC_{xx}	concentration that results in xx% inhibition
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)

Ig	immunoglobulin (IgG, IgM)
INR	international normalized ratio
INSTI	integrase strand-transfer inhibitor
ITT	intent-to-treat
KM	Kaplan-Meier
LDL	low-density lipoprotein
LSM	least-squares mean
M21	cobicistat metabolite (carbamate cleavage); also named E1, GS-9454, and GS-342006
M26	cobicistat metabolite (dealkylation at methylurea); also named E5 and GS-341842
M31	cobicistat metabolite (isopropyl methine hydroxylated); also named E3, GS-9612, and GS-364751
M39	cobicistat metabolite (cleavage and deethylation of the morpholine)
MAA	marketing authorization application
MATE	multidrug and toxin extrusion protein
MDZ	midazolam
MedDRA	Medical Dictionary for Regulatory Activities
M = F	missing = failure
MH	Mantel-Haenszel
mRNA	messenger ribonucleic acid
MRP	multidrug resistance-associated protein
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PDE-5	phosphodiesterase-5
Pgp or MDR1	P-glycoprotein
PI	protease inhibitor
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PR	electrocardiographic interval occurring between the onset of the P wave and the QRS complex, representing time for atrial and ventricular depolarization, respectively
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QUAD	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, coformulated
/r	boosted with ritonavir
RAL	raltegravir

RTV	ritonavir
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
STR	single-tablet regimen
TDF	tenofovir disoproxil fumarate (Viread®)
TFV	tenofovir
TLOVR	time to loss of virologic response
TPV	tipranavir
TVD	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of the normal range
ZDV	zidovudine

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Ltd submitted on 26 April 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Tybost, 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 23 June 2011.

The applicant applied for the following indication.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that cobicistat was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0239/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of the submission of the application, the PIP 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.

Applicant's requests for consideration

New active Substance status

Based on the review of the data the CHMP considered that the active substance cobicistat contained in the medicinal product Tybost was to be qualified as a new active substance at the time of submission of this application.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

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

Gilead Sciences Limited
IDA Business & Technology Park
Carrigtohill, County Cork
Ireland

1.3. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Philippe Lechat

- The application was received by the EMA on 26 April 2012.
- The procedure started on 23 May 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 August 2012 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 August 2012 (Annex 2).
- During the meeting on 20 September 2012, 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 21 September 2012 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 May 2013 (Annex 5).
- During the CHMP meeting on 30 May 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 6).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 June 2013.
- During the meeting on 25 July 2013, 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 Tybost.

2. Scientific discussion

2.1. Introduction

Problem statement

There are approximately 33 million people worldwide living with HIV-1. HIV-1 infection remains is a life-threatening disease in infected persons who do not receive adequate treatment sufficiently early in the course of the infection and/or are infected with virus that is resistant to anti-retroviral agents of several classes such that an adequate treatment regimen cannot be constructed from approved agents.

Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral (ARV) therapy (HAART). The introduction of HAART was associated with a dramatic decrease in AIDS-related mortality and morbidity in the US and Europe. The goal of ARV therapy for HIV-1 infection is to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication.

Current treatment guidelines suggest that initial therapy for ARV treatment-naive HIV-1 infected patients should consist of 2 NRTIs/NtRTIs and either an NNRTI, a boosted protease inhibitor (PI) (e.g. darunavir, atazanavir) or the integrase inhibitor (INSTI) raltegravir (RAL). Boosted PIs are also used in treatment-experienced subjects infected with susceptible virus.

Advantages of PI-based regimens include excellent anti-viral activity, a relatively high barrier for development of drug resistance and sparing treatment with NNRTIs. However, PIs have the potential for multiple drug interactions and may be associated with metabolic complications such as dyslipidaemia, lipodystrophy and insulin resistance. In addition, they require co-administration of low-dose ritonavir (PI/r) to boost exposure through inhibition of CYP3A-mediated metabolism. Indeed, systemic exposure of PIs can be increased by co-administration of low-dose ritonavir (RTV). This pharmacokinetic boosting effect of RTV is achieved through the inhibition of drug metabolism mediated by cytochrome P450 3A enzymes (CYP3A). Consequently, RTV has been widely used at sub-therapeutic doses in combination with many PIs. Of note, RTV itself is an active HIV PI with potent anti-retroviral effect.

About the product

The applicant has developed Cobicistat (COBI, CO) as a pharmaco-enhancer for in HIV-infected subjects with either once daily darunavir (DRV 800 mg) or once daily atazanavir (ATV 300 mg). COBI was intended as an alternative to low dose RTV to achieve pharmaco-enhancement of the plasma profiles of DRV or ATV.

ATV (Reyataz) and DRV (Prezista) are both indicated in the European Union (EU) for coadministration with low-dose RTV for the treatment of HIV-1 infected adults and some subsets of the paediatric population.

Of note, COBI has recently been authorised in the European Union for the fixed drug combination (FDC) Stribild (QUAD; also referred as single tablet regimen STR) which contains three ARVs (emtricitabine [FTC] and tenofovir disoproxil as fumarate [TDF] and elvitegravir

[EVG; an INSTI]) plus COBI which in this FDC modifies the pharmacokinetic profile of EVG. Reports of clinical studies with the Quad STR were also presented in this dossier since these provide additional supportive data on the long-term safety of COBI when used as a pharmacoenhancer in patients with HIV-1 infection.

Initial proposed indication for use:

Tybost is indicated as a pharmacokinetic enhancer of the human immunodeficiency virus 1 (HIV 1) protease inhibitors atazanavir and darunavir in adults.

Initial proposed posology:

150 mg COBI co-administered with atazanavir or darunavir, taken orally, once daily with food.

2.2. Quality aspects

2.2.1. Introduction

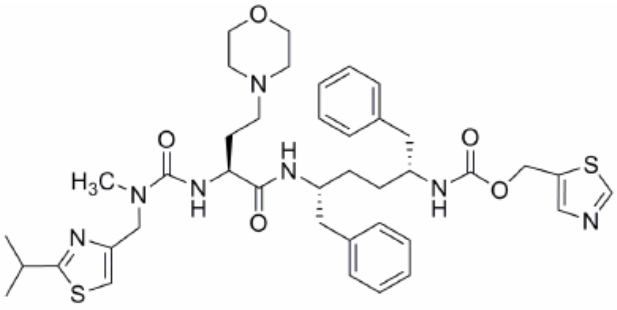
Tybost is a film-coated tablet containing a new active substance not previously authorised in the EU at the time of the submission of this application.

The finished product is presented as film-coated tablets, containing 150 mg of cobicistat. Other ingredients are: microcrystalline cellulose, silicon dioxide, croscarmellose sodium , magnesium stearate, sunset yellow FCF (FD&C yellow #6) aluminium lake (E110), polyethylene glycol, polyvinyl alcohol, talc (E553B), titanium dioxide (E171), iron oxide yellow (E172).

The product is available in bottles with desiccant as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance cobicistat is adsorbed on silicon dioxide. Cobicistat appears as a white to pale yellow, very 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. 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 molecular formula is $C_{40}H_{53}N_7O_5S_2$ and its relative molecular mass 776.0 g/mol. 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 vapor 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

Two sites are proposed for the manufacture of the active substance. Due to its physiochemical properties (see above) cobicistat is manufactured adsorbed on silicon dioxide. Cobicistat on silicon dioxide is manufactured in four well defined synthetic steps. Details about possible reprocessing have been provided. 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. Because the actual loading value of cobicistat on silicon dioxide is subject to manufacturing variability, a target loading with an appropriate range was adopted to ensure a robust down-stream manufacturing process.

Both sites have manufactured commercial scale batches of cobicistat on silicon dioxide and many smaller scale batches during the development of the product. The first site has made 9 large scale batches and the second has made 7 large scale batches. Batch analysis data show that the active substance produced by both manufacturers is of similar quality and can be manufactured reproducibly.

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 drug 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 drug 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 9 representative large scale batches from the first site and 7 representative large scale batches from the second manufacturer have been provided. In addition data for (smaller) 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 and one production scale batch from the first manufacturer and one full scale batch from the second manufacturer packaged in the proposed container were put on stability testing in accordance with the ICH Q1A (R2) Guideline under long-term conditions at 5 °C for up to 24 months and accelerated at 25 °C/60% RH for up to 24 months. 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 24 months of 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, three of the above batches were also tested under 30 °C/75% RH for up to 12 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

Pharmaceutical Development

Tybost is an immediate-release tablet containing 150 mg of cobicistat. A solid oral dosage form was desired in order to provide patient dosing convenience for daily administration. The choice

of dosage form for the cobicistat drug product was also determined by the physical and chemical stability of the active ingredient, degradation pathways of the active ingredient, size of the unit dose, manufacturability, and biopharmaceutical performance of the active substance. Cobicistat is a BCS Class 2 compound, because its solubility is high under acidic conditions but not over the entire range of physiologically relevant pH.

Different approaches were evaluated during development to enable the incorporation of cobicistat into a solid dosage formulation. Based on the evaluation of these approaches, cobicistat adsorbed onto silicon dioxide was the one chosen to be pursued further in development. The primary considerations for choosing cobicistat on silicon dioxide over spray dried material were the physicochemical properties of the material. There are no crystalline forms of cobicistat. Cobicistat is an amorphous solid and is used adsorbed on silicon dioxide because unlike cobicistat itself, the moisture uptake for cobicistat on silicon dioxide is reversible, whereas cobicistat that has been exposed to high humidity undergoes deliquescence and becomes a rubber-like material that is difficult to process and which does not revert back to its original state. The isolation of cobicistat on a solid carrier (silicon dioxide) resulted in avoiding an organic solvent used in the early stages of development that was necessary to prepare cobicistat in solution during the manufacture of the finished product. The product manufacture has been designed to allow for the range of loading levels of cobicistat on silicon dioxide. Silicon dioxide has specific use in this formulation apart from typical use as a glidant and it is used to adjust for the variability of cobicistat loading level on silicon dioxide.

All the excipients used in the cobicistat tablet formulation are commonly used and meet the standards defined in Ph. Eur., except for the film-coating material. This film-coat material is commercially available and tested according to an in-house standard. All the components of the film-coating comply with the standards in Directive 2008/128/EC. The physical and chemical compatibility between cobicistat and the excipients in the formulation has been evaluated by studying prototype formulation matrices.

The formulation composition was optimised by screening several prototype formulations in a high shear granulation process and evaluating different fillers and binders. Based on processing observations and dissolution profiles, a formulation with microcrystalline cellulose as filler and hydroxypropyl cellulose as binder was chosen for further studies. This blend was shown to have excellent compressibility and good tablet characteristics and satisfactory dissolution and was used for Phase 1 and Phase 2 clinical studies.

Based on clinical findings in the Phase 1 study, cobicistat tablets, 150 mg were chosen for further clinical evaluation. The formulation composition and manufacturing process for Phase 2 studies were identical to those used in Phase 1 studies.

The formulation was further adjusted for a dry granulation process. A pivotal bioequivalence (BE) study GS-US-216-01163 was performed to evaluate the formulation and process change for the incorporation of cobicistat active ingredient loaded on the silicon dioxide carrier as part of the final active substance isolation step. Both tablet formulations (dry granulation formulation and Phase 1/2 formulation) were confirmed to be bioequivalent for all three pharmacokinetic (PK) parameters tested: AUCtau, Cmax, and Ctau.

During scale-up manufacturing of the dry granulated formulation a design of experiments (DOE) was performed on multiple small scale batches to establish the critical formulation and

process parameters that affect surface defect formation. Based on the DOE results the formulation for the Phase 3 studies, primary stability batches and commercial formulation was selected. The tablet formulation for the Phase 3 study and the intended commercial product are of the identical formulation, manufactured by the same process, and compressed into tablets in the same dimensions and coating.

A discriminatory dissolution method with regard to formulation and process changes has been developed for quality control purposes for release and stability testing. It was found that granulation particle size and underlying granulation processing parameters have no impact on dissolution and since the variables that affect dissolution are tightly controlled by the tablet manufacturing process, a single point acceptance criterion is appropriate for quality control dissolution testing of the drug product.

Design of experiments was used to establish proven acceptable ranges (PARs) and normal operating ranges (NORs). PARs and NORs for the dry granulation, tablet compression and film-coating steps have been established. Moving inside the PARs would be acceptable without regulatory post approval change assessment when the other process parameters are maintained at their target/ normal operating value. Overall, process optimization studies demonstrated the formulation and manufacturing process are robust, yielding drug product with desired quality attributes over a wide range of processing parameters.

Adventitious agents

None of the excipients used in the manufacture of Tybost tablets are of human or animal origin. Appropriate BSE/TSE declarations from the manufacturers of excipients have been provided.

Manufacture of the product

The manufacturing procedure for Tybost tablets is divided into four sets of unit processes: (1) dry granulation and final blending, (2) tablet compression, (3) film-coating, and (4) packaging. The manufacturing process is a standard process and a full description is provided. Intermediates of manufacturing are satisfactorily described and controlled and holding time is defined on these intermediates.

The robustness of the manufacture has been demonstrated by successful process validation of 3 representative batches at the lower end for the proposed batch size range. Process validation will be completed at the high end of the batch size range according to an agreed protocol prior to marketing. The robustness of the manufacturing procedure for the clinical and the proposed commercial formulation has been demonstrated by the successful manufacture of representative batches.

Product specification

The finished product release specifications include appropriate tests for appearance (visual examination), identification (HPLC and UV), water content (Ph. Eur.), assay (UPLC), degradation products (UPLC), uniformity of dosage unit (Ph. Eur.), dissolution (Ph. Eur.) and microbiological examination (Ph. Eur.).

Batch analysis results are submitted for 2 commercial scale and 5 smaller batches used throughout development and manufactured with active substance sourced from both suppliers. The batch analysis data are within the set specification limits and show that the Tybost tablets can be manufactured reproducibly.

Stability of the product

One commercial scale and three smaller batches in the proposed packaging were placed on stability according to ICH guidelines under the following conditions: long term 25 ± 2 °C / 60 ± 5% RH, intermediate 30 ± 2 °C / 75 ± 5% RH and accelerated 40 ± 2 °C / 75 ± 5% RH. Results were provided for up to 24 months in long term and intermediate conditions and for 6 months in accelerated conditions. Assay, degradation product content, and water content results were well within specifications at all conditions. No change in the dissolution profile was observed for the four batches tested.

Potential enantiomers have been monitored in order to demonstrate that chiral purity is not affected under storage. Analytical methods were the same as for release and have been shown to be stability indicating.

Statistical analysis was performed for assay, total degradation products, COBI-NOx, and COBI-HIP, showing that the proposed shelf-life is appropriate.

A photostability study was conducted on one batch of cobicistat tablets following the ICH Q1B Guideline. No degradation was noted after exposure to light. Additional stress studies under extreme temperature and humidity conditions were performed at 50 °C/ambient humidity and at 25 °C / 80% RH for 6 weeks. In addition to evaluate the stability of cobicistat tablets in the situation where tablets may be removed from the original container, tablets were directly exposed to 25 °C / 60% RH or 30 °C / 75% RH in an open dish for 6 weeks. Results met the specification for all quality test attributes after 6 weeks storage. No degradation was noted under any of the stress conditions: 25 °C / 80% RH; 50 °C; 25 °C / 60% RH on Petri dish or 30 °C / 75% RH on Petri dish.

The overall stability results support the proposed shelf life and storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. Development of the drug product had to take into account the particular characteristics of the active substance and especially the need to ensure a physically and chemically stable form of cobicistat. The choice of formulation, of excipients and the manufacturing process has been justified. 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 the clinic.

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 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. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive non clinical package was provided, including single-dose oral toxicity studies in mice and rats; repeat-dose oral toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks) and dogs (up to 39 weeks), genotoxicity tests both *in vitro* and *in vivo*; and a full developmental and reproductive toxicity program. Two-year oral carcinogenicity studies in mice and rats have also been provided within this submission.

The pivotal toxicology and the majority of the safety pharmacology studies conducted by the applicant were reported to be GLP compliant. The safety studies that were not conducted to GLP were conducted to an appropriate scientific standard.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Cobicistat is a structurally modified analogue of the protease inhibitor, ritonavir (RTV), which is devoid of anti-retroviral activity. COBI has been shown to inhibit the activity of human CYP3A enzymes (IC_{50} 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.

Despite the extensive use of RTV, the precise mechanism of action remains unclear and there are data to suggest that RTV acts as a mechanism-based, competitive, mixed competitive-noncompetitive CYP3A4 inhibitor and more recently an irreversible Type II inhibitor [Sevrioukova & Poulos, 2010]. 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 agrees that the precise molecular mechanism of inhibition is not completely understood and that overall, the mechanism may be mixed.

Secondary pharmacodynamic studies

During a radioligand binding assay to screen for interactions at a panel of receptor and ion channels, COBI showed significant binding to the benzothiazepine sensitive L-type calcium

channel, hERG potassium channel and sodium channel, site 2 at a concentration of 10 µM, which is 105 fold higher than the proposed clinical C_{max} (free). The effects of COBI on cardiac ion channels have been investigated further and the results are summarised in the safety pharmacology programme section.

In vitro data indicate that when compared to the protease inhibitor, RTV; COBI shows a lower potential to inhibit host proteases (such as cathepsin D), affect adipocyte functions (such as lipid accumulation and inhibition of glucose uptake) and cause cytotoxicity in MT-2 lymphoblastoid T-cells. The effects of COBI on the inhibition of chymotryptic-like activity of the 26S proteasome and the viability of HepG2 hepatoma cells were similar to that observed with RTV.

Safety pharmacology programme

A series of safety pharmacology studies have been performed in order to evaluate the effects of COBI on the central nervous, cardiovascular, respiratory and renal systems.

A single oral dose of COBI at 50 mg/kg had no effects on the central nervous system (CNS) in the rat. At higher doses (≥ 150 mg/kg), salivation along with decreased arousal, locomotor activity, motor activity and a decrease in body temperature were noted 2 and 6 hours post dose. The corresponding C_{max} at the no-effect level was 5 ug/mL, which is approximately 4.2-fold higher than that observed clinically. In the rat, following single oral doses of up to 500 mg/kg, COBI had no effects on the respiratory rate, tidal volume, or derived minute volume.

During electrophysiology studies, COBI inhibited the hERG potassium current and the hCav1.2 L-type calcium channel, but was a weak inhibitor of the hNav1.5 sodium channel (with IC_{50} values of 1.8-1.9 µM, 6 µM and 86.5 µM, respectively). Given that the safety margin between the IC_{50} value for hERG inhibition and the observed clinical C_{max} (free) was below 30, a series of additional studies were performed to further evaluate the potential for QT prolongation. In the rabbit purkinje fibre assay, COBI at ≥1 µM caused a significant shortening of action potential duration (APD60 and/or APD90); however, no changes in the other action potential parameters (that are predictive of QT prolongation) were observed. 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.

Pharmacodynamic drug interactions

Given that the use of ATV is associated with PR prolongation in man, that COBI also appears to increase PR interval (*in vitro* and *in vivo*), and that in man, COBI is to be used in combination with ATV (as part of an anti-retroviral treatment regimen), 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. It is noted that during this study, COBI alone had no effect on the QT interval or MAPD at up to 1.5 µM, which is in contrast to the findings from the first study conducted in the isolated rabbit heart. The low concentrations of COBI within the post-perfusion buffer (as observed during the second study) along with differences in the experimental methods are thought to be responsible for the observed difference in the results.

2.3.3. Pharmacokinetics

The *in vitro* absorption, metabolism of COBI, and the potential to cause drug interactions were studied in the appropriate model systems.

In support of the studies conducted to GLP, analysis of COBI in plasma from mice, rats, rabbits and dogs utilized fully validated methods based upon LC/MS/MS.

In fasted male animals, the absolute oral bioavailability for COBI (in solution) was estimated to be 33%, 11% and 7% in the rat, dog and monkey, respectively. Although there were some deviations, in general, following single or repeated oral administration in the mouse, rat and dog, systemic exposures increased in a manner that was greater than proportional with dose (reflecting saturation of first-pass metabolism) and following saturation, systemic exposures generally increased in a dose-proportional manner. In the mouse and rat, exposures to COBI did not appear to change significantly over time; however, in the dog, there was some evidence of accumulation upon repeated dosing (possibly due to differential effects on the induction of CYP3A enzymes). In the mouse and dog, there were no appreciable sex differences in systemic exposure. However, in the female rat, exposures were approximately 2-fold higher than in males, which is consistent with the known gender difference in CYP3A expression in this species.

In the rat, combination studies have been performed where COBI was administered in combination with the protease inhibitor, atazanavir (ATV) or the integrase strand-transfer inhibitor, elvitegravir (EVG). In a 13-week study, exposures to ATV were higher when ATV was administered in combination with COBI; which generally supports its proposed use.

In the species evaluated, the binding to plasma proteins (*in vitro*) was considered to be moderately high (90.9 to 97.7%) and the distribution to red blood cells (*in vivo*) was low. Following single oral administration of radiolabelled-COBI to the Sprague Dawley rat, drug related radioactivity was widely distributed. The peak tissue concentrations were achieved at 1 hour post-dose and the highest tissue:plasma ratios were observed in the liver, adrenal gland, kidney, pituitary gland and thyroid gland, which correlates with the principal findings from the toxicity studies. The distribution profile in pigmented (Long Evans) rats was comparable to that of albino rats; however, the levels of radioactivity in the eyes (uveal tracts) of pigmented rats were higher and higher concentrations of radioactivity were observed in pigmented skin, when compared to non pigmented skin; which suggests an association of COBI and/or its metabolites with melanin. Data from a pre/post-natal study in the rat indicate that COBI distributes into the milk of lactating rats, whereby the milk:plasma ratios ranged from 1.3 to 1.9.

In vitro metabolism in all species yields 3 predominant primary oxidative metabolites [M21, M26, and M31 (GS-9612)]. *In vivo*, COBI is the major radioactive component circulating in plasma and the 3 metabolites, along with M39, another common primary metabolite, were the

4 most abundant metabolites in the mouse, rat, dog, and human. There are no unique or major (> 10%) human metabolites. For M31 and M26, the observed inhibition of CYP3A was similar to or marginally lower than that observed with COBI. M21 and M26 had no effect on the activities of the other CYP enzymes, but M31 was shown to inhibit CYP2C19 (IC_{50} 2.95 µM) and CYP2D6 (IC_{50} 0.21 µM). As the circulating levels of these metabolites in man are extremely low, the observed CYP enzyme inhibition is unlikely to contribute to the observed pharmacological effects of COBI or potential drug interactions.

Cobicistat is metabolized 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 and there is no evidence for metabolism by direct conjugation.

Following oral administration of [^{14}C]COBI in the rat and dog, the majority of the radioactivity (≥ 65%) was recovered in bile, faeces and urine (the majority in the bile), confirming absorption *in vivo*.

2.3.4. Toxicology

The general toxicity, genotoxicity, reproductive toxicity, local tolerance, immunotoxicity and the potential for hypersensitivity to COBI alone have been characterized during a series of *in vitro* and *in vivo* studies (Table 1). Combination toxicity studies with ATV or EVG, compounds that are boosted by COBI, were also conducted. Apart from the different mechanism of action on CYP inhibition between humans and rats and dogs, the rat and dog were considered appropriate species for the toxicology studies because of the similar metabolism of COBI in humans and the ability to achieve high systemic exposures in these species.

All *in vivo* studies conducted with COBI, utilized oral administration, which is the proposed clinical route, with the exception of the sensitization, eye and dermal irritation studies.

Table 1. Toxicology studies performed with COBI

Study Type & Duration		Route of Administration	Species	Compound Administered
SINGLE-DOSE TOXICITY				
		Oral	Mouse, Rat	COBI
REPEAT-DOSE TOXICITY				
	1 week	Oral	Dog	COBI
	2 weeks	Oral	Mouse, Rat	COBI
	4 weeks	Oral	Mouse, Dog	COBI
	13 weeks	Oral	Mouse, Dog[a]	COBI
	26 weeks	Oral	Rat	COBI
	39 weeks	Oral	Dog	COBI
	5 days (combination toxicity with ATV)	Oral	Rat	COBI/ATV
	13 weeks (combination toxicity with ATV)	Oral	Rat	COBI/ATV
	13 weeks (combination toxicity with EVG)	Oral	Rat	COBI/EVG

Study Type & Duration	Route of Administration	Species	Compound Administered
GENOTOXICITY			
In vitro: non-mammalian system (reverse mutation assay)	*In Vitro*	Bacteria	COBI
In vitro: mammalian cell system (forward mutation)	*In Vitro*	Mouse lymphoma cells	COBI
In vivo: micronucleus assay	Oral	Rat	COBI
CARCINOGENICITY			
2 years	Oral	Mouse, Rat	COBI
REPRODUCTIVE TOXICITY			
Fertility and early embryonic development	Oral	Rat	COBI
Embryo-fetal development	Oral	Rat, Rabbit	COBI
Prenatal and postnatal development	Oral	Rat	COBI
Juvenile toxicity	Oral	Rat	COBI
LOCAL TOLERANCE			
Eye irritation	Topical/Ex *Vivo*	Bovine	COBI
Skin irritation	Topical	Rabbit	COBI
OTHER STUDIES			
Sensitization	Topical	Mouse	COBI
Immunotoxicity	Oral	Rat	COBI
Impurities – Qualification studies	Oral	Rat	COBI
Impurities – Qualification studies	Oral	Rat	COBI/EVG
Impurities – Genotoxicity; non-mammalian system (reverse mutation assay)	*In Vitro*	Bacteria	COBI-related impurites
Impurities – Genotoxicity; mammalian cell system (forward mutation)	*In Vitro*	Mouse lymphoma cells	COBI-related impurites
Combination toxicity studies	Oral	Rat, Dog	COBI/GS-8374

a 13-week interim sacrifice

Single dose toxicity

Following single oral administration in the mouse and rat, no test article related signs were observed at up to 100 mg/kg and 500 mg/kg respectively. In mouse, the NOAEL was 100 mg/kg. In rat, the NOAEL was 500 mg/kg. The corresponding C_{max} values in the mouse and plasma concentrations at 1 hour post-dose in the mouse and rat respectively, were 13.2- and 4.54 to 5.6-fold higher than the observed clinical C_{max}.

Repeat dose toxicity

The NOAEL of COBI when administered to CD-1 mice via daily oral gavage for 13 weeks was 50 mg/kg/day in females based on the absence of any toxicologically significant adverse effects; and 5 mg/kg/day in males. The NOAEL for COBI was 30 mg/kg/day when administered daily via oral gavage to rats for 26 weeks. The NOAEL for COBI was 10 mg/kg/day when administered daily by oral gavage to dogs for 39 weeks.

Following repeated oral administration of COBI, the primary target organs were the liver (mouse, rat, and dog) and thyroid (rat only). Slight, non-adverse haematological changes were noted in the rat and slight changes in clinical chemistry parameters were observed in the mouse, rat, and dog, with urinalysis changes (increases in albumin:globulin ratio, urine volume and pH and lower urine specific gravity) noted primarily at high doses in rat and dog, where the exposures exceeded those proposed clinically. 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. Urinalysis changes (higher urine volume, lower urine specific gravity, increases in electrolyte excretion) showed no progression after long term dosing, were not associated with remarkable serum chemistry or histopathological correlates, and were reversible.

Other potential toxicities related to COBI that were observed in non-clinical studies include PR interval prolongation in the 4-week dog study and decreases in left ventricular (LV) function in isolated rabbit hearts. The safety pharmacology data as described previously suggest that there may be a potential for additive effects when COBI is administered in combination with ATV; however the observed effects were not considered to be clinically significant. Overall, the combination toxicity studies of COBI with EVG or ATV did not result in unexpected or additive toxicities.

Genotoxicity

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.

Carcinogenicity

In the mouse, following repeated oral administration for a minimum of 95 weeks (males) or 87 weeks (females), COBI was not carcinogenic at exposures that were 7 to 16 fold higher than those observed clinically. In the rat, following repeated oral administration for a minimum of 97 weeks at 10, 25, and 50 mg/kg/day (males) and 5, 15, and 30 mg/kg/day (females), COBI caused an increased incidence of combined thyroid follicular cell adenoma and carcinomas at exposures (AUC) that were lower than that observed clinically. It is acknowledged that the 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.

Reproduction Toxicity

No adverse effects on male or female fertility and reproductive performance were observed at up to 100 mg/kg/day, where the corresponding exposures (AUC) are at least 3 fold higher than that observed clinically. During a rat embryofetal development study, increased post-implantation loss and skeletal variations (ossification changes in the spinal column and sternebra) along with decreased fetal weights (associated with significant decreases in maternal body weights) were observed at 125 mg/kg/day. 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 treatment-related effects on embryo/fetal viability and growth and no fetal anomalies at systemic exposures that were 6 fold higher than that proposed clinically.

The applicant has indicated that no remarkable findings occurred during the reproductive toxicity studies conducted with ATV and that darunavir was associated with a transient reduction in body weight gain during lactation.

2.3.5. Ecotoxicity / environmental risk assessment

Table 2. Summary of main study results

Substance (INN/Invented Name): COBI					
CAS-number (if available):					
PBT screening		Result			Conclusion
Bioaccumulation potential- log K_{ow}	OECD122	3.05-4.10			Not > 4.5; not PBT.
Phase I					
Calculation	Value	Unit			Conclusion
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	For Fpen (1%): 0.75 For Fpen (for phase I 0.28%): 0.21	µg/l			PEC_{SW} > 0.01 µg/l
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OECD 106	K_{oc} soil: 3624-9012L/Kg K_{oc} sludge: 830-1287L/Kg			K_{OC}<10000 L/Kg.
Ready Biodegradability Test	OECD 301	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	>10% associated with sediment from Day 7 DT50 (dissipation) 171-241 days WaterDT50 5.6-12days No significantmetabolites formed			10% radioactivity associated with sediment at Day 7 or beyond. Progress to Sediment-dwelling studies. The DT50 (dissipation) value suggests that COBI is persistent
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae Growth Inhibition *Pseudokirchneriella*	OECD 201	NOEC	29.3	mg/ L	N/A

subcapitata)					
Daphnia sp. Reproduction Test	OECD 211	NOEC	17.5	mg/L	N/A
Fish, Early Life Stage Toxicity	OECD 210	NOEC	4.84	mg/L	N/A
Activated Sludge	OECD 209	NOEC	≥1000	mg/L	N/A
Phase IIb Studies :					
Bioaccumulation	OECD 305	BCF	<2		Minimal bioconcentration

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:

- An updated environmental risk assessment which clarifies the effects of COBI on sediment dwelling organisms should be provided (by Q2 2015).

2.3.6. Discussion on non-clinical aspects

Cobicistat is a structurally modified analogue of the protease inhibitor, ritonavir (RTV), which is devoid of anti-retroviral activity. COBI has been shown to inhibit the activity of human CYP3A enzymes (IC_{50} values 0.03 to 0.15 µM) and enzyme kinetic studies have demonstrated that it is an efficient inactivator of human CYP3A activity. Data from the secondary pharmacology studies suggest that the potential for side effects (that are due to interactions at these secondary targets) with COBI is roughly similar to that observed with RTV.

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. 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.

In vitro metabolism in all species yields 3 predominant primary oxidative metabolites [M21, M26, and M31 (GS-9612)]. Cobicistat is metabolized 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.

The intended, positive pharmacokinetic interaction between COBI and darunavir/atazanavir is an increase in the bioavailability and a decrease in the rate of elimination of the antiviral agent due to inhibition of CYP3A activity by COBI. This interaction has been well characterized *in vitro*. The data suggest that COBI does not inactivate CYP3A enzymes appreciably in rat, dog and monkey, which would suggest that the mode of inhibition is different in these species when compared to man.

A comprehensive toxicology package was provided, including single-dose oral toxicity studies in mice and rats; repeat-dose oral toxicity studies in mice (up to 13 weeks), rats (up to 26

weeks), dogs (up to 39 weeks), genotoxicity tests both *in vitro* and *in vivo*; and a full developmental and reproductive toxicity program. Two-year oral carcinogenicity studies in mice and rats have also been provided.

During a rat embryofetal development study, increased post-implantation loss and skeletal variations and decreased fetal weights (associated with significant decreases in maternal body weights) were observed at 125 mg/kg/day. The exposures at the no-effect level for embryo/fetal viability and growth and developmental toxicity were similar to that proposed clinically. Data from a pre/post-natal study in the rat indicate that COBI distributes into the milk of lactating rats, whereby the milk:plasma ratios ranged from 1.3 to 1.9 and hence; a risk to newborns or infants cannot be excluded.

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

A long term carcinogenicity study of cobicistat in rats revealed tumorigenic potential specific for this species, these findings were not considered to be clinically relevant. A long term carcinogenicity study in mice did not show any carcinogenic potential.

The applicant has conducted a full environmental risk assessment. The water-sediment-study (OECD 308) clearly shows that the active ingredient cobicistat is persistent in the total water-sediment system; with a DT50 of 171-241 days, which exceeds 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 on sediment organisms and the data will be submitted post-authorisation.

2.3.7. Conclusion on the non-clinical aspects

Cobicistat is a structurally modified analogue of the protease inhibitor, ritonavir (RTV), which is devoid of anti-retroviral activity and is a selective inhibitor of cytochrome P450 CYP3A.The non-clinical data reveal no specific hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, toxicity to reproduction and development, genotoxicity and carcinogenicity. However, non-clinical data have demonstrated excretion of cobicistat in milk and hence, a risk to the newborns/infants cannot be excluded. Therefore COBI should not be used during breast-feeding.

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.

- Tabular overview of clinical studies (COBI as a single-agent tablet or as a component of the QUAD STR)

Clinical Study	COBI			Dosage Form of Coadministered or Control Drugs
	Dosage Form	Dose	n	
Mass-Balance of COBI in Healthy Subjects				
GS-US-216-0111	COBI 150-mg tablets COBI 150-mg capsules 148.5 mg nonradiolabeled COBI plus 100 μCi [1.5 mg] [^{14}C]COBI	150 mg	8	Not applicable
Single- and Multiple-Dose PK of COBI in Healthy Subjects				
GS-US-216-0113	COBI 100-mg tablets	300, 400 mg	24	Not applicable
GS-US-201-0101 food-effect study	COBI 150-mg tablets	150 mg	33	GS-8374 50- and 150-mg tablets GS-8374 placebo tablets COBI placebo tablets
GS-US-236-0105 food-effect study	QUAD fixed-dose combination 150/150/200/300-mg tablets	150/150/ 200/300 mg	24	Not applicable
Single- and/or Multiple-Dose PK and PK-PD Relationships of COBI in Healthy Subjects				
GS-US-216-0101 proof-of-concept	COBI 25- or 100-mg tablets	50, 100, 200 mg	42	RTV 100-mg soft gelatin capsules (overencapsulated) and matching placebo capsules COBI placebo tablets MDZ hydrochloride 5 mg (2.5 mL of a 2-mg/mL oral syrup)
GS-US-216-0112	COBI 150-mg tablets	150 mg	51	Desipramine 50-mg tablets Digoxin 0.25-mg tablets EFV 600-mg tablets
GS-US-216-0110	COBI 100- and 150-mg tablets	100, 150 mg	41	ATV 300-mg capsules RTV 100-mg soft gelatin capsules
GS-US-216-0115 (see Table 10 for further details)	COBI 150-mg tablets	150 mg	33	DRV 400-mg tablets RTV 100-mg soft gelatin capsules
Effect of Intrinsic Factors: Healthy Subjects and Subjects with Impaired Hepatic or Renal Function				
GS-US-183-0133 hepatic impairment	COBI 150-mg tablets	150 mg	20	EVG 150-mg tablets
GS-US-216-0124 renal impairment	COBI 150-mg tablets	150 mg	24	EVG 150-mg tablets
Effect of Extrinsic Factors: Concomitant Administration of COBI with Other Drugs				
Administration of COBI with Other Antiretrovirals (Healthy Subjects)				

Clinical Study	COBI			Dosage Form of Coadministered or Control Drugs
	Dosage Form	Dose	n	
GS-US-216-0119	COBI 150-mg tablets	150 mg	47	EVG 150-mg tablets DRV 600-mg tablets RTV 100-mg capsules ETV 100-mg tablets TPV 250-mg capsules
GS-US-201-0104	COBI 150-mg tablets	150 mg	18	EVG 150-mg tablets GS-8374 150-mg tablets DRV 400-mg tablets
Administration of COBI with Drugs Other than Antiretrovirals (Healthy Subjects)				
GS-US-216-0120	COBI 150-mg tablets	150 mg	33	EVG 150-mg tablets Famotidine 40-mg tablets Omeprazole 20-mg capsules
GS-US-216-0116	COBI 150-mg tablets (original formulation 1 and new formulation 2)	150 mg	62	EVG 150-mg tablets RTV 100-mg soft gelatin capsules MDZ hydrochloride 5 mg oral syrup
GS-US-216-0122	COBI 150-mg tablets	150 mg	16	EVG 150-mg tablets Famotidine 40-mg tablets
GS-US-216-0123	COBI 150-mg tablets	150 mg	34	EVG 85- or 150-mg tablets Rosuvastatin 10-mg tablets ATV 300-mg capsules RTV 100-mg capsules Rifabutin 150-mg capsules
GS-US-236-0106	QUAD fixed-dose combination 150/150/200/300-mg tablets	150/150/ 200/300 mg	16	Ortho Tri-Cyclin Lo tablets (NGM 0/0.180/0.215/ 0.250 mg/EE 0/0.025 mg)
Multiple-Dose PK and PK-PD Relationships of COBI in HIV-1 Infected Subjects				
GS-US-216-0105 Phase 2 (see Table 10 for further details)	COBI 150-mg tablets	150 mg	69	ATV 300-mg capsules RTV 100-mg soft gelatin capsules and matching placebo capsules FTC/TDF 200/300-mg tablets COBI placebo tablets
GS-US-216-0114 Phase 3 (see Table 10 for further details)	COBI 150-mg tablets	150 mg	344	ATV 300-mg capsules RTV 100-mg tablets FTC/TDF 200/300-mg tablets RTV placebo tablets COBI placebo tablets
Additional PK studies				
GS-US-216-0107 Phase 1 TQT study	COBI 100- or 150-mg tablets	250, 400 mg	48	COBI placebo tablets Moxifloxacin 400-mg tablets
GS-US-216-0121 Phase 1, effect on renal function	COBI 150-mg tablets	150 mg	30	RTV 100-mg soft gelatin capsules and matching placebo capsules COBI placebo tablets Iohexol 1500 mg (5 mL of 300-mg iodine/mL solution) as IV bolus over 1 to 2 minutes

ATV, atazanavir; ^{14}C, radiolabeled carbon 14; COBI, cobicistat; DRV, darunavir; ECG, electrocardiogram; ECHO, echocardiogram; EE, ethinyl estradiol; EFV, efavirenz; ETV, etravirine; EVG, elvitegravir; FTC/TDF, emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada); GS-8374, investigational HIV-1 protease inhibitor; HIV-1, human immunodeficiency virus, type 1; IV, intravenous; MDZ, midazolam; NGM, norgestimate; RTV, ritonavir; STR, single-tablet regimen; TPV, tipranavir

In addition, the following studies were provided:

- GS-US-216-0125: multiple-dose DDI study of once-daily EVG/COBI and methadone or buprenorphine/naloxone in healthy subjects
- GS-US-216-0134: a DDI study between COBI and TDF
- GS-US-216-0130: DRV/COBI+2 NRTIs in treatment-naive and experienced through 24 weeks
- GS-US-236-0118: effects on renal parameters in HIV-1 infected subjects with mild to moderate renal impairment. Comparison of STB with ATV/co or DRV/co, each with 2 NRTIs.

Of note, in the original MAA (also referred as "the original submission), 48 weeks of exposure data from Phase 3 GS US 216 0114 and 60 weeks of exposure during a blinded treatment phase from Phase 2 GS US 216 0105 were provided. During the evaluation, updated data from GS-US-216-0114 (Week 96 data cut) and GS-US-236-0118 (Week 24 data cut) as well as new data from GS-US-216-0130 (Week 24 CSR) were provided.

2.4.2. Pharmacokinetics

The pharmacokinetic (PK) properties of cobicistat (COBI) were assessed in Phase 1 studies with COBI alone, on co-administration with elvitegravir (EVG) and as a component of the QUAD STR. The Phase 2 and 3 studies of efficacy included intensive PK sub-studies and sparse sampling. A population PK analysis was conducted.

Formulations

The immediate release formulation used in the Phase 3 study (F2) and the proposed commercial product are of identical formulation, manufactured by the same process and compressed into tablets with the same dimensions and coating. Other formulations (e.g. F1) were used throughout the clinical development.

Analytical methods

Determination of COBI concentrations (GS-9350) in plasma involved SPE followed by LC-MS/MS with positive ionisation. The method was validated. Calibration curves for initial assays ranged from 5 (LLQ) to 1000 or 2500 ng/mL. In a later version of the assay the range was 10-5000 ng/mL. The range for the human metabolite GS-9612 (also numbered GS-364751 [E3] or M31) was 5-2500 ng/mL while the range for the human metabolites GS-341842 (also numbered [E5] or M26) and GS-342006 (or GS-9454 also numbered [E1] or M21) was 5-5000 ng/mL.

Absorption

Bioavailability

The absolute bioavailability of COBI has not been investigated. COBI was found to have high forward permeability through Caco-2 cells and showed no evidence for marked efflux. It was found to be a substrate for MDR1 or BCRP based on increased efflux ratios in MDR1 and BCRP over-expressing cells. COBI efflux ratios were decreased by the MDR1 inhibitor cyclosporin A (10 µM) and the BCRP inhibitor Ko134 (10 µM).

GS-US-216-0101 (50 - 200 mg) and GS-US-216-0113 (300 - 400 mg) evaluated the administration of COBI in the fed state. There were much greater than dose-proportional increases in C_{max} and AUC that were considered to be due to reduced clearance (apparent clearance 10-15% of hepatic blood flow) and higher bioavailability (reduction in first pass effect) consistent with metabolic auto-inhibition properties.

GS-US-216-0116 compared the Phase 3 formulation of COBI (F2) with the Phase 2 version (F1) on dosing with 150 mg daily for 10 days. The 90% CIs around the GMRs for COBI AUC_{tau}, C_{tau}, and C_{max} showed bioequivalence between the formulations.

Influence of food

A food effect study was not conducted for COBI. GS-US-236-0105 evaluated the effect of fasting, light and high-fat meals on the PK of COBI when the F1 formulation of the QUAD STR was administered. COBI AUC_{inf}, AUC_{last} and C_{max} met bioequivalence criteria for light meal and fasted conditions. There were decreases (ranging from 17% to 27%) observed with a high-calorie/high-fat meal vs. the fasted state or vs. dosing after light meal.

The decreased COBI AUC_{last} (6570.2 [49.1] ng•h/mL) observed following the high-calorie, high-fat meal (relative to the light meal or fasting conditions) did not affect the exposures of COBI-boosted EVG, suggesting that regardless of the type of food COBI plasma levels provided adequate CYP3A inhibition. COBI was to be taken with food (unspecified) in the Phase 2 and 3 studies. Following administration of ATV/co in GS-US-216-0105 and GS-US-216-0114 the mean (%CV) COBI AUCs were 9034.0 (44.6) ng•h/mL and 11,113.2 (40.5) ng•h/mL, respectively. In addition, the population PK analysis of data from these studies gave a mean COBI AUC of 8923.9 ng•h/mL.

Distribution

When [^{14}C] COBI (150 mg COBI dose) was administered on the last day of a multiple-dose period to healthy subjects (GS-US-216-0111) the blood-to-plasma ratio of total ^{14}C - radioactivity was time-independent and ~ 0.5, indicating that COBI is excluded from the cellular components of the blood.

Based on equilibrium dialysis studies COBI was ~97% to 98% bound to human plasma proteins regardless of concentration. In GS-US-183-0133 COBI was highly protein bound in plasma from normal subjects and those with moderate hepatic impairment with overall unbound fractions of 2.71% ± 0.56% and 3.23% ± 0.63%, respectively. In GS-US-216-0124 COBI was highly protein bound in plasma from normal subjects and those with severe renal impairment with overall unbound fractions of 2.49% ± 0.92% and 2.47% ± 0.62%, respectively.

Elimination

In the steady state mass balance study GS-US-216-0111 radiolabeled COBI (150 mg dose of [^{14}C]COBI) was given on day 7 following administration of 150 mg daily for 6 days in the fed state. Peak [^{14}C]COBI plasma concentrations were observed at 4.5 h post-dose. The estimates for C_{max} and AUC_{tau} were similar to values seen in other studies but the half-life was longer.

COBI was the predominant species in plasma in the first 24 h (98.6% of the circulating radioactivity) with no quantifiable metabolites. In most subjects, plasma radioactivity was not detectable beyond 32 h and was BLQ in all subjects by 96 h.

Total recovery of radioactivity was 94% and most (86.2%) of the dose was recovered in faeces, consistent with hepatobiliary excretion. A mean of 62.3% of the total radioactive dose was quantified and comprised primarily the parent drug or the oxidative metabolites M21 or M31. COBI was the major species in the faeces (27%) followed by M31 (14%), and M21 (5.5%). All other metabolites in the faeces were in trace amounts and did not exceed 3% of the dose. Only 8.2% was recovered in urine, primarily as unchanged parent drug (5.5%) and with low levels of metabolites M21 and M31 (each < 1%). Most of the recovered dose in urine (8%) appeared within 48 h. COBI displayed both dose- and time-dependent changes in apparent clearance (CL/F), consistent with the properties of a mechanism-based inhibitor.

Metabolism

In-*vitro* studies showed that COBI is extensively metabolised via CYP3A (major) and CYP2D6 (minor) mediated oxidation with no evidence of direct Phase 2 metabolism. There are no unique or major (>10%) human metabolites.

Primary metabolites include isopropyl oxidation (M31), cleavage at the N-methylurea (M26), cleavage of the carbamate (M21) and cleavage and deethylation of the morpholine (M39). CYP3A can catalyse all reactions, while CYP2D6 contributes to the generation of M31. Mean plasma exposures of M31 were < 3% of COBI exposure (AUC) after a single 150 mg dose in the mass-balance study. The three most abundant human metabolites of COBI are weaker inhibitors of CYP3A compared to COBI and are not considered likely to contribute to CYP3A inhibition.

Population PK analysis

The population PK report for COBI was based on a model derived from intensive sampling data from:

- 11 Phase 1 studies in healthy subjects (8 with COBI; 3 with QUAD STR)
- 5 studies in HIV-infected subjects, comprising:

  Two COBI studies - GS-US-216-0105 (Phase 2) and 0114 (Phase 3)

  Three QUAD STR studies GS-US-236-0104 (Phase 2) and the two Phase 3 studies 0102 and 0103

The model was based on log-normalised COBI concentration-time data and consisted of one central compartment with linear and nonlinear elimination pathways.

A one-compartment PK model with zero- and first-order absorption rate constant, an absorption lag time and including the effect of body weight on the apparent volume of distribution of COBI provided a good description of COBI PK after repeated dosing with 150 mg in healthy subjects and HIV-infected patients.

Inclusion of body weight resulted in a marginal decrease in the inter-individual variability associated with the apparent volume of distribution (COBI Vc/F 8.9% to 6.3%). A statistically significant positive correlation was observed between weight and COBI Vc/F but the effect was modest. Relative to the median weight (74.4 kg), the range of observed weights (57–101 kg; 5th to 95th percentile) resulted in differences of -22% and +24%, respectively, corresponding to a +37% and -27% change in exposure from the population median COBI AUC_{tau} of 10234 ng•hr/mL. Median COBI exposures within the bottom 5th and upper 95th percentile of weight were 14063 ng•hr/mL and 7507 ng•hr/mL, respectively, which were considered sufficient to achieve a robust boosting effect.

Phase 2 - GS-US-216-0105

See section on Clinical Efficacy for study design. An intensive PK sub-study was performed at the Week 2, 4 or 8 visit (target n = 24 evaluable) when dosing followed a standard breakfast. A single trough sample was collected from all subjects 20-24 h following an observed dose at Weeks 8, 24 and 48. Also, a single sample was collected at Weeks 2, 4, 12, 16, 32 and 40 from non sub-study subjects. The COBI and RTV levels fall within the range observed in other studies.

Plasma concentrations of ATV were slightly higher on boosting with RTV vs. COBI.

From the sampling at trough (20-24 h post-dose) at week 8, 24 and 48 in larger numbers the mean concentrations of ATV were slightly higher in the ATV/COBI group but at each time point the CV% in the ATV/COBI group was greater than that in the ATV/RTV group.

Table 3. 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)

Phase 3 - GS-US-216-0114

See section on Clinical Efficacy for study design. An intensive PK sub-study was performed in a subset (target n = 48 evaluable) at selected study sites with a sampling visit at Weeks 2-8 on ATV/co+TVD.

The ATV plasma levels tended to be slightly lower when given with COBI vs. RTV. PK parameters are summarised in the table below, in which the magnitude of the higher FTC and TFV but lower ATV plasma levels on co-administration with COBI are demonstrated. The CV% values should also be noted for the ATV C_{max} and AUC when given with either COBI or RTV.

Table 4. GS-US-216-0114: Summary of ATV, COBI, RTV, FTC and TFV PK 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.

Overall, the differences observed between PK parameters with ATV/co+TVD vs. ATV/r+TVD were not considered likely to be clinically important. The mean ATV C_{tau} values with ATV/COBI or ATV/RTV were 56.9-fold or 61.0-fold, respectively, above the protein-binding adjusted IC_{90} against wild-type HIV-1 (14 ng/mL).

The higher exposure to TFV (C_{max} and AUC) when co-administered with COBI rather than RTV was explored and the possible explanations were considered. The renal excretion of TFV involves uptake by OAT1 and OAT3 and efflux by MRP4. COBI showed no inhibition of OAT1 and minimal inhibition of OAT3 and MRP4. The magnitude of increase in TFV exposure when administered with COBI was comparable to that observed with other Pgp inhibitors such as RTV and rilpivirine (RPV). In the additional study GS-US-216-0134 that evaluated the interaction between TDF and COBI. The C_{max} and AUC of TFV were higher upon single- or multiple-dose administration of COBI plus TDF vs. TDF alone but COBI did not affect the elimination of TFV (median $t_{1/2}$: 10.96 h for TDF alone vs. 10.87 h on co-administration). These results were consistent with inhibition of Pgp-mediated intestinal efflux of TDF by COBI.

Dose proportionality and time dependencies

In the single- and multiple-dose administration of COBI in healthy subjects PK studies, cobicistat displayed both dose- and time-dependent changes in apparent clearance (CL/F) with nonlinear increases in systemic exposure.

Special populations

Impaired renal function

COBI AUCs observed in subjects with mild/moderate renal impairment in GS-US-216-0121 and in subjects with severe renal impairment in GS-US-216-0124 were higher than for matched normal controls but in both cases were within the range observed in healthy subjects with normal renal function ($CL_{cr} \geq 80$ mL/min using the Cockcroft-Gault method) at the 150 mg dose.

GS-US-216-0124 evaluated dosing subjects with severe renal impairment (eGFR < 30 mL/min; actual mean 23.5 mL/min) not on dialysis and matched [age, sex and BMI] healthy controls (eGFR ≥ 90 mL/min; actual mean 97.2 mL/min) with 150 mg of each once daily in the fed state for 7 days. The AUC_{tau}, C_{max} and C_{tau} were modestly higher (by 25%, 22% and 13%, respectively) in those with severe renal impairment but the differences were considered not clinically relevant. On Day 7 of co-administration the eGFRCG was 10.5% lower vs. baseline among subjects with severe renal impairment and 8.4% lower among controls. A similar pattern of change was observed for eGFRMDRD. Values returned to baseline levels by Day 14. The decreases in eGFR were attributed to inhibition of proximal tubular secretion of creatinine by COBI mainly via inhibition of MATE1.

Table 5. GS-US-216-0124: Statistical analysis of COBI PK parameters on day & between severely renally impaired and normal subjects (COBI PK analysis set)

COBI PK Parameter	Geometric Least-Squares Mean		Geometric Least-Squares Means Ratio (%) (90% CI)
	Test Severe Renal Impairment $eGFR_{CG}$ < 30 mL/min (N = 12)	Reference Normal Renal Function $eGFR_{CG}$ ≥ 90 mL/min (N = 11)	
AUC_{tau} (ng•h/mL)	17313.3	13797.50	125.48 (98.57, 159.73)
C_{max} (ng/mL)	2041.71	1667.84	122.42 (99.82, 150.13)
C_{tau} (ng/mL)	89.02	78.88	112.85 (56.75, 224.40)

Impaired hepatic function

GS-US-183-0133 evaluated dosing COBI 150 mg daily for 10 days to subjects with moderate hepatic impairment (CPT B; actual scores were 7-9) and matched [age, sex and BMI] healthy controls. Mean creatinine clearance was estimated at 98.7 ml/min and 116.8 ml/min in respective groups. AUC_{tau} and C_{max} were generally comparable between subjects with moderate hepatic impairment and controls while T_{max} was prolonged by 1 h (from 3 to 4 h). The median $T_{1/2}$ was longer (6.05 h vs. 3.99 h) resulting in a higher C_{tau} (Geometric Least-Squares Mean GLSM ratio 208%) in the presence of moderate hepatic impairment. The mean percent free fractions for COBI were 2.71% in the control subjects and 3.23% in subjects with moderate hepatic impairment.

There were no clinically relevant correlations between COBI exposures and CPT score or its individual laboratory components (i.e. albumin, total bilirubin, prothrombin time and INR) for subjects with moderate hepatic impairment, consistent with the lack of relevant PK changes.

Pharmacokinetic interaction studies

Effect of COBI alone on substrates of CYP3A4

During GS-US-216-0101 a dose of midazolam (MDZ) 5 mg (oral syrup) was administered on Day 0 and on the final day (D14) of dosing with COBI or RTV. MDZ plasma exposures increased and clearance decreased as a result of the effects of RTV and COBI doses from 50 – 200 mg.

COBI 200 mg and RTV 100 mg exhibited similar inhibition of MDZ CL/F (−94.8% and –95.6%, respectively) and gave 19.2- and 22.5-fold increases in MDZ AUC (vs. MDZ alone). COBI 100 mg achieved only slightly less inhibition of MDZ CL/F (−92.7% vs. MDZ alone). MDZ clearance was 247%, 166% and 118% with COBI doses of 50, 100 and 200 mg, respectively, relative to

that observed with 100 mg RTV and the corresponding AUC_{inf} were 41%, 60% and 85%, respectively, relative to RTV.

Plasma concentrations of 1-OH-MDZ also decreased with increasing doses of COBI. On D14 the 1-OH-MDZ PK values for the COBI 100 (n=11) and 200 (n=12) mg doses and RTV (n=9) suggested that 200 mg COBI behaved similarly to RTV 100 mg.

GS-US-216-0119 compared the effects of COBI 150 mg BID (twice daily) on DRV (600 mg BID) and Tipranavir (TPV) (500 mg BID) with the effects of RTV 100 mg (with DRV) or 200 mg (with TPV) twice daily. Other groups received DRV/COBI BID plus either EVG 150 mg QD or etravirine (ETR) 200 mg BID.

COBI 150 mg BID alone resulted in higher concentrations and exposures compared to data from studies using 150 mg QD. The COBI C_{max} of 2991.6 ng/mL (CV% 28.2) was ~2-fold higher (vs. 1598 ng/mL) and the AUC_{tau} of 23,083.4 ng•h/mL (giving AUC_{24} ~46,200 ng•h/mL) was ~4-fold higher (vs. 12430 ng.h/mL) than the corresponding data reported from GS-US-216-0116 for the final formulation.

COBI AUC_{tau} was ~ 50% lower when given with DRV vs. COBI alone. Addition of EVG to the DRV/COBI regimen did not affect COBI exposures further. After addition of ETR the COBI AUC_{tau} was lower (20%) but this was not considered to be of importance. COBI exposures were ~ 90% lower when given with TPV vs. COBI alone, which reflected the induction of CYP3A by TPV.

DRV exposure parameters, including C_{tau}, met bioequivalence criteria when it was given with COBI vs. RTV regardless of addition of EVG or ETV. In contrast, TPV exposures were markedly lower when given with COBI vs. TPV/RTV.

Effect of COBI alone on substrates of other CYP isoenzymes

GS-US-216-0112 was designed to evaluate the effects of COBI on CYP2D6 and 2B6 and on P-gp. Three Cohorts of subjects were enrolled to receive the following oral treatments in the fed state:

Cohort 1 (CYP2D6)	A: Desipramine 50 mg as a single dose in the morning
	B: COBI 150 mg once daily for 10 days + desipramine 50 mg on the 10th day
Cohort 2 (P-gp)	C: Digoxin 0.5 mg as a single dose in the morning
	D: COBI 150 mg once daily for 10 days + digoxin 0.5 mg on the 10th day
Cohort 3 (CYP2B6)	E: EFV 600 mg as a single dose in the morning
	F: COBI 150 mg once daily for 10 days + EFV 600 mg on the 10th day

Co-administration of desipramine with COBI resulted in lower plasma levels for the first 4 h but there were overall increases in C_{max}, AUC_{inf} and AUC_{0-last} compared to desipramine alone. Correspondingly, the desipramine $T_{1/2}$ was prolonged and CL/F reduced on co-administration. Based on 58% and 65% increases in desipramine AUC_{0-last} and AUC_{inf}, respectively, and a 24% increase in C_{max} the applicant classified COBI as a weak CYP2D6 inhibitor.

Digoxin C_{max} and AUC_{0-last} increased but AUC_{inf} remained unchanged with co-administration. The applicant considered that although COBI is regarded as a weak inhibitor of P-gp it is highly soluble and may achieve transient inhibition of gut P-gp during its absorption, which is the likely explanation for the increase in digoxin C_{max}. Following a COBI dose of 150 mg the reference theoretical concentration in the intestine is 10 × 150 mg/250 mL (7700 μM). When compared to the IC_{50} for Pgp (36 μM), this suggests that intestinal interactions between COBI and Pgp substrates will take place (ratio = 214). This prediction is consistent with GS-US-216-0112 in which COBI increased the C_{max} of the Pgp substrate digoxin (mean increase of 41%) without a significant effect on AUC_{inf} (7.7% increase). There was a numerical decrease in $T_{1/2}$ on co-administration, which the applicant described as unexpected since it was not predicted that COBI reaches sufficient concentrations to inhibit renal P-gp.

EFV C_{max} decreased (13%) but AUC_{0-last}/inf remained unchanged when co-administered with COBI. The 90% CI fell within the 80, 125% bounds but there were numerically lower plasma exposures to EFV when given with COBI. This was unexpected as the induction potential of COBI and the expression of CYP2B6 in the intestine are low. However, co-administration of COBI with EFV is anyway not recommended as co-administration of COBI with medicinal products that are moderate to weak inducers of CYP3A (e.g. EFV).

Other DDI studies

In the EVG+COBI (150/150 mg) study GS-US-201-0104 co-administration with 800 mg QD DRV gave plasma levels of all three agents that were lower than observed in other studies. In particular, co-administration resulted in 40% to 50% lower trough concentrations of EVG and DRV, relative to historical reference exposures for each boosted agent administered alone, indicating that COBI 150 mg is not sufficient for boosting both DRV and EVG. The mechanism for reduced exposure is likely induction. Activation of PXR by DRV can lead to increased expression of enzymes that metabolize COBI (CYP3A), EVG (CYP3A and UGT1A1) and DRV (CYP3A and CYP2C19). The same phenomenon was observed with the interaction between the inducer rifabutin and COBI and EVG. Therefore, cobicistat should not be used in combination with another ARV that requires boosting (i.e. another PI or EVG). Due to lack of data a similar warning is made regarding use of ATV/co with other agents requiring boosting.

The aqueous solubility of COBI free base (0.075 mg/mL, pH ~ 7) is significantly enhanced under acidic conditions at pH 2 (70 mg/mL). GS-US-216-0120 evaluated co-administrations over 8 days of EVG/COBI 150/150 mg each morning in the fed state alone (A) with omeprazole (C - 20 mg in the fasted state in the morning but 2 h before COBI/EVG; D – 20 mg in the fasted state in the evening) or with famotidine (B; 40 mg with food in the evening) in different cohorts of subjects. Omeprazole and famotidine did not affect PK EVG or COBI when dosing was separated by 12 h. When omeprazole was given 2 h before EVG/COBI (C) there was no appreciable effect on PK COBI.

GS-US-216-0122 then evaluated EVG/COBI 150/150 mg co-administered with famotidine 40 mg once daily in the fed state and showed no significant effects on PK EVG or COBI.

GS-US-216-0123 evaluated once daily dosing of EVG/COBI 150/150 mg in the fed state with and without each of a single dose of rosuvastatin 10 mg, ATV 300 mg QD vs. ATV/RTV 300/100 mg QD and rifabutin 150 mg every other day vs. rifabutin 300 mg once daily taken alone. COBI exposures were generally comparable across treatments except that concentrations were

substantially lower at 18 and 24 h following co-administration with rifabutin (see C_{tau} and $t_{1/2}$ in table 6).

Table 6. GS-US-216-0123: Summary of cobicistat PK parameters (analysis set: cobicistat PK)

COBI PK Parameter	EVG/ COBI + ROS in Cohort I (N=10)	EVG/ COBI in Cohort I (N=10)	EVG/ COBI + ATV in Cohort I (N=10)	EVG/ COBI + ATV in Cohort II (N=8)	EVG/ COBI + RIF in Cohort III (N=12)	EVG/ COBI in Cohort III (N=12)
AUC_{tau} (ng•h/mL), Mean (%CV)	11,065.7 (38.1)	10,389.4 (38.6)	12,147.5 (30.7)	12,941.9 (20.7)	11,409.7 (29.2)	11,215.2 (18.5)
C_{max} (ng/mL), Mean (%CV)	1451.1 (25.2)	1399.7 (32.3)	1612.0 (24.3)	1836.2 (21.7)	1877.3 (28.8)	1642.2 (19.0)
C_{tau} (ng/mL), Mean (%CV)	34.2 (113.4)	32.3 (123.2)	46.6 (106.2)	32.3 (38.0)	6.5 (71.7)	22.8 (61.2)
T_{max} (h), Median (Q1, Q3)	3.00 (2.00, 4.50)	4.25 (3.00, 4.50)	3.00 (3.00, 3.50)	2.00 (2.00, 3.75)	3.00 (2.00, 3.25)	3.00 (3.00, 4.00)
$T_{½}$ (h), Median (Q1, Q3)	3.19 (3.07, 3.87)	3.10 (3.02, 3.40)	3.68 (3.32, 3.82)	3.51 (3.33, 3.60)	2.49 (2.06, 2.60)	3.33 (2.81, 3.67)

The RTV AUC_{tau} and C_{max} values (10,947 ng•h/mL and 2191 ng/mL, respectively) were comparable to values observed with ATV/RTV dosing in GS-US-183-0106 and GS-US-183-0108.

Rosuvastatin C_{max} and AUC were greater (89% and 38%, respectively) following EVG/COBI co-administration, but the overall concentration-time profile (and $t_{1/2}$) was similar relative to ROS dosing alone. The applicant considered that this interaction did not require dose adjustment.

The ATV AUC_{tau} was lower (10-12%) when given with EVG/COBI vs. ATV/RTV. C_{max} was ~ 21-24% lower and C_{tau} was ~ 20-35% lower, although C_{tau} was well above the DHHS-recommended target (140 ng/mL) in all subjects.

The AUC_{tau}, C_{max} and C_{tau} rifabutin were comparable between the EVG/COBI + rifabutin 150 mg dose and 300 mg given alone. The median T½ was 11.7 h when rifabutin was given alone but was 28.6 h following concomitant administration. In contrast, co-administration with EVG/COBI resulted in large increases in AUC_{tau}, C_{max} and C_{tau} of 25-*O*-desacetylrifabutin vs. rifabutin alone. [The AUC_{tau} of 25-*O*-desacetylrifabutin after administration alone was doubled for the comparison because of the different dosing frequencies]. The applicant estimated that antimycobacterial activity was unaffected by co-administration (ratio 120.9 [107, 136]).

GS-US-216-0125 evaluated once-daily EVG/co given with methadone or buprenorphine/naloxone (BUP/NLX). Eligible subjects were assigned to a cohort based on their chronic regimen for opioid use (i.e. Cohort 1–methadone; Cohort 2- BUP/NLX) and received their dose with and without EVG 150 mg + COBI 150 mg once daily in the morning with a light meal. COBI PK parameters were comparable between treatments and with historical data with QUAD STR.

The 90% CI around the GLSMs for R- and S-methadone fell within 80, 125% for both AUC and C_{max}. Inhibition of CYP3A4 by COBI would not be expected to significantly influence methadone exposures and the comparable exposures of both methadone enantiomers observed in the presence or absence of EVG/co confirm there is no inductive effect on CYP2B6 and/or CYP2C19.

The primary comparison for BUP was co-administration vs. dosing alone, with each subject serving as their own control. BUP exposures were higher following co-administration with EVG/co. Plasma concentrations of norBUP were also higher following co-administration with EVG/co while T_{max} values were comparable. NLX plasma concentrations were slightly higher

when given as BUP/NLX alone vs. co-administration with EVG/co. Consistent with the short $T_{1/2}$, plasma concentrations of NLX in both treatments were BLQ at 24 hours post-dose.

Inhibition of CYP3A4 by COBI gave a modest increase in the BUP and norBUP (~2% as potent as parent compound), which is in line with the change expected when CYP3A does not have a predominant role in drug elimination. The BUP and norBUP exposures observed following BUP/NLX administration alone were in the range of historical data.

The reasons for the decrease in NLX exposures, which showed intersubject variability, were unclear. The range of NLX exposures across both treatments were comparable with those reported on dosing with BUP/NLX alone or in combination with ARVs. The totality of the data indicates there is no clinically relevant influence of EVG/co administration on the PK or PD of BUP/NLX. This is consistent with previous ARV-opioid DDI studies where a modest change in drug levels is not accompanied by a measurable change in pharmacodynamic endpoint.

Opioid PD was assessed using the standardized tests SOWS, OOWS, COWS, and OOAS daily prior to the morning dosing. The resulting scores observed were minimal in all treatments relative to the overall test score range. There were no meaningful changes in opioid pharmacodynamics and no subjects experienced withdrawal or overdose symptoms.

Pharmacokinetics using human biomaterials

The inhibitory effects of COBI on major human CYP450 enzymes and transporters is summarised and compared with ritonavir in the table 7.

Table 7. IC_{50} Values for Inhibition of Major Human Cytochrome P450 Enzymes, Uridine Glucuronosyltransferase Enzymes, and Transporters by COBI and RTV

		IC_{50} (μM)	
Protein	**Activity**	**COBI**	**RTV**
CYP1A2	Ethoxyresorufin O-deethylase	> 25	> 25
CYP2B6	Bupropion 4-hydroxylase	2.8	2.9
CYP2C8	Paclitaxel 6α-hydroxylase	30.1	5.5
CYP2C9	Tolbutamide 4-hydroxylase	> 25	3.9
CYP2C19	S Mephenytoin 4'-hydroxylase	> 25	> 25
CYP2D6	Dextromethorphan O-demethylase	9.2	3.4
CYP3A	Midazolam 1'-hydroxylase	0.15[a]	0.11[a]
	Testosterone 6β-hydroxylase	0.15[a]	0.12[a]
	Terfenadine t-butyl oxidase	0.29[a]	0.28[a]
UGT1A1	Estradiol 3-glucuronidation	16.3	4.73
Pgp	Calcein acetomethoxy ester transport	36.0	> 20[b]
BCRP	Hoechst 33342 transport	59.0	> 20[b]
MRP1	Calcein acetomethoxy ester transport	45.0–90.0[c]	10.0–20.0[c]
MRP2	Calcein transport	71.0	> 20[b]
MRP4	5-Dehydroepiandrosterone sulfate transport	20.7	> 20[b]
	Tenofovir transport	8	12
OATP1B1	Fluo 3 transport	3.50	2.05
OATP1B3	Fluo 3 transport	1.88	1.83

OAT1	p-Aminohippurate transport	> 100[b]	> 20[b]
	Tenofovir transport	> 15[b]	> 15[b]
OAT3	Estrone 3-sulfate transport	> 100[b]	8.46
	Tenofovir transport	6.6	4.8
OCT2	Metformin transport	8.24	22.6
OCTN1	Tetraethylammonium transport	2.49	2.08
MATE1	Tetraethylammonium transport	1.87	1.34
MATE2-K	Tetraethylammonium transport	33.5	100

a Representative value. Since COBI and RTV are mechanism-based inhibitors of human CYP3A, the measured IC_{50} value will be dependent upon the assay conditions. The values provided were determined with COBI and RTV being tested in parallel.
b Maximum concentration tested
c Concentration range bracketing 50% inhibition

Comment on pharmacokinetics

The applicant conducted a comprehensive investigation of the PK of COBI, including an evaluation of its ability to act as a pharmaco-enhancer of ATV and DRV.

Following oral administration of cobicistat with food in HIV 1 infected subjects, peak plasma concentrations were observed 4 hours post-dose for cobicistat. The steady-state mean C_{max}, AUC_{tau}, and C_{trough} (mean ± SD) following multiple doses of cobicistat in HIV 1 infected subjects (n = 68), respectively, were 1.2 ± 0.3 µg/mL, 10.9 ± 3.8 µg•hr/mL, and 0.07 ± 0.07 µg/mL. Cobicistat displayed both dose- and time-dependent changes in apparent clearance (CL/F) with nonlinear increases in systemic exposure.

A food effect study was not conducted for cobicistat. Since in clinical studies, cobicistat was co administered with atazanavir or darunavir under fed conditions, in accordance with the SmPCs for these medicinal products, it is recommended to administer it with food.

Cobicistat is 97-98% bound to human plasma proteins. The blood-to-plasma ratio of total ^{14}C-radioactivity was time-independent and ~ 0.5, indicating that COBI is excluded from the cellular components of the blood.

In-vitro studies showed that COBI is extensively metabolised via CYP3A (major) and CYP2D6 (minor) mediated oxidation with no evidence of direct Phase 2 metabolism. There are no unique or major (>10%) human metabolites. Primary metabolites include isopropyl oxidation (M31), cleavage at the N-methylurea (M26), cleavage of the carbamate (M21) and cleavage and deethylation of the morpholine (M39).

Following oral administration of [^{14}C]cobicistat, 86% and 8.2% of the dose were recovered in faeces and urine, respectively. The median terminal plasma half-life of cobicistat following administration of Tybost is approximately 3-4 hours.

It is possible that cobicistat is eliminated by CYP3A4 but there are no convincing data to support this assumption. As a post authorisation measure (see RMP section 2.8), the applicant should identify the major mode of elimination of cobicistat and which enzymes/transporters are involved. The applicant should carry out physiologically-based pharmacokinetic (PBPK) simulations of the effect of potent CYP3A4 inhibitors on COBI exposure. If the PBPK simulations are inconclusive or if they indicate that another enzyme or a transporter is likely involved in the

elimination of COBI, studies should be performed *in vitro* and *in vivo* to characterise the enzymes/proteins involved.

Based on the results from study GS-US-216-0124 conducted in non HIV 1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min), no meaningful differences in cobicistat pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of cobicistat.

Cobicistat is primarily metabolised and eliminated by the liver. In study GS-US-183-0133 in non HIV 1 infected subjects with moderate hepatic impairment, no clinically relevant differences in cobicistat pharmacokinetics were observed between subjects with moderate impairment and healthy subjects. Hence, no dose adjustment of COBI is necessary for patients with mild to moderate hepatic impairment. Since COBI is primarily metabolized in and eliminated by the liver and that COBI has not been studied in patients with severe hepatic impairment (Child Pugh Class C), the use of COBI in this population is contraindicated.

Drug drug interaction studies were conducted and their conclusions are adequately reflected in the SmPC.

COBI inhibits human CYP3A with kinact 0.47 min-1 and KI 1.1 µM. These values are comparable to those for RTV. On this basis COBI is expected to substantially increase the systemic levels of co-administered drugs whose bioavailability and elimination are affected by CYP3A enzymes (e.g. MDZ) and co-administration of COBI with these drugs has been contraindicated.

Inducers of CYP3A are expected to lower COBI exposures. Inhibitors of CYP3A are expected to increase COBI exposures. Co-administration of COBI with strong inducers of CYP3A has been contraindicated while co-administration with other inducers (e.g. EFV) is not recommended.

In the EVG+COBI (150/150 mg) study GS-US-201-0104 co-administration with 800 mg QD DRV gave plasma levels of all three agents that were lower than observed in other studies. Hence, COBI co-administered with ATV or DRV should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 to reach the desired therapeutic plasma concentrations (i.e., another protease inhibitor or elvitegravir).

Data from GS-US-216-0112 demonstrated that the peak concentration of digoxin is increased when co-administered with COBI. Hence, the lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effects.

Taking into account the perceived implications for patient management and data from GS-US-216-0123, it was concluded that co-administration of COBI with the CYP3A substrate and inducer rifabutin should not be contraindicated. If co-administration is deemed necessary then the recommended dose of rifabutin is 150 mg 3 times per week on set days accompanied by increased monitoring for rifabutin-associated adverse reactions (including neutropenia and uveitis) due to the increase in exposure to desacetylrifabutin.

Data from GS-US-216-0125 demonstrated that no dosage adjustement was necessary for the co administration of COBI with Buprenorphine/Naloxone.

No data are available to make recommendations on the use of atazanavir/cobicistat or darunavir/cobicistat with combined or progestogen-only oral or implanted contraceptives. Therefore, alternative forms of contraception should be used. Study GS-US-236-0128, which is being conducted in HIV-1 infected subjects, will further inform on the drug interaction profile observed in healthy subjects administered STB and norgestimate/ethinyl oestradiol in Study GS-US-236-0106. The effect of COBI inhibition of CYP3A on the PK of commonly used oral contraceptives will be evaluated and the results will be submitted (see RMP section 2.8).

As a post authorisation measures, the applicant should also provide the CSRs for the planned DDI study with COBI and rifabutin, the DDI with telaprevir (see RMP section 2.8).

COBI does not inhibit human CYP1A2, CYP2C9 or CYP2C19. It is a very weak inhibitor of CYP2C8 (IC_{50} 30.1 µM), a weak inhibitor of UGT1A1 (IC_{50} 16.3 µM), a weak inhibitor of CYP2D6 (IC_{50} 9.2 µM) and a modest inhibitor of CYP2B6 (IC_{50} 2.8 µM). These data suggest COBI is a more specific inhibitor than RTV, for which IC_{50} values include CYP2D6 3.4 µM, CYP2C9 3.9 µM and CYP2C8 5.5 µM.

Human aryl hydrocarbon receptor (AhR) was not induced by COBI or the three human metabolites tested, with findings similar to RTV (fold induction ~0.80). There was very weak activation of PXR by COBI and a lesser effect than was observed with RTV (3.6 to 10.1-fold across the same concentrations).

In human hepatocytes COBI showed little potential to induce CYP1A2, 2B6 or 3A at concentrations up to 30 µM. Other targets for induction (UGT1A1 mRNA, MDR1 mRNA, and CYP2B6 mRNA and protein) were all unaffected or weakly affected by COBI.

At human plasma concentrations following 150 mg doses, COBI would not be expected to inhibit the efflux transporters MDR1 (P gp), multi-drug resistance associated proteins 2 and 4 (MRP2 and MRP4, respectively), breast cancer resistance protein (BCRP), and multidrug and toxin extrusion protein 2-K (MATE2-K) and the renal uptake transporters, organic anion transporters 1 and 3 (OAT1 and OAT3).

At concentrations achievable briefly in the intestinal lumen during absorption ([I]2 = 770 µM) COBI is expected to inhibit intestinal efflux transporters such as MDR1 and BCRP ($[I]2/IC_{50}$ > 10). On this basis COBI may modestly increase exposures of substrates of P-gp. In addition, high concentrations of COBI in the intestinal lumen during absorption can increase systemic TFV exposure due to inhibition of P-gp-dependent efflux of TDF.

Cobicistat is a more potent inhibitor of the uptake transporters, OATP1B1 and OATP1B3 (IC_{50} values 3.5 µM and 1.88 µM, respectively), and organic cation transporter 2 (OCT2; IC_{50} 8.24 µM). It also inhibits the renal efflux transporters, novel organic cation transporter 1 (OCTN1; IC_{50} 2.49 µM) and multidrug and toxin extrusion protein 1 (MATE1; IC_{50} 1.87 µM). Inhibition of OCT2 and/or MATE1, and thus inhibition of active secretion of creatinine by the kidney, provides a plausible mechanistic explanation for the reduction in creatinine clearance observed with COBI, in the absence of changes of true GFR.

<u>Co-administration of COBI with ATV or DRV:</u>
Atazanavir is an inhibitor of CYP2C8, but this effect is reduced when it is given with RTV, likely due to induction of CYP2C8 by RTV. Since COBI is not an inducer, the inhibitory effect of the combination of ATV + COBI on CYP2C8 will most likely resemble that for unboosted ATV.

COBI is considered to be a weak inhibitor of UGT1A1 with IC_{50} 16.3 µM (vs. 4.7 for RTV and 0.83 for ATV) and is not expected to affect substrates of UGT1A1.

COBI can be transported by OATP1B1 and OATP1B3 but it shows good passive cellular permeability, so tissue penetration is unlikely to be dependent on OATP activity. This was supported by the lack of effect of ATV (a potent OATP1B1 inhibitor) on COBI plasma exposures.

Darunavir can inhibit CYP2C9, CYP2C19 and CYP2D6. Darunavir is an inducer *in vitro* and the combination of DRV+COBI may result in drug-drug interactions due to induction by DRV but no additive effect from COBI is expected.

2.4.3. Pharmacodynamics

Cobicistat is intended for pharmaco-enhancement of two HIV protease inhibitors (atazanavir and darunavir) as a replacement for low dose ritonavir. The primary pharmacology concerns the effects of COBI on cytochrome P450 isoenzymes, specifically on CYP3A4. COBI has been investigated for any potential direct antiviral activity. In addition, the potential for COBI to exert secondary pharmacological effects on adipocyte, cardiac and renal functions has been investigated.

Mechanism of action

Cobicistat is an inhibitor of human CYP3A enzyme activity.

Primary and Secondary pharmacology

CYP3A inhibition studies vs. RTV in human hepatic microsomes included established markers for activities of CYP3A enzymes as well as ATV, EVG and telaprevir. COBI was shown to be a strong inhibitor of all tested human hepatic microsomal CYP3A activities. The IC_{50} values for COBI and RTV were closely comparable. Kinetic parameters for COBI (kinact = 0.47 min-1, KI = 1.1 µM) were comparable to those of RTV (kinact = 0.23 min−1, KI = 0.26 µM).

The COBI IC_{50} for CYP2B6 was comparable with that for RTV while that for CYP2D6 was higher than for RTV.

PK/PD relationships for efficacy

The PK-PD relationship of COBI for anti-CYP3A activity was explored in the studies that assessed the effects of co-administration of COBI and each of MDZ, ATV, DRV and EVG (GS-US-216-0101 and GS-US-216-0116). Across these studies the effects of COBI on oral MDZ were assessed at four dose levels (from 50 mg to 200 mg) and compared with the effect of 100 mg RTV. The applicant concluded that COBI can inhibit CYP3A-mediated metabolism of MDZ to an extent comparable with RTV as reported in the literature.

The effectiveness of COBI as a booster for ATV was assessed in Phase 1 and during the Phase 2 and Phase 3 studies that compared ATV/co+TVD with ATV/r+TVD in treatment-naive subjects (see the section on Efficacy). Pharmacokinetic parameters of ATV were determined following multiple-dose administration in a subset of these HIV-1 infected subjects. The pooled ATV

C_{trough} values (756 and 847 ng/mL, respectively) were 54-fold and 61-fold above the IC_{90} (14 ng/mL) and were also consistent with historical data for ATV.

The assessment of the effectiveness of COBI as a booster for DRV was based primarily on data from the Phase 1 study GS-US-216-0115 which compared once daily DRV/RTV 800/100 mg with DRV/COBI 800/150 mg when each was dosed for 10 days in the fed state. The mean COBI C_{max} (1375.7 ng/mL) occurred at a median of 3.5 h while mean AUC_{tau} was 10,370 ng.h/mL. Healthy subjects were dosed with each of DRV/co or DRV/r for 10 days in the fed state in a cross-over study design.

The mean COBI C_{max}, median T_{max} and mean AUC_{tau} values were comparable with those reported from other studies with COBI given alone at this dose (e.g. GS-US-216-0110).

The DRV mean C_{max}, T_{max}, and AUC_{tau} values were comparable but $T_{1/2}$ was shorter on co-administration with COBI vs. RTV (8.29 vs. 13.79 h). There was an increase in DRV concentrations at 24 h in the RTV group that gave a higher C_{tau} (observed at end of dosing interval) compared to the COBI group, resulting in the difference observed (see table 8). In contrast, DRV C_0 (pre-dose) values were comparable and were > 37-fold the protein-adjusted EC50 for wild-type virus (55 ng/mL).

Comparable peak-to-trough variability was seen for DRV irrespective of whether the boosting agent was COBI (mean [SD] 1.99 [0.446]) or RTV (1.81 [0.512]). Differences in swing were noted when DRV was boosted with COBI (mean [SD], 8.12 [8.735]) compared with RTV (4.60 [3.574]). The applicant stated that the lower swing with RTV may be attributed to the increase in DRV trough as mentioned above.

Table 8. Summary of DRV steady-state PK parameters by treatment (DRV + GS-9350 or DRV + RTV) (DRV PK analysis set)

DRV Plasma PK Parameters	Treatment A DRV+GS-9350 (N = 31)	Treatment B DRV+RTV (N = 31)
C_{max} (ng/mL) Mean (%CV)	7737.1 (21.8)	7464.2 (20.3)
AUC_{tau} (ng·h/mL) Mean (%CV)	81,084.2 (31.0)	79,987.0 (34.0)
C_{tau} (ng/mL) Mean (%CV)	1332.7 (66.8)	1866.7 (83.3)
C_{last} (ng/mL) Mean (%CV)	1332.7 (66.8)	1866.7 (83.3)
C_{0h} (ng/mL) Mean (%CV)	2395.5 (50.7)	2483.8 (34.3)
T_{max} (h) Median (Q1, Q3)	3.00 (2.72, 3.50)	3.00 (3.00, 4.00)
$T_{½}$ (h) Median (Q1, Q3)	8.29 (5.74, 10.91)	13.79 (7.97, 16.34)[a]
T_{last} (h) Median (Q1, Q3)	24.00 (24.00, 24.00)	24.00 (24.00, 24.00)

The previous PK/PD analyses of DRV from ARTEMIS (TMC114-C211, Phase III Randomized, Controlled, Open-label Trial to Investigate the Antiviral Activity, Tolerability and Safety of DRV/r in Treatment- Naive HIV-1 Infected Patients) and ODIN [ODIN = TMC114-C229 randomised (1:1 ratio), open-label non-inferiority trial comparing DRV/ rtv 800/100 mg q.d versus drv/rtv 600/100 mg b.i.d (both in combination with an individually selected OBR consisting of ≥ 2 NRTIs) in treatment-experienced HIV-1 infected patients with screening genotype resistance

testing showing no darunavir RAMs] had indicated no relevant relationship between DRV AUC_{24h} or C_{0h} and efficacy.

In light of the results of GS-US-216-0115 the applicant performed additional PK/PD analyses from the Phase 3 studies of DRV/RTV 800/100 mg in HIV-1 infected subjects that modelled relationships between virological response and DRV PK parameters. The comparison of DRV/co and DRV/r PK data between those studies indicated closely comparable AUC_{24} and C_{0h} values. The results gave no indication that lower values within the observed DRV C_{0h} range would led to lower estimated virological response. A linear logistic regression model was also applied to model virological response as a function of DRV C_{0h} but no clear relationship could be established.

Taking into account the PK/PD data, the difference in C_{tau} between DRV/co and DRV/r were not considered to be of clinical importance.

Additional relevant efficacy data was provided with the study GS US 216 0130, which is a single arm study of DRV/co+2 fully active NRTIs (see Section on Efficacy). Overall 60 subjects (57 treatment-naive) were included in PK sub-study, of which 59 were receiving TVD as a background regimen. Overall, the PK exposure parameters of DRV, COBI, FTC and TFV were consistent with historical data.

The sub-study data were used to develop the population PK model of COBI-boosted DRV. The final population PK model was used for the Bayesian feedback analysis for all study subjects with evaluable PK data through Week 24 (n = 298).

The population PK-based DRV AUC and trough concentration (C_{0h}) in GS-US-216-0130 and in the DRV/r studies (ODIN and ARTEMIS) are compared in Table 9. The mean DRV trough concentrations were > 37-fold above the protein-binding adjusted EC50 for wild-type virus (55 ng/mL) and > 3.7-fold above the protein-binding adjusted EC50 for PI resistant HIV-1 strains (550 ng/mL), indicating adequate PK enhancement (boosting) of DRV by COBI.

Table 9. GS-US-216-0130: DRV PopPK in 0130 vs. DRV PK in pivotal studies

	PK Parameter	**GS-US-216-0130 DRV 800 mg + COBI 150 mg (N = 298) QD**	**ARTEMIS DRV 800 mg + RTV 100 mg (N = 335) QD**	**ODIN DRV 800 mg + RTV 100 mg (N = 280) QD**
AUC_{24h} (ng·h/mL)	Mean (SD)	100,152 (32,043)	93,026 (27,050)	93,334 (28,626)
	Median (Range)	96,900 (34,500-224,000)	87,854 (45,000-219,240)	87,788 (45,456-236,920)
C_{0h} (ng/mL)	Mean [SD]	2,043 (1,257)	2,282 (1,168)	2,160 (1,201)
	Median [Range]	1,875 (70-6,890)	2,041 (368-7,242)	1,896 (184-7,881)

PK/PD relationship for safety parameters

PK/PD analyses of the COBI exposure-safety relationship were performed using data from the ATV/COBI+TVD groups in the Phase 2 and 3 studies. COBI exposures were derived from population PK modeling. The safety parameters studied were commonly observed AEs including bilirubin-related AEs (jaundice, ocular icterus, hyperbilirubinaemia or blood bilirubin increased), nausea or diarrhoea. The relationships observed between COBI exposures (AUC_{tau} or C_{max}) and incidence of AEs (present/absent) indicated that there were no relevant exposure-AE trends.

Exploratory analyses were also performed using COBI exposures derived from population PK modeling and any of Grade 3 or 4 total bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum creatinine, $eGFR_{CG}$ and urine fractional excretion of phosphate. No convincing relationships were detected between COBI exposure (AUC_{tau} or C_{max}) quartiles and changes from baseline in these laboratory parameters.

No apparent relationships were observed between DRV AUC_{24h} and C_{0h} and the occurrence of selected AEs of interest (rashes, cardiac AEs, gastrointestinal or liver AEs, lipid or glucose-related AEs, nervous system or psychiatric AEs) following administration of DRV/r 800/100 mg once daily in ARTEMIS or ODIN.

Since COBI exposures (AUC_{tau} and C_{max}) documented in GS-US-216-0105 and GS-US-216-0114 were in the range observed with DRV/COBI 800/150 mg in GS-US-216-0115, the COBI exposure-safety relationship is expected to be comparable when used with ATV or DRV.

Secondary pharmacology

Antiviral activity

Cobicistat is a structural analogue of ritonavir and was fully assessed for any possible anti-viral activity *in vitro*. COBI is devoid of anti-HIV activity (HIV protease IC_{50} > 30 µM) and exhibited no antiviral activity against 17 HIV-1 and 2 HIV-2 primary isolates. COBI was also inactive against HBV (EC50 > 12.5 µM) and HCV (EC50 > 30 µM).

Adipocyte function

COBI exhibited no effect on lipid accumulation and had a less pronounced effect than RTV on glucose uptake.

Cardiac and renal functions

There were three clinical studies of effects of COBI on QTc, on left ventricular function and on renal function (GS-US-216-0107, GS-US-216-0116, GS-US-216-0121). Each study collected PK data. One additional study with COBI (as a single-agent tablet) is ongoing (GS-US-236-0118). This is a Phase 3 study of effects of COBI-containing regimens on renal parameters in HIV-1 infected subjects with mild to moderate renal impairment.

GS-US-216-0107 was a cross-over study that evaluated the effect of two doses of COBI, each administered once in the fed state on QTc. Subjects received each of COBI 250 mg, COBI 400 mg, placebo and moxifloxacin 400 mg at weekly intervals. The plasma levels of COBI actually achieved exceeded the predicted values. Assay sensitivity was established based on the differences between controls. COBI did not show prolongation of the QTcF interval. At these doses the PR interval difference vs. placebo reached a maximum of 9.6 ms at 250 mg and 20 ms at 400 mg at times that correlated with C_{max}. However the plasma concentrations at which these effects occurred were considerably higher than C_{max} values using 150 mg COBI (2169 and 3823 ng/mL vs. approximately 1125-1460 ng/mL at 150 mg doses).

GS-US-216-0116 included collection of ECGs and echocardiograms at baseline and at 3.5-6 h post-dose on one occasion between days 14-19 of dosing with 150 mg COBI daily. All subjects

had normal absolute PR (< 210 ms) and QTcF (< 450 ms) intervals. The ECHO assessments showed that the three measures of left ventricular function were normal.

GS-US-126-0121 evaluated the effect of COBI and RTV in normal function (cohort 1) or mild/moderate renal impairment (cohort 2). On day 7 higher COBI exposures (AUC_{tau}, C_{max}, and C_{tau}) were observed in cohort 2. Mean AUC_{tau} was moderately higher, mean C_{max} was slightly higher, and mean C_{tau} was considerably higher in cohort 2. Median T½ was longer and mean CL/F was reduced in Cohort 2. The differences in COBI exposures between Cohorts 1 and 2 observed in this study were unexpected based on the findings of GS-US-216-0124 in subjects with eGFRCG < 30 mL/min and the mass balance study GS-US-216-0111. The applicant considered that the higher plasma exposures in Cohort 2 may reflect the change in clearance with or without any increase in bioavailability.

Serum creatinine-based GFR estimations were statistically significantly decreased ($p < 0.05$) on Day 7 of COBI administration in both cohorts but not at Day 14. The eGFRMDRD and mGFR gave similar results to those based on serum creatinine eGFR. In contrast, the aGFR was unchanged from baseline at Day 7 and 14 in the COBI. There were also no statistically significant changes from baseline at Day 7 or Day 14 in cysGFR.

Additional information emerged from the study GS-US-236-0130 (Phase 3b, single-arm, open-label safety and efficacy study in HIV-1 infected ARV treatment-naive and treatment-experienced adults with no DRV RAMs - see Section on Clinical Efficacy 2.5). In this study, mean plasma concentrations of COBI when given alone were similar to those for subjects receiving COBI+TDF and slightly lower vs. dosing with STB. There was the expected effect on eGFR for COBI-containing regimens.

The on-treatment (Day 15 and Day 30) aGFR (Iohexol Plasma Clearance) data showed decreases from baseline and vs. placebo for COBI alone and for COBI+TDF. The 90% CI around ratios vs. placebo did not fall within 80, 125% except for COBI+TDF at day 15. Similar analyses based on Day 15 and 30 vs. D0 within each treatment group gave 90% CI around the ratios that just fell within 80, 125% except for Day 15 in the COBI group. The study could not rule out the possibility that COBI alone does have a small effect of aGFR but the effect of co-administration of COBI+TDF was not consistently greater than the effect of COBI alone (or TDF alone).

2.4.4. Discussion on clinical pharmacology

COBI was shown to be a strong inhibitor of all tested human hepatic microsomal CYP3A activities. The IC_{50} values for COBI and RTV were closely comparable. Cobicistat is a structural analogue of ritonavir and is not expected to exert an antiviral effect at clinically achievable concentrations.

Cobicistat is a weak CYP2D6 inhibitor and is metabolised to a minor extent by CYP2D6. Cobicistat inhibits the transporters p glycoprotein (P gp), BCRP, MATE1, OATP1B1 and OATP1B3. Unlike ritonavir, cobicistat is not an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGT1A1.

COBI is expected to weakly-modestly increase exposures of substrates of MATE1 and OATP1B1/3. Inhibition of OCT2 and MATE1 is associated with disrupted active renal secretion of

creatinine, resulting in a reduction in creatinine clearance in the absence of changes in true GFR. The potential for a reduction in creatinine clearance is adequately reflected in the SmPC and no further action is considered necessary by the CHMP.

The effectiveness of COBI as a booster for ATV was assessed in treatment-naive subjects. The pooled ATV C_{trough} values were consistent with historical data for ATV.

The assessment of the effectiveness of COBI as a booster for DRV was based primarily on data from the Phase 1 study GS-US-216-0115. GS-US-216-0115 demonstrated bioequivalent exposures for DRV assessed based on AUC_{tau}, C_{max} and C_{0h}, while C_{tau} was ~ 30% lower with DRV/COBI vs. DRV/RTV. The difference in C_{tau} between DRV/co and DRV/r could not be explained. However, it is not expected to be of clinical relevance provided that the use of DRV/co is entirely restricted to the DRV once daily regimen.

In light of the results of GS-US-216-0115 the applicant performed additional PK/PD analyses from the Phase 3 studies of DRV/RTV 800/100 mg in HIV-1 infected subjects that modelled relationships between virological response and DRV PK parameters. The comparison of DRV/co and DRV/r PK data between those studies indicated closely comparable AUC_{24} and C_{0h} values. The results gave no indication that lower values within the observed DRV C_{0h} range would led to lower estimated virological response. A linear logistic regression model was also applied to model virological response as a function of DRV C_{0h} but no clear relationship could be established.

2.4.5. Conclusions on clinical pharmacology

Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates (such as atazanavir or darunavir) that have limited oral bioavailability and a short half-life due to CYP3A-dependent metabolism.

Cobicistat has no detectable antiviral activity against HIV-1, HBV or HCV and does not antagonise the antiviral effect of HIV inhibitors.

The effectiveness of COBI as a booster for ATV was assessed in treatment-naive subjects. The pooled ATV C_{trough} values were consistent with historical data for ATV.

Bioequivalent exposures for DRV was demonstrated based on AUC_{tau}, C_{max} and C_{0h}; however, C_{tau} was ~ 30% lower with DRV/COBI vs. DRV/RTV. Based on PK/PD analyses, it was concluded that the lower C_{tau} observed with DRV/COBI compared with DRV/RTV in GS US 216 0115 would not result in a difference in virological response between the two once daily regimens provided that the use of DRV/co is entirely restricted to the DRV once daily regimen.

In the setting of boosting ATV or DRV, COBI 150 mg has the possibility of resulting in a slightly smaller range of potential DDIs vs. RTV 100 mg. Drug drug interaction studies were conducted and their conclusions are adequately reflected in the SmPC. As a post authorisation measures, the applicant should provide the CSRs for the planned DDI study with COBI and rifabutin, the DDI with telaprevir and the study with QUAD STB in women (see RMP section 2.8).

2.5. Clinical efficacy

Table 10. Table of clinical efficacy studies

Type of Study	Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects by Treatment	Study Population / Entry Criteria
Efficacy and Safety	GS-US-216-0105	Evaluate the safety and efficacy of a regimen containing cobicistat (COBI)-boosted atazanavir (ATV) plus emtricitabine/ tenofovir disoproxil fumarate (Truvada [TVD]) versus RTV-boosted ATV plus TVD in HIV-1 infected, antiretroviral treatment-naive (ARV-naive) adult subjects.	Phase 2, double-blind, multicenter, randomized, active-controlled study	Study medication was administered once daily with food. COBI 150 mg once daily+RTV placebo once daily+ATV 300 mg once daily+TVD (single-tablet FTC/TDF 200/300 mg) once daily RTV 100 mg once daily+COBI placebo once daily+ATV 300 mg once daily+TVD (single-tablet FTC/TDF 200/300 mg) once daily	60 weeks of double-blind treatment, followed by optional open-label ATV/co+ TVD extension until study drug commercially available or study terminated by sponsor	Enrolled: 85 (56 ATV/co +TVD and 29 ATV/r+TVD) (6/56 subjects in the ATV/co +TVD group were never treated.) Completed Randomized Phase: 69 (45 ATV/co +TVD and 24 ATV/r+TVD) Entered Open-Label Extension: 63 44 ATV/co +TVD and 19 ATV/r+TVD)	HIV-1 infected, ARV-naive, screening plasma HIV-1 RNA levels ≥ 5000 copies/ mL, CD4 cell count > 50 cells/μL, no prior use of approved or experimental anti-HIV drug, and no nucleoside or nucleotide reverse transcriptase inhibitor, nonnucleoside reverse transcriptase inhibitor, or primary protease inhibitor resistance mutations
Efficacy and Safety	GS-US-216-0114	Evaluate the safety and efficacy of a regimen containing cobicistat (COBI)-boosted atazanavir (ATV) plus emtricitabine/ tenofovir disoproxil fumarate (Truvada [TVD]) versus RTV-boosted ATV plus TVD in HIV-1 infected, antiretroviral treatment-naive (ARV-naive) adult subjects.	Phase 3, double-blind, multicenter, randomized, active-controlled study	Study medication was administered once daily with food. COBI 150 mg once daily+RTV placebo once daily+ATV 300 mg once daily+TVD (single-tablet FTC/TDF 200/300 mg) once daily RTV 100 mg once daily+COBI placebo once daily+ATV 300 mg once daily+TVD (single-tablet FTC/TDF 200/300 mg) once daily	96 weeks of double-blind treatment, followed by optional open-label ATV/co+ TVD extension until study drug commercially available or study terminated by sponsor	Randomized 698 (349 ATV/co +TVD and 349 ATV/r+TVD) Randomized and treated: 692 (344 ATV/co +TVD and 348 ATV/r+TVD) Completed Week 48 treatment: 603 (294 ATV/co +TVD and 309 ATV/r+TVD)	HIV-1 infected, ARV-naive, screening plasma HIV-1 RNA levels ≥ 5000 copies/ mL, CD4 cell count > 50 cells/μL, no prior use of approved or experimental anti-HIV drug, and no prior use of any approved or experimental antiretroviral drug for any length of time

2.5.1. Dose response study(ies)

The applicant selected the dose of COBI (150 mg) based on GS-US-216-0110 and GS-US-216-0115 in which the effect of COBI on PK of ATV and DRV was evaluated.

GS-US-216-0110 showed comparable ATV AUC_{tau}, C_{max} and C_{tau} as well as T_{max} and $t_{1/2}$ on daily dosing with ATV/COBI 300/150 mg vs. ATV/RTV 300/100 mg. ATV with 100 mg COBI gave lower ATV exposures (15-20%) and a shorter $T_{1/2}$ vs. ATV/RTV. Greater than dose-proportional increases in COBI exposures were observed at 150 mg vs. 100 mg.

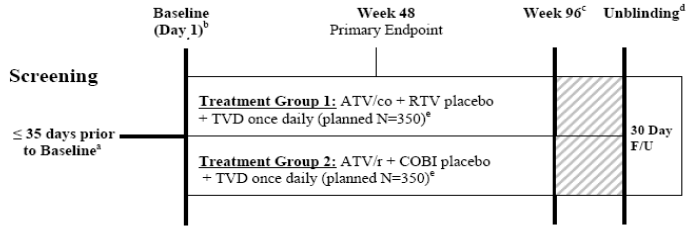
GS-US-216-0115 compared once daily DRV/RTV 800/100 mg with DRV/COBI 800/150 mg when each was dosed for 10 days in the fed state (see Section on Pharmacodynamics 2.4).

2.5.2. Main study (GS-US-216-0114)

GS-US-216-0114 is the single pivotal efficacy study conducted in treatment-naïve HIV-infected subjects that directly compared ATV/RTV and ATV/COBI, each given with Truvada (emtricitabine and tenofovir).

Methods

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-Naive Adults.



ATV/co, cobicistat-boosted atazanavir; ATV/r, ritonavir-boosted atazanavir; COBI, cobicistat; RTV, ritonavir; TVD, Truvada (single tablet FTC/TDF); F/U, follow-up

a The screening window could be extended to up to 42 days prior to baseline for subjects who required repeat HIV-1 genotype testing.

b Following the baseline visit, subjects returned for study visits at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48; subsequent visits are scheduled every 12 weeks through Week 96.

c Subjects will continue to attend visits every 12 weeks following Week 96 until treatment assignment is unblinded.

d Once Gilead Sciences provides unblinded treatment assignments to the investigators, all subjects will return to the study center (preferably within 30 days) for an unblinding visit. At the unblinding visit all subjects will discontinue their blinded study drug and will be given the option to participate in an open-label rollover study. Subjects who do not wish to participate in the open-label rollover study will discontinue their blinded study drug and return for a 30-day follow-up visit following the unblinding visit. Subjects who discontinue study drug prior to the unblinding visit will not be eligible for the open-label rollover study; these subjects will be asked to continue attending scheduled study visits through the unblinding visit and will discontinue the study after the unblinding visit.

e The COBI and RTV tablets and their matching placebos, ATV, and TVD were administered orally, once daily with food at approximately the same time each day.

Figure 1 Study design GS-US-216-0114

Study Participants

Critical inclusion criteria were:

- Plasma HIV-1 RNA ≥ 5000 copies/mL

- No prior use of any approved or investigational antiretroviral drug for any length of time
- Screening HIV-1 genotype report must have shown sensitivity to FTC, TDF and ATV
- Normal ECG
- Adequate renal function: CG formula GFR ≥ 70 mL/min
- AST and ALT ≤ 5 × ULN, total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin, absolute neutrophil count ≥ 1000/mm3; platelets ≥ 50,000/mm3; haemoglobin ≥ 8.5 g/dL; serum amylase ≤ 5 × ULN (or if amylase > 5 × ULN, serum lipase was to be ≤ 5 × ULN)

Critical exclusion criteria were:

- A new AIDS-defining condition diagnosed within 30 days prior to screening
- On treatment for HCV or anticipated to need treatment during the course of the study

Treatments

During the randomised, double-blind phase all treatment was administered once daily with food and at approximately the same time each day as follows:

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

Primary objective:

- To evaluate the efficacy of a regimen containing ATV/COBI versus ATV/RTV, 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

Secondary objective:

- To evaluate the efficacy, safety, and tolerability of the 2 treatment regimens through 96 weeks of treatment

Outcomes/endpoints

- HIV-1 RNA in plasma was measured using the COBAS Amplicor HIV-1 Monitor Test (Version 1.5).

- At screening, the PR/RT genotype was assessed using the GeneSeq™ assay (Monogram Biosciences, South San Francisco, CA). This assay also determined the HIV-1 subtype.
- Post-baseline resistance analyses of viruses obtained from subjects with virological failure or failure to achieve plasma HIV-1 RNA < 400 copies at study discontinuation (at or after Week 8 and on study drugs) included PR/RT genotyping and phenotyping. The PhenoSense GT™ (PhenoSense IN) and GeneSeq IN assays (Monogram Biosciences, South San Francisco, CA) were used for this purpose.
- CD4 counts were assessed using flow cytometry.

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. Non-inferiority of ATV/COBI+TVD relative to ATV/RTV+TVD was assessed using 95% CI with a pre-defined non-inferiority margin of 12%.

Secondary efficacy endpoints were as follows:

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 96, as defined by the snapshot analysis algorithm
- The achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48 and 96, as defined by TLOVR

Sample size

A sample size of 700 HIV-1 infected subjects (randomised 1:1) had at least 95% power to establish non-inferiority with respect to the primary efficacy endpoint. It was assumed that both treatment groups would have a response rate of 0.795 (based on 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.

Randomisation

Randomisation was by IVRS stratified according to HIV-1 RNA ≤ 100,000 or > 100,000 copies/ml.

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* - all randomised subjects (added for analysis in the SAP).
- *Intent-to-Treat Analysis Set* - all randomised who received at least 1 dose of study drug. This was the primary analysis set for efficacy analyses.

- *Per Protocol Analysis Set* –all randomised and treated (grouped by actual treatment received) with no major protocol violation. This was the secondary analysis set for the primary endpoint.

Primary Analysis

The 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 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.

There were two interim IDMC analyses performed at Weeks 12 and 24 in which data were provided with treatment groups coded as A and B. IDMC members did not request decodes prior to Week 48. However, as a consequence of the interim IDMC analyses, 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.

Snapshot Analysis Algorithm

In the snapshot analysis for the Week 48 virological outcome the following definitions applied:

- 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.

Secondary and Sensitivity Analyses for the Primary Efficacy Endpoint

In addition to the analysis based on the PP population a series of sensitivity analyses were performed using the ITT population as follows:

- 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.
- 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 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.

Results

Participant flow

At week 48 698 subjects were enrolled, including 692 who received at least one dose of study medication, at 143 sites in 18 countries. Up to the data cut-off 12.9% had discontinued study drug (14.5% ATV/COBI and 11.2% ATV/RTV) while 7.9% had discontinued from the study (9.9% vs. 6%, respectively) the most common reasons being AEs and LTFU in both treatment groups.

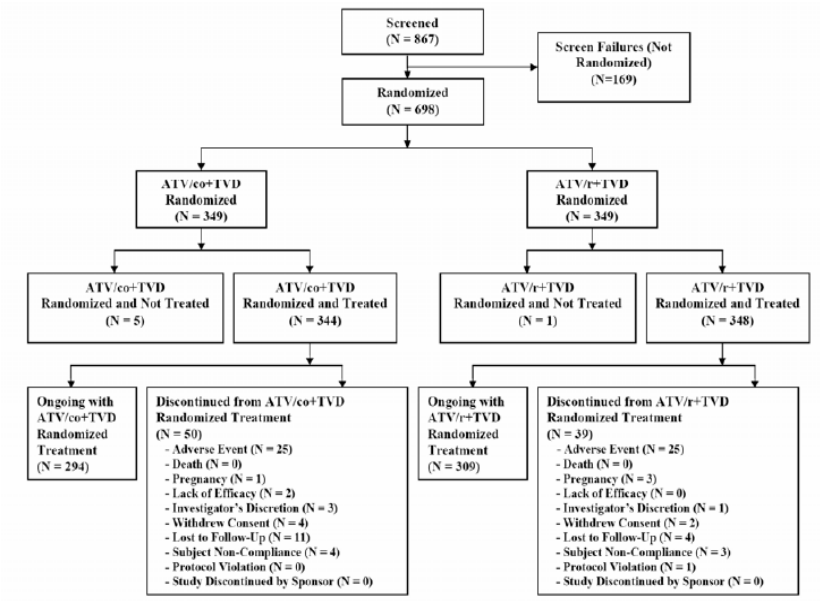


Figure 2 GS-US-216-0114: Disposition of study subjects– 48 weeks analysis

In the 96 weeks analysis, of the 692 subjects randomised, 20.7% (143; 72 and 71 in the two treatment groups) had discontinued study drug prior to the Week 96 analysis cut-off date. The most common reasons for premature discontinuation of study drug were AEs (10.2% in the ATV/co+TVD group and 10.1% in the ATV/r+TVD group), lost to follow-up (4.1% and 2.3%) and investigator's discretion (2.6% and 2.3%). The median duration of exposure to study drug was 108.1 weeks in both groups.

Recruitment

The study started on 26 April 2010 (First Subject Screened) and the last subject observation for the 48 weeks analysis was 29 November 2011.

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 but were not of a nature to affect the integrity of the study.

Baseline data

In general the baseline subject and disease characteristics were comparable between treatment groups. The majority of subjects were white (~60%) and male (~83%) aged between 30-40 years. About 40% had > 100,000 copies/ml at baseline with mean and median values ~ 4.8 log10 copies/ml. Most subjects had HIV-1 subtype B (82%). Just under half had > 350 CD4 cells/µl and > 80% were asymptomatic. Few (< 6%) were co-infected with HBV or HCV.

Table 11. GS-US-216-0114: Baseline disease characteristics (safety analysis set) – 48 weeks analysis

Disease Characteristic[a]	ATV/co+TVD (N=344)	ATV/r+TVD (N=348)	Total (N=692)	ATV/co+TVD vs. ATV/r+TVD p-value[b]
HIV-1 RNA (log10 copies/mL)				
N	344	348	692	0.44
Mean (SD)	4.81 (0.585)	4.84 (0.594)	4.83 (0.589)	
Median	4.78	4.84	4.81	
Q1, Q3	4.36, 5.20	4.43, 5.27	4.41, 5.24	
Min, Max	3.22, 6.43	3.21, 6.44	3.21, 6.44	
HIV-1 RNA Category (copies/mL)				
<= 100,000	212 (61.6%)	205 (58.9%)	417 (60.3%)	0.47
> 100,000	132 (38.4%)	143 (41.1%)	275 (39.7%)	
CD4 Cell Count (/uL)				
N	344	348	692	0.64
Mean (SD)	353 (170.5)	351 (175.5)	352 (172.9)	
Median	348	341	343	
Q1, Q3	240, 452	250, 442	242, 448	
Min, Max	1, 1075	10, 1455	1, 1455	
CD4 Cell Count Category (/uL)				
<= 50	11 (3.2%)	12 (3.4%)	23 (3.3%)	0.89
51 to <= 200	49 (14.2%)	45 (12.9%)	94 (13.6%)	
201 to <= 350	114 (33.1%)	126 (36.2%)	240 (34.7%)	
351 to <= 500	123 (35.8%)	117 (33.6%)	240 (34.7%)	
> 500	47 (13.7%)	48 (13.8%)	95 (13.7%)	
CD4 Percentage (%)				
N	344	348	692	0.54
Mean (SD)	20.4 (8.72)	20.8 (8.42)	20.6 (8.57)	
Median	20.2	20.4	20.4	
Q1, Q3	13.7, 26.0	15.6, 26.3	14.6, 26.2	
Min, Max	0.4, 49.3	0.6, 46.5	0.4, 49.3	
HIV Risk Factors[c]				
Heterosexual Sex	112 (32.6%)	123 (35.3%)	235 (34.0%)	
Homosexual Sex	226 (65.7%)	227 (65.2%)	453 (65.5%)	
IV Drug Use	7 (2.0%)	8 (2.3%)	15 (2.2%)	
Transfusion	0	0	0	
Vertical Transmission	0	0	0	
Other	5 (1.5%)	6 (1.7%)	11 (1.6%)	
Unknown	9 (2.6%)	5 (1.4%)	14 (2.0%)	
HIV Disease Status				
Asymptomatic	285 (82.8%)	292 (83.9%)	577 (83.4%)	0.60
Symptomatic HIV Infection	31 (9.0%)	32 (9.2%)	63 (9.1%)	
AIDS	28 (8.1%)	24 (6.9%)	52 (7.5%)	
HBV Surface Antigen Status				
Positive	16 (4.7%)	9 (2.6%)	25 (3.6%)	0.15
Negative	328 (95.3%)	339 (97.4%)	667 (96.4%)	
HCV Antibody Status				
Positive	21 (6.1%)	16 (4.6%)	37 (5.3%)	0.42
Negative	323 (93.9%)	331 (95.1%)	654 (94.5%)	
Indeterminate	0	1 (0.3%)	1 (0.1%)	
Estimated Glomerular Filtration Rate by Cockcroft-Gault (CG) Formula (mL/min)				
N	344	348	692	0.39
Mean (SD)	116.1 (28.59)	118.3 (31.48)	117.2 (30.08)	
Median	111.5	115.5	112.3	
Q1, Q3	98.2, 128.5	96.2, 133.8	97.2, 131.6	
Min, Max	68.3, 273.8	54.2, 260.5	54.2, 273.8	
Estimated Glomerular Filtration Rate by Modification of Diet in Renal Disease (MDRD) Formula (mL/min/1.73 m^2)				
N	344	348	692	0.88
Mean (SD)	101.7 (17.08)	103.0 (20.22)	102.4 (18.73)	
Median	100.4	100.2	100.2	
Q1, Q3	89.5, 111.9	89.0, 114.4	89.3, 112.6	
Min, Max	61.8, 150.6	57.5, 215.9	57.5, 215.9	
Estimated Glomerular Filtration Rate by Cystatin C Clearance, Adjusted for Age, Sex, and Race Formula (mL/min/1.73 m^2)				
N	339	335	674	0.86
Mean (SD)	101.2 (22.23)	100.4 (19.94)	100.8 (21.11)	
Median	100.6	99.4	99.8	
Q1, Q3	87.0, 114.4	88.3, 113.5	87.5, 113.8	
Min, Max	43.1, 232.8	47.2, 154.6	43.1, 232.8	

Numbers analysed

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/µL 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.

Adherence to active study drug, as measured by pill count, was comparable (median 99% per group) between groups and 80% and 84% per group had an adherence rate of ≥ 95%.

Outcomes and estimation

Results up to Week 48 (primary analysis)

In the primary analysis at Week 48 non-inferiority was demonstrated for ATV/COBI vs. ATV/RTV with a lower bound of the 95% CI at -7.4. In addition, 5.8% and 4.0% in respective groups had virological failure while 9.0% and 8.6% had no virological data in the Week 48 analysis window.

Table 12. GS-US-216-0114: Virological 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 (98%; 95% CI were -2.5, 2.3). Sensitivity analysis of the primary endpoint showed:

- After excluding study drug discontinuations not related to virological response and including all HIV-1 RNA data for late discontinuation (ITT analysis set) the success rates were 87.5% and 89.4% (95% CI: −6.9% to 2.8%).
- Including study drug discontinuations not related to virological response as successes and all HIV-1 RNA data for late discontinuation (ITT analysis set) the rates were 87.8% vs. 89.7% (95% CI: −6.7% to 2.8%).
- In the third sensitivity analysis Odds ratios were 0.83 (95% CI: 0.54 to 1.28) for baseline HIV-1 RNA level and 0.81 (95% CI: 0.52 to 1.26) for region. These were similar to the unadjusted odds ratio (0.83, 95% CI 0.54, 1.28), indicating that the treatment effect for the primary endpoint was not confounded by these factors.

Non-inferiority was also demonstrated in the analysis based on TLVOR with < 50 copies/mL in 82.8% and 85.3% (95% CI -8.1, 2.8). In the KM analysis of TLOVR the percentages were comparable between treatment groups with Week 48 rates of 19% and 16% (p=0.44).

Pure virological failure (PVF; HIV-1 cut-off at 50 copies/mL and premature study drug discontinuation by Week 48) occurred in 10.5% (36/344) in the ATV/COBI group and 9.8% (34/348) in the ATV/RTV group.

In each of the Missing=Failure (M=F) analysis and Missing=Excluded (M=E) analysis percentages with HIV-1 RNA levels < 50 copies/mL were comparable between treatments and the lower bound of the 95% CI fell within -6%. In the corresponding analyses in the PP analysis percentages with < 50 copies/mL (M=F) were higher than in the ITT analysis set at 98% in each group while the rates when applying M=E were 98.3% and 98%.

Table 13. GS-US-216-0114: Number and percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at week 48 (ITT analysis set)

Subjects with Plasma HIV-1 RNA < 50 copies/mL (n, %)[a]	ATV/co+TVD (N=344)	ATV/r+TVD (N=348)	ATV/co+TVD vs. ATV/r+TVD[b]	
			p-value[c]	Difference in Percentages (95% CI)[d]
Missing = Failure				
HIV-1 RNA at Week 48				
< 50 copies/mL	306/344 (89.0%)	312/348 (89.7%)	0.75	-0.7% (-5.4% to 3.9%)
95% CI[e]	85.2% to 92.1%	86.0% to 92.6%		
50 to < 400 copies/mL	2/344 (0.6%)	6/348 (1.7%)		
400 to < 1000 copies/mL	2/344 (0.6%)	1/348 (0.3%)		
>= 1000 copies/mL	5/344 (1.5%)	6/348 (1.7%)		
Missing	29/344 (8.4%)	23/348 (6.6%)		
Missing = Excluded				
HIV-1 RNA at Week 48				
< 50 copies/mL	306/315 (97.1%)	312/325 (96.0%)	0.43	1.1% (-1.8% to 4.1%)
95% CI[e]	94.6% to 98.7%	93.3% to 97.9%		
50 to < 400 copies/mL	2/315 (0.6%)	6/325 (1.8%)		
400 to < 1000 copies/mL	2/315 (0.6%)	1/325 (0.3%)		
>= 1000 copies/mL	5/315 (1.6%)	6/325 (1.8%)		

a For the M = F analysis, denominator for percentages was the number of subjects in the ITT analysis set. For the M = E analysis, the denominator for percentages was the number of ITT subjects with nonmissing HIV-1 RNA data at each visit.

b P-value, percentage difference, and 95% CI were based on a dichotomized response: success (HIV-1 RNA < 50) or failure (HIV-1 RNA >= 50 or missing).

c P-value was from the CMH tests stratified by baseline HIV-1 RNA level (<= 100,000 or > 100,000 copies/mL).

d Difference in percentage of success (< 50 copies/mL) and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

e The 95% CI for percentage estimate of HIV-1 RNA < 50 copies/mL for each treatment was obtained using Exact method.

Mean decreases from baseline in HIV-1 RNA levels were identical between treatment groups at Week 48 (-3.08, -3.09).

Mean increases from baseline in CD4 cell counts were comparable between treatments at Week 48 at 213 and 219 cells/µL. Mean increases in CD4% were also comparable at 9.7% and 9.8%.

Subgroup analyses mostly revealed virological success rates (HIV < 50 copies/mL; snapshot analysis; ITT) that were numerically higher in the ATV/RTV group. The exceptions were in subjects aged > 40 years and in female subjects, where rates were slightly higher for ATV/COBI. In subjects with HIV RNA > 100,000 copies/ml at baseline the success rates were 86.4% for ATV/COBI and 86% for ATV/RTV. For those with CD4 < 350 at baseline rates were 89.7% and 89.6%, respectively.

Leaving aside the comparison for the relatively small subgroup with adherence < 95% the lower bound of the 95% CI fell within -13% in each case. Only for the subgroup aged < 40 years and the group with baseline CD4 count > 350 did the lower 95% CI exceed -12% (-12.3% and -12.8% respectively) and most values were within -10%.

Homogeneity tests performed for the primary endpoint did not show a significant difference in treatment effects between subgroups.

All subjects showed genotypic sensitivity to FTC, TDF and ATV at screening and no subject had a K65R or M184V/I RT mutation at study entry. Primary PI-R mutations were observed in 18/692 (2.6%), most commonly L33F and L90M, but these viruses were considered fully sensitive to ATV on their screening report. NRTI resistance (NRTI-R) mutations were observed in 8.4% of subjects (58 of 692), most commonly V118I in 36/692 (5.2%).

There were 24 virological failures included in the Resistance Analysis Population (RAP).

- Post-baseline genotypic and phenotypic PR and RT data were available for viruses from 11/12 subjects in the ATV/COBI group. Two of these viruses developed an RT M184V mutation and one had measured phenotypic resistance to FTC. None developed a K65R mutation. The remaining 9 viruses lacked emergent resistance mutations in PR and RT and remained phenotypically susceptible to all drugs in the assigned regimen.
- Post-baseline genotypic and phenotypic PR and RT data were available for viruses from all 12 subjects in the ATV/RTV group. None of these had emergent resistance to a study drug and all remained phenotypically susceptible to TDF, FTC and ATV.

Results up to Week 96

At Week 96 a slightly greater proportion of subjects in the ATV/co group had virological failure (7.0% [24/344] vs. 4.6% [16/348] for ATV/r) principally because of the greater percentage of subjects in the ATV/co group who discontinued study drug due to other reasons whose last available HIV-1 RNA was ≥ 50 copies/mL. The percentages with no virological data in the Week 96 window were similar (15.1% ATV/co+TVD and 16.1% ATV/r+TVD) and the reasons for lack of virological data were balanced between the treatment groups.

Based on the TLOVR analysis using the Week 96 dataset, 82.8% (285/344) in the ATV/co+TVD group and 85.3% (297/348) in the ATV/r+TVD group achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48 and were considered responders.

The Week 96 mean (SD) increases from baseline in CD4 cell count were 277 (176.8) cells/μL in the ATV/co+TVD group and 287 (181.5) cells/μL in the ATV/r+TVD group. The difference in least square means (LSM) was -10 (95% CI: –38 to 19).

Summary of main study(ies)

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

Table 14. Summary of Efficacy for trial GS-US-216-0114

Title: 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-Naive Adults		
Study identifier	GS-US-216-0114	
Design	Phase 3, Randomized, Double-Blind Study	
	Duration of main phase:	48 weeks
Hypothesis	Non-inferiority	

Treatments groups	Treatments group 1	COBI 150 mg + ATV 300 mg + TVD (single tablet FTC/TDF 200/300 mg) + RTV placebo, once daily with food, number of subjects planned 349
	Treatments group 2	RTV 100 mg + ATV 300 mg + TVD (single tablet FTC/TDF 200/300 mg) + COBI placebo, once daily with food, number of subjects planned 349
Endpoints and definitions	Primary efficacy endpoint	The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot analysis

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, 48 weeks analysis		
Descriptive statistics and estimate variability	Treatment group	1	2
	Number of subject	n=344	n=348
	HIV-1 RNA < 50 copies/mL	85.2%	87.4%
	P value	0.40	
	Treatment difference (95.2% CI)	-2.2% (-7.4%, 3.0%)	

Supportive studies

Data in support of the use of ATV/co: GS-US-216-0105

GS-US-216-0114 is supported by a single Phase 2 study GS-US-216-0105 that was of a similar design but in much smaller numbers.

This US study randomised treatment-naïve subjects (2:1; 50 and 25 per group) to ATV/COBI (300/150 mg) or ATV/RTV (300/100 mg), each administered once daily in combination with TVD in a double-blind and double dummy design. Randomisation was stratified by HIV-1 RNA ≤ 100,000 copies/mL or > 100,000 copies/mL at screening. Up to Week 60, subjects continued to take their blinded study drugs and attended scheduled visits until treatment assignments were unblinded, when they were given the option to participate in an open-label rollover extension and receive ATV/COBI+TVD.

There were 79 randomised and treated subjects (50 ATV/COBI) of which 69 completed study treatment in the randomised phase. The demographic and other baseline characteristics were comparable between the treatment groups. Subjects were mostly male, with a mean age of 36 years and no significant differences in baseline viral load, CD4 cell count or CD4 percentage between treatment groups. The mean (standard deviation [SD]) baseline HIV-1 RNA value was 4.61 (0.614) $\log_{10}$ copies/mL, mean CD4 cell count was 357 (192.2) cells/μL and mean CD4% was 22.0 (9.01). Overall, 70.9% of subjects had baseline HIV-1 RNA level ≤ 100,000 copies/mL.

The week 24 and 48 HIV RNA data showed that ATV/COBI was not quite as effective as ATV/RTV.

Table 15. GS-US-216-0105: Virologic outcomes at weeks 24 and 48 using snapshot analysis and HIV-1 RNA < 50 copies/mL (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		

Changes in CD4 counts to Weeks 24 and 48 were comparable between groups.

Virological suppression was maintained and immunological improvement continued through 96 weeks of treatment with ATV/COBI+TVD. Using the M = F method 75.5% (37/49) had < 50 copies/mL at week 96 and the mean (SD) change from baseline in CD4 cell count was 317 (186.1) cells/μL.

Data in support of the use of DRV/co

GS-US-216-0130

GS-US-216-0130 is an ongoing Phase 3b, single-arm, open-label safety and efficacy study in HIV-1 infected ARV treatment-naive and treatment-experienced adults with no DRV RAMs. Subjects receive DRV/co plus 2 investigator-selected (fully active) NRTIs.

Overall 259/295 (87.8%) treatment-naive subjects and 15/18 (83.3%) treatment-experienced subjects in the full analysis set (FAS) were still on study drugs up to the Week 24 analysis cut-off. The majority of subjects received TDF-based regimens (294/295 and 17/18), usually as Truvada (292/295 and 11/18). The treatment-naive cohort was mostly male (90.2%) and had a mean age of 36 years. The treatment-experienced cohort included 13 male subjects and had a mean age of 45 years. The baseline mean HIV-1 RNA was 4.8 $\log_{10}$ copies/mL for both cohorts but mean CD4 counts were 378.2 (199.94) cells/μL for the naïve and 197.8 (214.30) cells/μL for the experienced with CD4% of 22.6% vs. 11.9%.

A lower percentage of subjects had an adherence rate of ≥ 95% up to the Week 24 visit in the treatment-experienced cohort (77.8% vs. 94.6%).

In the treatment-naive cohort a higher percentage achieved virological success at Week 24 among those with baseline viral load ≤ 100,000 copies/mL (87.9%) compared with the subset with > 100,000 copies/mL (77.9%). The difference in virological success between subgroups primarily reflected the higher numbers with ≥ 50 copies/mL at Week 24 in the > 100,000 copies/mL subgroup i.e. 13.1% [16/122 subjects] vs. 0.6% [1/173 subjects] among those with ≤ 100,000 copies/mL at baseline.

Table 16. GS-US-216-0130: Treatment Outcomes at Week 24 (< 50 copies/mL; Snapshot FAS)

HIV-1 RNA Category	Treatment-Naïve (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Virologic Success at Week 24			
HIV-1 RNA < 50 copies/mL	247 (83.7%)	11 (61.1%)	258 (82.4%)
95% CI[a]	79.0% to 87.8%	35.7% to 82.7%	77.8% to 86.5%
Virologic Failure at Week 24	29 (9.8%)	7 (38.9%)	36 (11.5%)
HIV-1 RNA ≥ 50 copies/mL	17 (5.8%)	5 (27.8%)	22 (7.0%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL	12 (4.1%)	2 (11.1%)	14 (4.5%)
No Virologic Data in Week 24 Window	19 (6.4%)	0	19 (6.1%)
Discontinued Study Drug Due to AE/Death	14 (4.7%)	0	14 (4.5%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	3 (1.0%)	0	3 (1.0%)
Missing Data During Window but on Study Drug	2 (0.7%)	0	2 (0.6%)

a 95% CI is the 2-sided exact 95% CI for binomial proportions.

Ten (10) subjects met the criteria for resistance analysis (5 naïve). One treatment-experienced subject (with poor pill bottle returns indicative of poor adherence) developed a resistance mutation to DRV at position I84 as a mixture with wild-type (I84I/V). No phenotypic resistance to DRV or other PIs was associated with that mutation. No subject developed NRTI resistance mutations to their concomitant NRTI regimen.

GS-US-236-0118

GS-US-236-0118 is an ongoing Phase 3 open-label safety and efficacy study in HIV-1 infected subjects with mild to moderate renal impairment in which COBI is used as a booster of DRV or ATV in treatment-experienced subjects (Cohort 2) or is administered as part of STB (Cohort 1). New non-comparative interim data through Week 24 provide further support for the efficacy of COBI as a booster of DRV. Twenty out of twenty one (20/21) subjects administered DRV/co+2 NRTIs remained virologically suppressed at Week 24. The remaining subject discontinued study drug due to other reasons and had last available HIV-1 RNA < 50 copies/mL.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant selected the dose of COBI (150 mg) based on GS-US-216-0110 and GS-US-216-0115 in which the effect of COBI on PK of ATV and DRV was evaluated.

The assessment of the effectiveness of COBI as a booster for ATV was based on the data from phase 2 and 3 studies. GS-US-216-0114 is the single pivotal efficacy study (Phase 3, Randomized, Double-Blind Study to evaluate the safety and efficacy of COBI-boosted ATV versus RTV-boosted ATV each administered with Truvada in HIV-1 Infected treatment-naive adults). GS-US-216-0114 is supported by a single Phase 2 study GS-US-216-0105 that was of a similar design but in much smaller numbers of subjects.

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. Non-inferiority of ATV/COBI+TVD relative to ATV/RTV+TVD was assessed using 95% CI with a pre-defined non-inferiority margin of 12%.

The assessment of the effectiveness of COBI as a booster for DRV was based primarily on data from the Phase 1 study GS-US-216-0115. No randomised clinical trial was conducted by the Applicant. Data from the Phase 3 studies investigating the use of DRV/RTV 800/100 mg in HIV-1 infected subjects (ARTEMIS and ODIN) and from uncontrolled efficacy data (GS-US-236-0118, GS-US-216-0130) were submitted to support this indication. This information is reflected in the SmPC.

Efficacy data and additional analyses

In the primary analysis (ITT, 48 weeks), non-inferiority was demonstrated for ATV/COBI vs. ATV/RTV with a lower bound of the 95% CI at -7.4. In addition, 5.8% and 4.0% in respective groups had virological failure while 9.0% and 8.6% had no virological data in the Week 48 analysis window.

Non-inferiority was also demonstrated in the PP analysis set although actual success rates were higher (98%; 95% CI were -2.5, 2.3).

Non-inferiority was also demonstrated in the analysis based on TLVOR with < 50 copies/mL in 82.8% and 85.3% (95% CI -8.1, 2.8). In the KM analysis of TLOVR the percentages were comparable between treatment groups with Week 48 rates of 19% and 16% (p=0.44).

Mean increases from baseline in CD4 cell counts were comparable between treatments at Week 48 at 213 and 219 cells/µL. Mean increases in CD4% were also comparable at 9.7% and 9.8%.

Subgroup analyses mostly revealed virological success rates (HIV < 50 copies/mL; snapshot analysis; ITT) that were numerically higher in the ATV/RTV group. Since there was a single pivotal efficacy study it is not possible to comment further on this observation at present.

Primary PI-R mutations were observed in 18/692 (2.6%), most commonly L33F and L90M, but these viruses were considered fully sensitive to ATV on their screening report. NRTI resistance (NRTI-R) mutations were observed in 8.4% of subjects (58 of 692), most commonly V118I in 36/692 (5.2%). There were 24 virological failures included in the Resistance Analysis Population.

As a post authorisation measure, the applicant should provide the findings of the additional analysis of emergent resistance substitutions in the protease gene of patients treated with STB in Phase 3 studies (see Section 2.8 RMP).

At Week 96 a slightly greater proportion of subjects in the ATV/co group had virological failure (7.0% [24/344] vs. 4.6% [16/348] for ATV/r) principally because of the greater percentage of subjects in the ATV/co group who discontinued study drug due to other reasons whose last available HIV-1 RNA was ≥ 50 copies/mL.

Of note, the efficacy of ATV/COBI (300/150 mg once daily) has only been demonstrated in conjunction with Truvada and only against viruses known to be fully susceptible to all three ARV agents. This reduces the sensitivity of the study GS-US-216-0114 to detect any possible effects of slightly lower plasma levels of ATV on efficacy.

In study GS-US-216-0105, the mean SD baseline HIV-1 RNA value was 4.61 (0.614) $\log_{10}$ copies/mL, mean CD4 cell count was 357 (192.2) cells/μL and mean CD4% was 22.0 (9.01). Overall, 70.9% of subjects had baseline HIV-1 RNA level ≤ 100,000 copies/mL. The week 24 and 48 HIV RNA data showed that ATV/COBI was not quite as effective as ATV/RTV.

There are no efficacy data for DRV/COBI (800/150 mg once daily) and its use in conjunction with COBI is based solely on demonstrating a comparable DRV PK profile compared to DRV/r (800/100 mg once daily). While the DRV C_{max} and AUC met the bioequivalence criteria the C_{tau} was 30% lower for DRV/co vs. DRV/r. However, based on PK/PD analyses and cross-study comparisons with PK data obtained in previous DRV/r efficacy studies (see Section on Clinical Pharmacology), it was concluded that this difference would not result in a difference in virological response between the two once daily regimens provided that the use of DRV/co is entirely restricted to the HIV-infected sub-population described in the DRV SmPC when using the once daily DRV/r regimen.

2.5.4. Conclusions on the clinical efficacy

Non-inferiority for ATV/COBI vs. ATV/RTV regimen was demonstrated in study GS-US-216-0114. Indeed, COBI was shown to achieve pharmaco-enhancement of ATV resulting in efficacy comparable with that achieved by ATV/RTV.

Overall, the data support the comparable efficacy of DRV/co and DRV/r provided that the use of DRV/co is entirely restricted to the HIV-infected sub-population described in the DRV SmPC when using the once daily regimen. The SmPC reflects this information.

2.6. Clinical safety

The principal sources of safety data for the COBI tablet presented in the original MAA were from two double-blind, active-controlled studies in HIV-1 infected, ARV treatment-naive subjects:

- Phase 3 GS-US-216-0114 (48 weeks of exposure)
- Phase 2 GS-US-216-0105 (60 weeks of exposure during a blinded treatment phase).

During the evaluation, updated safety data from GS-US-216-0114 (Week 96 data cut) and GS-US-236-0118 (Week 24 data cut) as well as new data from GS-US-216-0130 (Week 24 CSR) were provided as well as Week 96 data from the Phase 3 STB studies. Data were analysed using MedDRA Version 14.0.

Patient exposure

In the COBI Phase 2 and 3 studies submitted with the initial submission, 394 subjects received ATV/COBI+TVD for a median duration of 48.4 weeks. The KM estimate for time to premature study drug discontinuation at Week 48 was 14% (95% CI: 10.7%, 18.1%) in the ATV/COBI+TVD group and 12% (95% CI: 8.1%, 14.9%) in the ATV/RTV+TVD group.

Adverse events

Comparable percentages of subjects in each group reported any AE or any Grade 2, 3 or 4 AE. A slightly higher percentage of subjects in the ATV/COBI group (17.8%) reported a Grade 3 or 4 AE compared with ATV/RTV (13.3%). Percentages reporting a Grade 3 or 4 AE considered related by the investigator to study drug were low but slightly higher in the COBI group (6.9% vs. 4.5%). The SAE reporting rate was also slightly higher with COBI.

In the pooled safety analysis set 92% in each group reported any AE. The table 17 shows details of those AEs most commonly reported.

Table 17. GS-US-216-0105 and GS-US-216-0114: TEAEs reported by ≥5% of subjects (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[c]	**ATV/COBI+TVD (N=394)**	**ATV/RTV+TVD (N=377)**
Number of Subjects Experiencing 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%)
Diarrhoea	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 and 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%)
Hyperbilirubinaemia	43 (10.9%)	34 (9.0%)
Infections and 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 and 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%)

Adverse Events by System Organ Class and Preferred Term[c]	ATV/COBI+TVD (N=394)	ATV/RTV+TVD (N=377)
Respiratory, Thoracic and Mediastinal Disorders	76 (19.3%)	80 (21.2%)
Cough	26 (6.6%)	23 (6.1%)
Skin and Subcutaneous Tissue Disorders	115 (29.2%)	105 (27.9%)
Rash	24 (6.1%)	23 (6.1%)

Multiple AEs were counted only once per subject for each SOC and preferred term, respectively.

Among the most frequently reported AEs (≥ 10% incidence in either treatment group) four (jaundice, nausea, hyperbilirubinaemia and upper respiratory tract infection) were reported by a numerically higher percentage of subjects in the ATV/COBI group and four (diarrhoea, headache, nasopharyngitis and ocular icterus) were reported for a numerically lower percentage in the ATV/COBI group. A similar percentage of subjects overall experienced bilirubin-related AEs. Differences in rates of ≥ 5% were observed for diarrhoea (ATV/COBI 15.0% vs. ATV/RTV 21.2%) and nasopharyngitis (9.4% vs. 14.9%).

The majority of the AEs reported were mild (Grade 1) or moderate (Grade 2) in severity. Similar percentages of subjects in both treatment groups reported AEs of Grade 2, 3 or 4 and the most frequently reported were:

- ATV/COBI - hyperbilirubinaemia (8.9%), jaundice (6.1%), headache and nausea (each 3.6%)
- ATV/RTV - hyperbilirubinaemia (7.2%), diarrhoea (4.8%), urinary tract infection (4.0%)

Grade 3 or 4 AEs were reported by a slightly higher percentage in the ATV/COBI group (17.8%) compared to ATV/RTV (13.3%). This difference was driven by the difference in Grade 3 AEs and reflected the rates of bilirubin-associated AEs.

Table 18. GS-US-216-0105 and GS-US-216-0114: TEAEs Grade 3 or 4 reported by at least 1% of subjects

Adverse Events by System Organ Class, Preferred Term and Highest Severity[a,b,c]	ATV/COBI+TVD (N=394)	ATV/RTV+TVD (N=377)
Number of Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	70 (17.8%)	50 (13.3%)
Grade 3 (Severe)	68 (17.3%)	47 (12.5%)
Grade 4 (Life-Threatening)	2 (0.5%)	3 (0.8%)
Hepatobiliary Disorders	25 (6.3%)	17 (4.5%)
Grade 3 (Severe)	25 (6.3%)	17 (4.5%)
Hyperbilirubinaemia	21 (5.3%)	16 (4.2%)
Grade 3 (Severe)	21 (5.3%)	16 (4.2%)
Jaundice	4 (1.0%)	3 (0.8%)
Grade 3 (Severe)	4 (1.0%)	3 (0.8%)
Investigations	10 (2.5%)	8 (2.1%)
Grade 3 (Severe)	8 (2.0%)	8 (2.1%)
Grade 4 (Life-Threatening)	2 (0.5%)	0
Blood Bilirubin Increased	5 (1.3%)	1 (0.3%)
Grade 3 (Severe)	5 (1.3%)	1 (0.3%)
Renal and Urinary Disorders	6 (1.5%)	6 (1.6%)
Grade 3 (Severe)	6 (1.5%)	4 (1.1%)

Adverse Events by System Organ Class, Preferred Term and Highest Severity[a,b,c]	ATV/COBI+TVD (N=394)	ATV/RTV+TVD (N=377)
Grade 4 (Life-Threatening)	0	2 (0.5%)
Renal Failure Acute	0	4 (1.1%)
Grade 3 (Severe)	0	2 (0.5%)
Grade 4 (Life-Threatening)	0	2 (0.5%)

a Adverse events were coded using MedDRA 14.0.
b SOC was presented alphabetically and PT was presented by descending order of the total frequencies.
c Multiple AEs were counted only once per subject for the highest grade for each SOC and PT, respectively.

Percentages reporting any AE considered related to study drug by the investigator were comparable between treatment groups (56.9% vs. 57.3%). In both treatment groups, the most frequently reported drug-related AEs were ocular icterus, nausea and jaundice. Gastrointestinal and hepatobiliary AEs were commonly considered related to study drug in both treatment groups. Rates for individual TEAEs (Treatment-Emergent Adverse Event) were mostly closely comparable between treatment groups.

At Week 96 in GS-US-216-0114 the most frequently reported AEs in the ATV/co group were jaundice (21.2%), ocular icterus (19.5%) and nausea (17.7%) while in the ATV/r group the most common were diarrhoea and ocular icterus (each 20.4%), jaundice (17.0%) and nausea (16.4%). Several SOCs showed a slightly higher rate for total AEs for ATV/co vs. ATV/r (e.g. cardiac disorders 11 [3.2%] vs. 5 [1.4%], mainly reflecting differences in rates of bradycardia and palpitations) but the reverse pattern also occurred several times and numbers are small so that no definite conclusions can be drawn.

Hepatic events

There were no reports of acute hepatic failure, hepatic failure or liver injury in the Phase 2 and 3 studies. No subjects up to the Week 96 cut-off met Hy's law criteria.

A slightly higher rate of bilirubin-related AEs occurred with ATV/co vs. ATV/r (none was serious). At Week 48 in GS-US-0114 40.7% ATV/co+TVD and 36.2% ATV/r+TVD subjects were reported as having experienced bilirubin-related AEs. In contrast 12 (3.5%) and 11 (3.2%) in respective groups discontinued study drug due to bilirubin-related AEs (i.e. jaundice, ocular icterus, blood bilirubin increased or hyperbilirubinaemia), suggesting that the small difference in the rates of bilirubin-related AEs was not clinically meaningful. These subjects mostly had liver function tests expected with the use of boosted ATV, chronic HBV or HCV, abnormal baseline transaminases or other causative factors. All study drug-related hepatic AEs were largely reversible upon discontinuation.

COBI and RTV have similar inhibitory potencies against UGT1A1 and MRP2 and there are no known effects of COBI that could explain the difference between the ATV/co and ATV/r treatment groups. Although COBI has not been evaluated for its inhibitory potency for MRP3, it is unlikely to be substantially different from that of RTV.

Rash events

In the Phase 2 and 3 studies the percentages with any rash were comparable between treatment groups (17.8% vs. 19.6%). There were three SAEs of rash including two in the

ATV/COBI group who had rashes considered unrelated to study drug by the investigator. They continued on treatment without recurrence.

ECG effects

In the Phase 3 study there were no notable differences between treatment groups in the percentages of subjects with ECG abnormalities. In the Phase 2 study there were no clinically relevant changes from baseline in median values for ECG parameters.

Summary of Renal events

In the Phase 2 and 3 studies in which COBI was given as ATV/co+TVD there were 8 subjects in the ATV/co+TVD group, 1 subject in the ATV/r→ATV/co+TVD group (Phase 2) and 15 subjects in the ATV/r+TVD group with either a renal SAE, discontinued study drug due to a renal AE and/or had a pre-specified renal AE of interest. One additional ATV/co subject discontinued due to IgA nephropathy. A summary of these events is as follows:

Renal SAEs

- Two subjects (0.6%) in the ATV/co+TVD group each had one renal SAE reported (Fanconi syndrome acquired and nephropathy) in GS-US-216-0114.
- Eight subjects (2.4%) in the ATV/r+TVD group had a renal SAE reported (4 cases of acute renal failure; one each for renal failure, renal tubular necrosis and Fanconi syndrome; one case of renal tubular acidosis type 2 reported after the Week 96 data cut.

Discontinuation due to renal AEs

- Eight subjects (2.3%) in the ATV/co+TVD group discontinued study drug due to renal events (blood creatinine increased, creatinine renal clearance decreased, Fanconi syndrome acquired, GFR abnormal, GFR decreased, renal impairment, nephropathy and IgA nephropathy [original PT renal failure]).
- Eleven subjects (3.2%) in the ATV/r+TVD group discontinued study drug due to renal events (blood creatinine increased for 2 subjects; proteinuria and glycosuria for 1 subject; creatinine renal clearance decreased, Fanconi syndrome acquired, GFR abnormal, renal failure, acute renal failure, renal impairment and renal tubular necrosis all in 1 subject each; renal tubular acidosis type 2 (verbatim term) for 1 subject.

Renal AEs of interest

- For the 2 subjects (0.6%) in the ATV/co+TVD group the renal AEs of interest reported were Fanconi syndrome acquired and renal failure.
- For the 7 subjects (2.0%) in the ATV/r+TVD group the renal AEs of interest reported were Fanconi syndrome acquired (1 subject), renal failure (2 subjects) and renal failure acute (4 subjects).

Proximal renal tubulopathy (PRT)

Overall, 13 subjects had evidence of PRT. For 6 subjects (1.7%) in the ATV/co+TVD group and 7 subjects (2.0%) in the ATV/r+TVD group, the renal AEs and laboratory findings were consistent with PRT. Each of these subjects discontinued study drug due to renal AEs. Five of

the 6 in the ATV/co+TVD group and 2/7 in the ATV/r+TVD group were reported in the Week 48 CSR. The additional four subjects reported at Week 96 were all in the ATV/r group. There were also 2 in the ATV/co+TVD group plus one who switched to ATV/co in the Phase 2 study and 9 in the ATV/r+TVD group who had renal AEs reported but did not have evidence of PRT.

Other relevant data from GS-US-216-0114 to week 96 were as follows:

Serum Creatinine

The median change from baseline at 2 weeks was 0.11 mg/dL in the ATV/co+TVD group and 0.05 mg/dL in the ATV/r+TVD group. Values generally stabilized by Week 24 with median changes from baseline at Week 96 of 0.12 mg/dL and 0.08 mg/dL, respectively. Similar percentages of subjects in each treatment group had graded treatment-emergent serum creatinine abnormalities (ATV/co 7.3% [25]; ATV/r 5.2% [18]). Two subjects in the ATV/co group had a Grade 3 serum creatinine abnormality with no Grade 4 abnormalities. In the ATV/r group one had a Grade 3 and 2 subjects had a Grade 4 abnormality.

Serum Phosphate

Hypophosphataemia of any grade was observed in 10.8% (37) in the ATV/co group and 7.8% (27) in the ATV/r group. One in each treatment group had Grade 3 hypophosphataemia but none reached Grade 4.

Glycosuria

Glycosuria occurred in 6.4% (22 subjects) in each group with Grade 3 reported for 8 subjects (2.3%) in the ATV/co+TVD group and 9 subjects (2.6%) in the ATV/r+TVD group.

Proteinuria

Proteinuria was observed in ATV/co+TVD 42.1% and ATV/r+TVD 40.5%. Most were Grade 1 (ATV/co 34.2%; ATV/r 33.5%). One subject in the ATV/co group had Grade 3 proteinuria.

Subclinical Kidney Disease

No subject who did not discontinue study drug due to a renal AE met the criteria for subclinical kidney disease (i.e. confirmed creatinine increase $\geq$ 0.4 mg/dL and confirmed abnormalities in at least 2 of hypophosphataemia, urine protein [2-grade increase] and normoglycaemic glycosuria occurring at the same visit at least once with no alternative aetiology).

Exploratory analyses attempted to find additional cases of PRT based on 1-grade increase in combination with other renal abnormalities (serum creatinine, normoglycaemic glycosuria, hypophosphataemia). No subjects in either group met all criteria but 4 subjects (2 ATV/co and 2 ATV/r) had at least 2 of the 3 markers of tubular dysfunction without confirmed creatinine increase $\geq$ 0.4 mg/dL. Therefore, there were no additional cases of PRT through Week 96 that were not identified through AEs.

Reversibility of PRT after discontinuing ATV/co+TVD

- Serum creatinine values returned to within approximately 30% of baseline after study drug discontinuation in 5/6 in the ATV/co+TVD group with PRT and improved in the other. Two subjects started a regimen containing RTV, which has an inhibitory effect on renal tubular secretion of creatinine. One subject had only 1 post-dose value due to being lost to follow up.

- Hypophosphataemia returned to baseline levels after study discontinuation for all 3 subjects with hypophosphataemia as a manifestation of PRT.
- Normoglycaemic glycosuria normalized after study discontinuation for all 3 subjects with normoglycaemic glycosuria as a manifestation of PRT. None of these subjects had diabetes.
- Urine protein values returned to baseline after study drug discontinuation for all 4 subjects with PRT and sufficient follow up data. One subject had negative urine protein at baseline and +2 urine protein at the time of study drug discontinuation, which improved to +1 after study drug discontinuation; the subject did not have a sufficient follow up period. One subject was lost follow up after study drug discontinuation and did not have follow-up urine protein values.

Bone Fractures

In GS-US-216-0114 fractures occurred in 9 in the ATV/co+TVD group (2.6%) and 11 in the ATV/r+TVD group (3.2%). Non-traumatic fractures were reported for 2 subjects in the ATV/co+TVD group (hand fracture while using hedge trimmers; wrist fracture after fall from bicycle) and 1 in the ATV/r+TVD group (spinal compression fracture).

GS-US-216-0130 included 311 (of 313; 99.4%) who received TDF as a background NRTI therapy. No subject experienced a renal AE of interest, a renal SAE or discontinued due to a renal event and there was no association with PRT in any subject.

GS-US-236-0118 required subjects to have $eGFR_{CG}$ between 50 and 89 mL/min at baseline. Interim results are available when all subjects had completed 24 weeks or had discontinued.

Serious adverse event / deaths / other significant events

The single death was due to an accident in the Phase 2 study GS-US-216-0105.

One SAE of spontaneous abortion in a subject with a prior similar event and two terminations were reported in Phase 1 studies with COBI in healthy volunteers and one SAE of diabetic foot ulcer was reported in a subject with severe renal impairment.

In the initial submission, SAEs in Phase 2 and 3 studies were reported for 38 subjects in the ATV/COBI group (9.6%) compared with 25 in the ATV/RTV group (6.6%). There was no apparent pattern in the types of SAEs by treatment and the only SAE reported in > 1% of subjects in either group was acute renal failure (all 4 were in the ATV/RTV group). The organ system most commonly associated with SAEs was Infections and Infestations (14 subjects per group).

SAEs considered related to treatment occurred in 5 (1.3%) and 6 (1.6%) subjects in respective groups. In the ATV/COBI group these were rhabdomyolysis, spontaneous abortion, depression, Fanconi Syndrome (acquired) and nephropathy. In the ATV/RTV group these were pyrexia, GGT increased, Fanconi Syndrome (acquired), renal failure, renal failure (acute), priapism and rash.

In the Phase 2 study GS-US-216-0105, the additional SAEs that occurred after the randomised phase included pericarditis, accidental death, alcoholic hepatitis + jaundice, suicide attempt and renal colic in the group initially randomised to ATV/COBI and a case of meningitis in the group initially randomised to ATV/RTV.

In GS-US-216-0114 up to Week 96, SAEs were reported for a slightly greater percentage in the ATV/co group (14.8% [51 subjects] vs. 10.1% [35 subjects]). The differences reflected imbalances in several SOCs but the most marked occurred for gastro-intestinal disorders (8 vs. 1). Nevertheless, the numbers for individual types of events were low and it is not possible to comment further. One SAE of acute renal failure occurred in ≥ 1% of subjects in either treatment group but all four cases [1.1%] were in the ATV/r group.

In contrast, SAEs considered by the investigator to be related to study drug were reported for 1.7% [6] in the ATV/co group and 2.3% [8] in the ATV/r group while percentages with any AE considered related to study drug by the investigator were 60.8% and 63.8%, respectively. Grade 3 or 4 drug-related AEs occurred in 7.8% [27] and 6.6% [23].

Pregnancies

Four pregnancies were reported in Phase 1 studies with COBI and one in study GS-US-201-0101 but one occurred in a subject who did not receive COBI. One resulted in a healthy term infant, one in spontaneous abortion (see SAE above), one in termination and one in a live birth.

There were no pregnancies in the Phase 2 study but 6 occurred in the Phase 3 study (3 per treatment group) and study drug was discontinued in 4 subjects. In the ATV/COBI group one had a spontaneous abortion on Day 336, which was considered by the investigator to be related to study drug. No action was taken with study drug. One had an induced abortion and remained on study drug. For the other 4 subjects the pregnancies were either ongoing or the outcomes were unknown at the data cut-off date.

Laboratory findings

In the Phase 2 and 3 studies almost all subjects had at least one laboratory abnormality reported (98.5% and 98.9%) and most had at least one Grade 3 or 4 laboratory abnormality (75.0% and 63.5%). The most frequently reported Grade 3 or 4 abnormalities in both treatment groups were total bilirubin (which accounted for much of the overall treatment group difference), lipase and creatinine kinase. The lipase test was only performed for subjects with serum amylase > 1.5 x ULN and the denominator is the number tested.

Renal effects

Renal laboratory parameters were extensively evaluated due to the recognised effect of COBI on serum creatinine and its inhibition of OCT2 and MATE1 (active secretion accounts for 10% to 40% of creatinine clearance in patients with normal renal function).

In the Phase 2 and 3 studies increases in median values for serum creatinine in the ATV/COBI group were noted as early as Week 2 (0.11 mg/dL) but stabilised through Week 48 (0.13 mg/dL). While the same pattern occurred in the ATV/RTV group the changes from baseline were smaller (median change at Week 2 was 0.05 mg/dL and at Week 48 it was 0.09 mg/dL).

A higher percentage of subjects in the ATV/COBI group had Grade 1 abnormalities in serum creatinine (6.4% vs. 3.7%). There was one Grade 2 and two Grade 3 abnormalities compared

to none in the ATV/RTV group but there was one subject in the ATV/RTV group with a Grade 4 increase on Days 112 and 114 associated with acute renal failure ascribed to *Salmonella* enteritis.

The data from the Phase 2 and 3 studies on eGFR by Cockcroft-Gault showed decreases in median $eGFR_{CG}$ post baseline in both groups (baseline median 111.2 mL/min [ATV/COBI+TVD] and 114.5 mL/min [ATV/RTV+TVD]; median change from baseline at Week 48 –12.9 mL/min [ATV/COBI+TVD] and –9.3 mL/min [ATV/RTV+TVD]. The decreases in $eGFR_{CG}$ as early as Week 2 of treatment with only minimal changes after Week 4 were consistent with inhibition of active tubular secretion of creatinine. Median values remained within the normal range.

- The results for eGFR calculated using the modified diet in renal disease equation ($eGFR_{MDRD}$) were consistent with those observed for $eGFR_{CG.}$ Decreases in median $eGFR_{MDRD}$ gave median change from baseline at Week 48 of -14.5 mL/min/1.73 m^2 [ATV/COBI+TVD] and –10.4 mL/min/1.73 m^2 [ATV/RTV+TVD].
- Results for cysGFR showed increases to Week 48 in both treatment groups of 5.3 mL/min/1.73 m^2 and 6.6 mL/min/1.73 m^2.
- No subjects had $eGFR_{CG}$ below 50 mL/min during the study, including the subjects that switched to open label ATV/COBI+TVD. One subject that switched had decreased GFR levels reported that led to study drug discontinuation.

Serum Phosphorus

Median values for serum phosphorus were within normal ranges throughout the randomized parts of the Phase 2 and 3 studies. Hypophosphataemia was observed in 7.4% in the ATV/COBI+TVD and 5.6% in the ATV/RTV+TVD group but there were no Grade 3 or 4 events.

Glycosuria

Glycosuria was observed for comparable percentages in the two treatment groups (4.9% and 4.5%). Glycosuria tended to occur transiently and in isolation. Grade 3 urine glucose abnormalities were reported for 2.6% and 1.3% and these subjects typically also had notable urine glucose at screening or baseline.

Proteinuria

Proteinuria was observed for 33.0% and 32.3% per group. Most events were Grade 1 in severity (27.4% and 27.5%). One subject in the ATV/COBI+TVD group had Grade 3 proteinuria on study and had trace proteinuria and Grade 2 haematuria at baseline that fluctuated through Week 48. In the group that switched to COBI, Grade 1 proteinuria was reported for 30.9% and Grade 2 for 4.4%.

Urine Fractional Excretion of Phosphate

Urine phosphate was assessed in the Phase 3 study in which there were small increases in median urine fractional excretion of phosphate in the ATV/COBI+TVD group (median change from baseline was 2.0% at Week 2 and was stable within a range of 1.1% – 2.1% through Week 48). In the ATV/RTV+TVD group the median change from baseline was 1.8% at Week 2 and was stable within a range of 1.4% – 1.7% through Week 48.

Liver-Related Laboratory Tests

In the initial submission the elevated ALT rates were 18.4% in the ATV/COBI and 12.5% in the ATV/RTV groups while elevated AST rates were 21.2% and 14.1%. Abnormalities in GGT and alkaline phosphatase as well as elevated total bilirubin occurred in comparable percentages. There were 14 subjects in each treatment group with 3xULN AST or ALT concurrent with 2xULN total bilirubin. However, direct bilirubin > 2xULN occurred infrequently (ATV/COBI 0.5%; ATV/RTV 1.1%). Subjects with significant LFT test abnormalities generally had abnormal baseline AST or ALT, underlying chronic HBV or HCV co-infection or a history of alcoholism or alcohol abuse.

During the review of the present application, another two subjects in each of the ATV/co and ATV/r groups in GS-US-216-0114 had elevations in AST or ALT > 3 times the ULN along with elevations of total bilirubin of > 2 times the ULN. In all four cases the hyperbilirubinaemia was due to an elevation in indirect bilirubin, which is consistent with the effect of ATV. The AST and ALT values normalised in all cases despite continuation of study drug. One ATV/co subject had AST or ALT > 3 times the ULN that appeared to have occurred in association with the use of fenofibrate. Therefore, it remains the case that no subject has experienced laboratory abnormalities that would meet the Hy's law criteria for drug-induced liver injury.

In the safety update analysis dataset 66 subjects had AST or ALT > 3 times ULN with or without concurrent increase in total bilirubin > 2 times ULN at least once while on study treatment. These 66 subjects comprised 64 from the randomised phase of GS-US-216-0114 and GS-US-216-0105 [36 ATV/co and 28 ATV/r] and 2 from the ATV/co open-label phase of GS-US-216-0105.

The presence of HBV surface antigen or HCV antibody as well as abnormal ALT/AST values at baseline all occurred more commonly in these subjects than in the overall study population. None of the 66 subjects was suspected to have developed severe drug-induced liver injury and all fell into one of the following categories:

- Pre-existing viral hepatitis B or C at baseline,
- Acquisition of viral hepatitis B or C post-baseline,
- Pre-existing medical condition or concurrent AE as a potential cause of liver laboratory abnormalities, such as alcohol use or syphilitic hepatitis,
- Concomitant use of another potentially hepatotoxic drug, such as isoniazid or fenofibrate,
- Normalisation or no progressive worsening of ALT/AST while continuing study drug.

Fasting Glucose and Lipid Parameters

Numerically smaller increases in fasting total cholesterol and triglycerides were observed at Week 48 in the ATV/COBI group. Mean increases from baseline through Week 48 in LDL cholesterol and HDL cholesterol were comparable between treatments. There were no clinically relevant changes from baseline through Week 48 in mean values for fasting glucose in either group. Abnormalities in fasting and non-fasting glucose and lipid parameters were generally Grade 1 or Grade 2 in severity. There was no pattern in the occurrence of Grade 3 or 4 abnormalities.

Safety in special populations

There were no notable effects of gender, age or race on AE rates or patterns although the low proportion of female subjects limits the conclusions.

In the Phase 2 and 3 studies numbers co-infected with HBV were 3.2% (25 subjects) and co-infection with HCV occurred in 4.8% (37 subjects). The hepatic AE profile in these subjects was consistent with underlying hepatitis infection in that elevations in AST and ALT occurred more frequently than in the general HIV-1 infected population.

Discontinuation due to adverse events

Discontinuations due to TEAEs in Phase 1 studies involving COBI did not show treatment-related trends. In the Phase 2 and 3 studies the initial submission reported that comparable percentages in the ATV/COBI (6.9%) and ATV/RTV groups (7.2%) discontinued study prematurely due to an AE. Events associated with hyperbilirubinaemia such as jaundice (2.3%, 9 subjects; 1.9%, 7 subjects) and ocular icterus (2.0%, 8 subjects; 1.3%, 5 subjects) were the only AEs that led to discontinuation in > 1% in either treatment group.

2.6.1. Discussion on clinical safety

Patient exposure

The clinical trial population has been adequately quantified and stratified by relevant categories, including special populations, to allow assessment of the limitations of the human safety database and implications for the safety of the target population. Additional data from patients exposed to COBI as a component of the QUAD STR showed a similar distribution of patients.

In terms of under-represented populations, the study population was male-dominated (about 87% male to 13% female) and the study patients of Asian ethnicity were underrepresented (about 7% of the clinical trial population, compared with 58% white and 27% black).

Adverse events and SAEs

Among the most frequently reported AEs (≥ 10% incidence in either treatment group) four (jaundice, nausea, hyperbilirubinaemia and upper respiratory tract infection) were reported by a numerically higher percentage of subjects in the ATV/COBI group.

Grade 3 or 4 AEs were reported by a slightly higher percentage in the ATV/COBI group (17.8%) compared to ATV/RTV (13.3%). This difference was driven by the difference in Grade 3 AEs and reflected the rates of bilirubin-associated AEs.

There was no apparent pattern in the types of SAEs by treatment and the only SAE reported in > 1% of subjects in either group was acute renal failure.

Renal effect

As a result of known safety profile for the QUAD STR, the CHMP placed a special emphasis on the review of the effect of COBI on the renal function. Indeed, there is a known risk of adverse renal effects associated with TDF.

Background QUAD STR application

It is important to summarise the assessment on this risk perfomed in the context of the QUAD STR application. There is a known risk of adverse renal effects associated with TDF. Though consistent with the known safety profile for TFV, the renal adverse reactions observed during the QUAD STR application was of concern for the CHMP. Hence, the CHMP requested the study GS-US-236-0130 to examine the effect of 5 treatments (COBI, TDF, COBI+TDF, Stribild and placebo) when given once daily for 30 days followed for a further 30 days. Day 60 data from this study showed that the QUAD STB had the greatest effect on aGFR and the follow-up data indicate that the 90% CI around the comparison vs. placebo did not span 100% after 30 days off treatment. The comparisons within treatments for change in renal plasma flow from baseline point to the most marked effect in the COBI + TDF and the QUAD STB groups. The reason for the apparent greater effect of QUAD STB was not clear. Given the variability observed in aGFR and renal plasma flow it is not impossible that the observations could have arisen by chance in this parallel group study. Also, there was no known reason why the QUAD STB might have a greater effect on aGFR than TDF + COBI.

Currently there is no known mechanism by which COBI may have a causative role in PRT. Non-clinical data suggest that FTC, COBI and EVG do not affect the cytotoxicity of TFV in renal proximal tubule cells and that COBI has no effect on TFV accumulation in isolated renal cortical tissue. *In vitro* experiments were completed in cultured primary human renal proximal tubule cells (RPTECs) to assess the cytotoxicity of TFV alone and in the presence of QUAD STB components. The results generated with cells from two independent donors indicated low cytotoxicity of TFV (CC50 > 4,000 µM) that was not affected by COBI, EVG, or FTC at pharmacologically relevant concentrations. Since it is known that RPTECs may down-regulate some of the active renal transport functions due to de-differentiation process triggered by their *in vitro* culturing, the applicant has also initiated studies in HEK-293 cells co-transfected with OAT1 and MRP4, the two key transporters responsible for the active tubular secretion of TFV. Preliminary experiments confirmed the functionality of both transporters following co-transfection and the applicant will proceed to optimize cytotoxicity measurement in the HEK-293 cell culture model. The studies will continue with the assessment of the effect of individual QUAD STB components on the cytotoxicity of TFV.

From the above it can be concluded that there are currently inadequate data to determine whether co-administration of tenofovir disoproxil fumarate and cobicistat is associated with a greater risk of renal adverse reactions compared with regimens that include tenofovir disoproxil fumarate without cobicistat. The CHMP requested a SAG consultation to have the views of additional experts on this issue. The minutes are included below:

“Based on the data available at present, there was a consensus from the HIV/AV SAG that there was no firm evidence pointing to an increased risk of PRT with Stribild or with COBI + TDF versus other TDF-containing products. More extensive and longer term exposure to Striblid

and or COBI associated to TDF should be requested in the 'real life situation' to better assess characteristics and risk factors for renal toxicity.

Given the uncertainties related to the results of study 0130 (in healthy subjects) the experts recommended by consensus that the applicant should be requested to conduct a comparative study in HIV-infected subjects to further evaluate the possible relevance of the data generated by study 130 and suggested a study design for CHMP's consideration.

In addition, some experts expressed interest in understanding the mechanism of the potential renal effect of Stribild and TDF + COBI on aGFR and encouraged the applicant to investigate it.

Given uncertainties on reversibility of renal effects, the experts recommended the applicant gather additional information on this point.

Overall the SAG considers the risks can be managed via appropriate advice in the SmPC and recommended the inclusion of further comments on the SmPC."

Following consideration of the SAG recommendations, the CHMP concluded that the renal effects of the QUAD STB can be addressed via adequate advice in the SmPC that will allow early identification of patients at risk of developing STB-related renal toxicity.

COBI application

In the Phase 2 and 3 studies in which COBI was given as ATV/co+TVD there were 8 subjects in the ATV/co+TVD group, 1 subject in the ATV/r→ATV/co+TVD group (Phase 2) and 15 subjects in the ATV/r+TVD group with either a renal SAE, discontinued study drug due to a renal AE and/or had a pre-specified renal AE of interest. One additional ATV/co subject discontinued due to IgA nephropathy.

Renal laboratory parameters were extensively evaluated as COBI has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine. An increase from baseline in serum creatinine solely due to COBI's inhibitory effect generally does not exceed 0.4 mg/dL.

In study GS-US 216 0114, decreases in estimated creatinine clearance occurred early in treatment with COBI, after which they stabilised. The mean (± SD) change in estimated glomerular filtration rate (eGFR) by Cockcroft-Gault method after 48 weeks of treatment was 13.4 ± 15.2 ml/min in the COBI-boosted atazanavir plus Truvada and 8.7 ± 14.5 ml/min in the RTV-boosted ATV plus emtricitabine and Truvada.

There remains some degree of uncertainty regarding the potential combined effects of TFV and COBI on renal function. Therefore, although there is no remaining major objection regarding use of COBI as a pharmaco-enhancer of ATV or DRV and there are no grounds to preclude its use in conjunction with TDF, it cannot be ruled out that further data could reveal an additive risk of renal issues if the PI/co is administered as part of a regimen that also includes TDF. A warning has been added in the SmPC to reflect this information.

In addition, the applicant has planned to conduct a study to evaluate the effect of the QUAD STR, a TDF regimen without COBI and a regimen without COBI or TDF in HIV-1 infected ARV treatment naïve patients. The objectives of this study are to evaluate the effect on TDF, on the renal fucntion and on to markers of renal tubular function with and without COBI. In addition,

the applicant has initiated *in vitro* studies of the individual components of the QUAD STR on the cytotoxicity of TFV in HEK-293 cells co-transferred with OAT1 and MRP4. The objectives of this study are to evaluate the effect of the individual components of the QUAD STR on the cytotoxicity of TFV and will provide useful information for COBI MA. The results of these studies will be submitted as post authorisation measures (see RMP Section 2.8).

The use of COBI in patients with renal impairment has been identified as an important item of missing information. A clinical study of COBI boosted darunavir and atazanavir in HIV-1 infected adults with mild to moderate renal impairment is currently in progress (GS-US-236-0118). However, in the light of data showing no meaningful differences in the pharmacokinetics of COBI in non-HIV infected subjects with severe renal impairment and healthy subjects (GS US 216 0124), no restrictions on use in patients with renal impairment are proposed except in cases where dosage adjustment based on creatinine clearance is required for co-administered medicinal products.

Hepatic effect

In study GS-US-216-0114, hyperbilirubinaemia (> 1 x ULN) was common: 97.7% in the COBI-boosted ATV plus Truvada group, and 97.4% in the RTV-boosted ATV plus Truvada group. However, a higher percentage of subjects in the COBI-boosted group had increases in total bilirubin > 2 x ULN than those in the RTV-boosted group (85.7% vs 77.7%). The rates of study drug discontinuation due to bilirubin-related adverse events were low and similar in both groups (4.9% in the COBI-boosted group and 3.4% in the RTV-boosted group). An increase of > 3 x ULN in ALT or AST was recorded in 12.0% of subjects in the COBI-boosted group and 8.7% in the RTV-boosted group.

There were no reports of acute hepatic failure, hepatic failure or liver injury in the Phase 2 and 3 studies. No subjects up to the Week 96 cut-off met Hy's law criteria. A slightly higher rate of bilirubin-related AEs occurred with ATV/co vs. ATV/r (none was serious).

Hepatobiliary disorders are not considered as an important potential risk for COBI. The safety specification in the RMP includes information about hyperbilirubinaemia and increased AST / ALT laboratory abnormalities from clinical studies. The ongoing studies for COBI (GS-US-216-0114 and GS-US-216-0130) will provide additional long-term safety information for ATV/co and DRV/co, including information of hyperbilirubinaemia and increased AST and ALT. The results of these studies will be submitted as post authorisation measures (see RMP Section 2.8).

Safety in patients with moderate hepatic impairment has been studied and no dose adjustment is required. Since COBI is primarily metabolized in and eliminated by the liver and that COBI has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), the use of COBI in this population is contraindicated.

There was a higher incidence of other hepatic AEs and in hepatic grade 3 and 4 laboratory abnormalities in subjects co-infected with HBV or HCV compared with subjects without co-infection. Based on the data submitted with the present application, the overall safety profile in the HIV-1 infected subjects co-infected with HBV and/or HCV at baseline was consistent with underlying hepatitis co-infection and the safety profile of ATV, and was generally similar to that in the wider safety population without co-infection.

Missing information

The main patient sub-populations not studied in clinical trials are adults (long-term safety), children, the elderly, women who are pregnant or lactating, those with renal impairment and those with severe hepatic impairment. Studies to provide missing data on long-term use in adults (GS-US-216-0114 and GS-US-216-0130) and safety in patients with renal impairment (GS-US-236-0118) are currently underway. Studies on use in children are planned (GS-US-236-0128 and GS-US-183-0154). Of note, COBI is not recommended for use in children. The results of these studies will be submitted as post authorisation measures (see RMP Section 2.8).

Although safety in elderly patients is considered as missing information for COBI, no specific recommendations are made with regard to use in this group and no studies are currently envisaged.

In the absence of adequate well-controlled studies of COBI in pregnant women, and indeed with pregnancy as an exclusion criterion in all clinical studies, the applicant recommends use of COBI only if the clinical condition of the woman requires treatment with COBI boosted ATV or DRV. Monitoring of exposure in pregnancy will be carried out through the Antiretroviral Pregnancy Registry (APR). The data from this registry will be submitted as post authorisation measures (see RMP Section 2.8).

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

The use of ATV/COBI in conjunction with Truvada over at least 48 weeks has not raised any major concerns regarding safety. The Week 96 data from the COBI Phase 2 and 3 studies indicate no excess of renal AEs when COBI was co-administered with TDF (i.e. in the ATV/co+TVD group vs. the ATV/r+TVD group).

However, there are currently inadequate data to determine whether co-administration of TFV and COBI is associated with a greater risk of renal adverse reactions compared with regimens that include TFV without cobicistat. A warning has been added in the SmPC.

The applicant committed to perform a study to evaluate the effect on TDF, on the renal function and on to markers of renal tubular function with and without COBI. In addition, the applicant has initiated *in vitro* studies to evaluate the effect of the individual components of the QUAD STR on the cytotoxicity of TFV. The results of these studies will be submitted as post authorisation measures (see RMP Section 2.8).

The available data also point to a slight excess of hyperbilirubinaemia of higher grades and of raised transaminases with ATV/co vs. ATV/r. Due to the modest size of the current safety database, the safety specification in the RMP includes information about hyperbilirubinaemia and increased AST / ALT laboratory abnormalities from clinical studies. The ongoing studies for COBI (GS-US-216-0114 and GS-US-216-0130) will provide additional long-term safety information for ATV/co and DRV/co, including information of hyperbilirubinaemia and increased AST and ALT. The results of these studies will be submitted as post authorisation measures (see RMP Section 2.8).

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

PRAC Advice

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (v0.3):

The RMP (v0.3) is acceptable.

The CHMP endorsed this advice with changes. Indeed, the CHMP requested the applicant to specify the timelines for the PhV measures. In response to this request, the MAA submitted an updated version of the RMP (v0.4).

The content of the Risk Management Plan (v0.4) is as follows:

- **Safety concerns**

Table 19. Summary Table of Safety Concerns

Important Identified Risks	None
Important Potential Risks	Concurrent use of drugs whose coadministration with cobicistat (COBI) is contraindicated
	Off-label use of COBI to boost PIs other than atazanavir (ATV) or darunavir (DRV) once daily
Important Missing Information	Long-term safety of cobicistat-boosted atazanavir (ATV/co) and cobicistat-boosted darunavir (DRV/co) in adults with HIV-1 infection
	Safety in children
	Safety in elderly patients
	Safety in pregnancy
	Safety in lactation
	Safety in patients with severe hepatic impairment (Child-Pugh-Turcotte classification [CPT] score C)
	Safety in patients with renal impairment
	Safety in patients with cardiac conduction disorders
	Drug-drug interaction

- **Pharmacovigilance plans**

Table 20. Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
Category 3 Interventional clinical studies				
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/co+TVD versus ATV/r+TVD through 96 weeks of treatment and beyond	*Important missing information* Long-term safety of ATV/co in HIV-1 infected patients	Ongoing	Q3 2014 (Week 144 report) Final report (Week 192) Q3 2015
GS-US-216-0130 A Phase 3b, open-label, single arm study to evaluate the safety and efficacy of cobicistat-boosted darunavir plus two fully active nucleoside reverse transcriptase inhibitors in HIV-1 infected, antiretroviral treatment-naïve and -experienced adults with no darunavir resistance associated mutations	To evaluate the safety and tolerability of DRV+COBI plus 2 fully active nucleoside reverse transcriptase inhibitors (NRTIs) through 48 weeks of treatment and beyond	*Important missing information* Long-term safety of DRV/co in adults with HIV-1 infection	Ongoing	Q3 2015 (Final report)
GS-US-216-0128 An open-label, multicenter, multi-cohort, 2-part study evaluating the PK, safety and efficacy of ATV/co once daily or DRV/co twice daily administered with a background regimen (BR) in HIV-1 infected treatment experienced subjects aged 3 months to <18 years for the ATV/co regimen and 3 years to < 18 years for the DRV/co regimen.	To evaluate PK, safety and efficacy of ATV/co and DRV/co in children and adolescents	*Important missing information* Safety in children	Planned	February 2018 (Week 48 report) February 2022 (Final report)
GS-US-183-0154 A Phase 2/3, multicenter, open-label, nonrandomized, multicohort, 2 part study evaluating the PK, safety, and antiviral activity of EVG coadministered with COBI and 2 first-line NRTIs in HIV-1 infected, antiretroviral treatment-naïve subjects aged < 18 years.	To evaluate PK, safety and efficacy of EVG/co in children and adolescents	*Important missing information* Safety in children	Planned	March 2022 (Final report)
GS-US-236-0118 A Phase 3 open-label safety study of cobicistat-containing highly active antiretroviral regimens in HIV-1 infected patients with mild to moderate renal impairment	To evaluate the effect (including long-term effects), safety and tolerability of COBI-containing regimens (STB,	*Important missing information* Safety in patients with renal impairment	Ongoing	Q3 2015 (Final report)

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
	ATV/co or DRV/co) on renal parameters through 48 weeks of treatment and beyond			
Clinical study of STB, a TDF-containing regimen without COBI, and a regimen without TDF or COBI in HIV-1 infected ARV treatment-naïve patients	To evaluate the effect of TDF on renal function and markers of renal tubular function with and without COBI	*Important missing information* Drug-drug interaction	Planned[a]	May 2015 (Final report)
GS-US-236-0128 A randomized, double-blind Phase 3B study to evaluate the safety and efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus emtricitabine/tenofovir disoproxil fumarate in HIV-1 infected, antiretroviral treatment-naïve women	To evaluate the safety of STB in HIV-1 infected women	*Important missing information* Long-term safety of COBI in adults with HIV-1 infection	Ongoing	Q4 2016 (Week 48 report) Q4 2017 (Week 96 report)
GS US-236-0135 A Phase 1 multiple-dose study evaluating the drug interaction potential between telaprevir and elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate single tablet regimen (Part 1) or ritonavir-boosted atazanavir plus elvitegravir (Part 2) in healthy subjects	To evaluate the drug interaction between STB and telaprevir	*Important missing information* Drug-drug interaction	Ongoing	31 January 2014 (Final report)
GS US-216-0136 A Phase 1 study evaluating the pharmacokinetic drug interaction between elvitegravir/cobicistat and rifabutin	To evaluate the drug interaction between EVG/co and rifabutin	*Important missing information* Drug-drug interaction	Planned	31 December 2014 (Final report)
GS-US-216-0137 A Phase 1, multiple-dose study to evaluate the drug interaction potential between carbamazepine and cobicistat boosted elvitegravir in healthy subjects	To evaluate the drug interaction between EVG/co and carbamazepine	*Important missing information* Drug-drug interaction	Planned	31 December 2014 (Final report)
Category 3 Epidemiological studies				

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
DUS for COBI	To determine the concurrent use of drugs whose coadministration with COBI is contraindicated in the postmarketing setting.	*Important potential risk* Concurrent use of drugs whose coadministration with COBI is contraindicated	Planned	31 December 2013 (Feasibility assessment report)
	To determine off-label use of COBI with a PI other than ATV and DRV once daily in postmarketing setting.	*Important potential risk* Off-label use of COBI to boost PIs other than ATV and DRV once daily.		
Antiretroviral Pregnancy Registry[b]	To determine the risk of birth defects in patients exposed to COBI during pregnancy	*Important missing information:* Safety in pregnancy	Ongoing	Interim reports available every 6 months (June and December each year)
Category 3 Non-clinical studies				
PBPK simulations of the effect of potent CYP3A4 inhibitors on COBI exposure	To evaluate the potential effect of potent CYP3A4 inhibitors on COBI exposure	*Important missing information* Drug-drug interaction	Planned	Q2 2014 (Final report)
In vitro studies of the individual STB components on the cytotoxicity of TFV in HEK-293 cells co-transfected with OAT1 and MRP4	To evaluate the effect of individual STB components on the cytotoxicity of TFV	*Important missing information* Drug-drug interaction	Ongoing	Q3 2013 (Final report)
Category 3 other data				
Analysis of emergent resistance substitutions in the protease gene of patients treated with STB in Phase 3 studies	To assess possible COBI protease inhibitory activity *in vivo* by sequencing the protease in virologic failure subjects' isolates from various STB	*Important missing information* Long-term safety of COBI in adults with HIV-1 infection	Planned	28 February 2017 (Final analysis)

Study/Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
	studies			

a Feasibility assessment results and a draft protocol to be submitted by July 2013.
b Gilead co-sponsors this study along with other pharmaceutical companies.

- **Risk minimisation measures**

Table 21. Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important potential risk(s)		
Concurrent use of drugs whose coadministration with COBI is contraindicated	The Summary of Product Characteristics (SmPC) (Sections 4.3 and 4.5) provides information on contraindicated drugs The package leaflet lists contraindicated drugs.	None
Off-label use of COBI to boost PIs other than ATV or DRV once daily	The SmPC (Sections 4.1, 4.2 and 4.4) states that COBI is indicated as a pharmacokinetic enhancer of once daily 300 mg ATV or once daily 800 mg DRV only and that safety and efficacy have not been established for use of COBI to boost other PIs or ARV agents. The package leaflet contains information on PIs to be used with COBI.	None
Important missing information		
Long-term safety of ATV/co and DRV/co in adults with HIV-1 infection	None	None
Safety in children	The SmPC (Section 4.2 and 4.8) contains information that the safety and efficacy of COBI in children aged 0 to less than 18 years have not yet been established and that COBI is not recommended in this population.	None
Safety in elderly patients	The SmPC (Section 4.2, 4.8 and 5.2) contains information that no data are available on which to make a dose recommendation for patients over the age of 65 years.	None
Safety in pregnancy	The SmPC (Section 4.6) contains information that there are no or limited clinical data with COBI in pregnant	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	women and that COBI should not be used during pregnancy unless the clinical condition of the woman requires treatment with COBI co-administered with ATV or DRV.	
Safety in lactation	The SmPC (Section 4.6) contains information that it is unknown whether COBI/metabolites are excreted in human milk, that a risk to the newborns/infants cannot be excluded and therefore COBI should not be used during breast-feeding, and that in order to avoid transmission of HIV to the infant it is recommended that HIV infected women do not breast-feed their infants under any circumstances.	None
Safety in patients with severe hepatic impairment (CPT score C)	The SmPC (Sections 4.2, 4.4 and 5.2) contains information that COBI has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and therefore, the use of COBI is not recommended in these patients. The effect of severe hepatic impairment (Child Pugh Class C) on the PK COBI has not been studied.	None
Safety in patients with renal impairment	The SmPC (Sections 4.2, 4.4 and 4.8) contains information on use of COBI in patients with renal impairment, that no recommendation can be made for these patients receiving dialysis, and that COBI should not be initiated in patients with creatinine clearance less than 70 mL/min if any co-administered agent (e.g. emtricitabine, lamivudine, tenofovir disoproxil fumarate or adefovir) requires dose adjustment based on creatinine clearance.	None
Safety in patients with cardiac conduction disorders	None	None
Drug-drug interactions	The SmPC (Sections 4.4 and 4.5) contains information on co-administration of COBI with other medicinal products and on mechanisms for potential interactions with relevant	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	dosing recommendations.	

2.9. 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

Cobicistat is a selective, mechanism-based inhibitor of cytochromes P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates (such as atazanavir or darunavir) that have limited oral bioavailability and a short half-life due to CYP3A-dependent metabolism.

Cobicistat has no detectable antiviral activity against HIV 1, HBV or HCV and does not antagonise the antiviral effect of HIV inhibitors. On this basis its use would not contribute to the selection of virus bearing RAMs.

The assessment of the efficacy of COBI as a booster for ATV was mainly based on the data from phase 3 studies GS-US-216-0114. Non-inferiority for ATV/COBI vs. ATV/RTV regimen was demonstrated in this phase 3, randomized, double-blind study to evaluate the safety and efficacy of COBI-boosted ATV versus RTV-boosted ATV each administered with Truvada in HIV-1 Infected treatment-naive adults. Indeed, COBI was shown to achieve pharmaco-enhancement of ATV resulting in efficacy comparable with that achieved by ATV/RTV.

For DRV/COBI (800/150 mg once daily) there are no efficacy data and its use in conjunction with COBI is based solely on demonstrating a comparable DRV PK profile compared to DRV/r (800/100 mg once daily). Overall, the data support the comparable efficacy of DRV/co and DRV/r provided that the use of DRV/co is entirely restricted to the HIV-infected sub-population described in the DRV SmPC when using the once daily regimen.

Drug-drug interaction studies (DDIs) were conducted and their conclusions are adequately reflected in the SmPC. In the setting of boosting ATV or DRV, COBI 150 mg has the possibility of resulting in a slightly smaller range of potential DDIs vs. RTV 100 mg.

Uncertainty in the knowledge about the beneficial effects.

The efficacy of ATV/COBI (300/150 mg once daily) has only been demonstrated in conjunction with Truvada and only against viruses known to be fully susceptible to all three ARV agents. This reduces the sensitivity of the Phase 3 study to detect any possible effects of slightly lower plasma levels of ATV on efficacy. Nevertheless, the plasma exposures to ATV when given with

COBI (300/150 mg) met bioequivalence criteria when compared to ATV/RTV (300/100 mg) and comfortably exceed the recommended ATV C_{trough}.

The assessment of the effectiveness of COBI as a booster for DRV was based primarily on data from the Phase 1 study GS-US-216-0115. No randomised clinical trial was conducted by the Applicant. This is reflected in the SmPC. Data from the Phase 3 studies investigating the use of DRV/RTV 800/100 mg in HIV-1 infected subjects (ARTEMIS and ODIN) and from uncontrolled efficacy data (GS-US-236-0118, GS-US-216-0130) were submitted to support this indication.

While the DRV C_{max} and AUC met the bioequivalence criteria the C_{tau} was 30% lower for DRV/co vs. DRV/r. PK/PD considerations and cross-study comparisons with PK data obtained in previous DRV/r efficacy studies provide some reassurance that the difference in C_{tau} is not likely to be associated with lower efficacy for DRV/co vs. DRV/r. However, the use of DRV/co is entirely restricted to the HIV-infected sub-population described in the DRV SmPC when using the once daily DRV/r regimen.

Risks

Unfavourable effects

The use of ATV/COBI in conjunction with Truvada over at least 48 weeks has not raised any major concerns regarding safety. The Week 96 data from the COBI Phase 2 and 3 studies indicate no excess of renal AEs when COBI was co-administered with TDF (i.e. in the ATV/co+TVD group vs. the ATV/r+TVD group). Nevertheless, there are currently inadequate data to determine whether co-administration of TFV and COBI is associated with a greater risk of renal adverse reactions compared with regimens that include TFV without cobicistat.

COBI co-administered with ATV or DRV should not be used in combination with another antiretroviral agent that requires pharmacoenhancement by means of co-administration with an inhibitor of CYP3A4 to reach the desired therapeutic plasma concentrations (i.e., another protease inhibitor or elvitegravir). Indeed dosing recommendations for such combinations have not been established and co-administration may result in decreased plasma concentrations of ATV, DRV and/or the other ARV agents that require pharmacoenhancement leading to loss of antiviral activity and development of resistance.

Uncertainty in the knowledge about the unfavourable effects

There remains some degree of uncertainty regarding the potential combined effects of TFV and COBI on renal function. Therefore, although there is no remaining major objection regarding use of COBI as a pharmaco-enhancer of ATV or DRV and there are no grounds to preclude its use in conjunction with TDF, it cannot be ruled out that further data could reveal an additive risk of renal issues if the ATV/co or DRV/co is administered as part of a regimen that also includes TDF. The applicant has committed to perform a number of studies to obtain assurance of the acceptability of this risk (see Section 2.8 RMP). In addition, a warning has been added in the SmPC.

The available data also point to a slight excess of hyperbilirubinaemia of higher grades and of raised transaminases with ATV/co vs. ATV/r. Due to the modest size of the current safety database, the safety specification in the RMP includes information about hyperbilirubinaemia

and increased AST / ALT laboratory abnormalities from clinical studies. The applicant will provide additional long-term safety information for ATV/co and DRV/co, including information of hyperbilirubinaemia and increased AST and ALT, to gain further information on this risk (see Section 2.8 RMP).

Balance

Importance of favourable and unfavourable effects

COBI has potential to be an useful alternative to RTV as a pharmaco-enhancer of specific antiretroviral agents that are substrates of CYP3A4. Indeed, COBI has been shown to be effective as a pharmacokinetic enhancer 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.

There are no potential safety concerns that would preclude its use with ATV or DRV.

Benefit-risk balance

The benefit-risk balance is currently considered to be favourable for use of COBI as a pharmacokinetic enhancer 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.

Conclusions

The overall benefit risk balance of cobicistat is positive.

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 Tybost as a pharmacokinetic enhancer of once daily 300 mg atazanavir or once daily 800 mg darunavir as part of antiretroviral combination therapy in human immunodeficiency virus 1 (HIV-1) infected adults 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).

OTHER 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.

New Active Substance Status

Based on the review of the data the CHMP considered that the active substance cobicistat contained in the medicinal product Tybost was to be qualified as a new active substance at the time of submission of this application.