EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vitekta

International non-proprietary name: ELVITEGRAVIR

Procedure No. EMEA/H/C/002577/0000

Note

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

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Product information

Name of the medicinal product:	Vitekta
Applicant:	Gilead Sciences International Ltd Flowers Building Granta Park Abington Cambridge CB21 6GT UNITED KINGDOM
Active substance:	ELVITEGRAVIR
International Nonproprietary Name:	ELVITEGRAVIR
Pharmaco-therapeutic group (ATC Code):	Other antivirals, HIV-1 integrase strand transfer inhibitors (J05AX11)
Therapeutic indication(s):	In co-administration with a ritonavir-boosted protease inhibitor and with other antiretroviral agent, treatment of HIV-1 infection in adults who are infected with HIV-1 without known mutations associated with resistance to elvitegravir
Pharmaceutical form:	Film-coated tablet
Strengths:	85 mg and 150 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	30 tablets

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List of abbreviations

ABC	abacavir
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the plasma concentration-time curve
BID	twice daily
BLLQ	below lower limit of quantification
BMI	body mass index
BSA	body surface area
CC50	concentration that results in 50% cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL/F	apparent oral clearance
C_{max}	maximum observed concentration
COBI, /co	cobicistat
CRF	case report form
CSR	clinical study report
C_{tau} or C_{trough}	observed drug concentration at the end of the dosing interval
CV	coefficient of variation
d4T	stavudine
DAVG	difference between time-weighted average post baseline and baseline
DC	discontinuation of the study drug
ddI	didanosine
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DRV	darunavir
EC_{xx}	concentration of a compound inhibiting virus replication by xx%
EE	ethinyl oestradiol
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EVG	elvitegravir
FBRM	focus beam reflectance measurement
FDA	US Food and Drug Administration
FDC	fixed dose combination
FPV	fosamprenavir
FTC	emtricitabine
GCP	Good clinical practices
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GI	gastrointestinal
GLP	Good laboratory practices
GMP	Good manufacturing practices
GSS	genotypic sensitivity score
HAART	highly active antiretroviral therapy
HBV, HCV	hepatitis B or C virus, respectively
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
IDMC	Independent Data Monitoring Committee
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
ITT	intent-to-treat
KTZ	ketoconazole
LLQ	lower limit of quantification
LPV	lopinavir
LSM	least-squares mean

LTFU	lost to follow-up
M = E	missing = excluded
M = F	missing = failure
M/S = F	missing or antiretroviral therapy switch = failure
M1	elvitegravir metabolite (hydroxylation of the chlorofluorophenyl group)
M4	elvitegravir metabolite (glucuronide conjugate of the carboxylic acid)
MDZ	midazolam
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MVC	maraviroc
NAS	new active substance
NORs	normal acceptable ranges
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
OATP	organic anion transporting polypeptide
OBR	optimised background regimen
PARs	proven acceptable ranges
PD	pharmacodynamics
Pgp	P glycoprotein
PI	protease inhibitor
PIP	Paediatric Investigation plan
PK	pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PSS	phenotypic sensitivity score
PVF	pure virological failure
PVRs	pure virological responders
QUAD, STR	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
RAL	raltegravir
RMP	Risk Management Plan
RNA	ribonucleic acid
RTV, /r	ritonavir
S9	tissue post-mitochondrial (9,000 x g) supernatant
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
t½	estimate of the terminal elimination half-life of the drug
T20	enfuvirtide
TDF	tenofovir disoproxil fumarate
TEAE	treatment emergent adverse event
TLOVR	time to loss of virological response
UGT	uridine glucuronosyltransferase
VF	virological failure
ZDV	zidovudine

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Gilead Sciences International Ltd submitted on 22 May 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Vitekta, 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 19 May 2011.

The applicant applied for the following indication: in co-administration with a ritonavir-boosted protease inhibitor and with other antiretroviral agent, treatment of HIV-1 infection in adults who are infected with HIV-1 without known mutations associated with resistance to elvitegravir.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC – complete and independent application.

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0010/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0010/2012 was not yet completed as all 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.

New active Substance status

The applicant requested the active substance elvitegravir contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

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 application was received by the EMA on 22 May 2012.
- The procedure started on 20 June 2012.
- The Rapporteur's first Assessment Report including Assessment report on the claim of new active substance (NAS) was circulated to all CHMP members on 3 September 2012 (Annex 1). The Co-Rapporteur's first Assessment Report including Assessment report on the claim of new active substance (NAS) was circulated to all CHMP members on 7 September 2012 (Annex 2).
- During the meeting on 18 October 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 19 October 2013 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 May 2013 (Annex 4).
- During the meeting on 13 June 2013, the PRAC agreed RMP Advice and assessment overview.
- During the CHMP meeting on 27 June 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 16 August 2013.
- During the meeting on 5 September 2013, PRAC endorsed PRAC Rapporteur assessment report on the RMP.
- During the meeting on 19 September 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 Vitekta.

2. Scientific discussion

2.1. Introduction

Problem statement

There are approximately 33 million people worldwide living with HIV-1. HIV-1 infection remains 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. In treatment naïve subjects who have not acquired multi-resistant virus *de novo*, suppression of HIV RNA to < 50 copies/ml has been achieved in ~80% of subjects in clinical studies.

Current treatment guidelines suggest that initial therapy for ARV treatment-naïve HIV-1 infected patients should consist of 2 NRTIs/NtRTIs and either an NNRTI (usually efavirenz—a boosted protease inhibitor (PI)) or the integrase inhibitor (INSTI) raltegravir (RAL), which is currently the only licensed medicine in this class. Ritonavir (RTV) - boosted PIs are also used in treatment-experienced subjects infected with virus susceptible to the specific PI to be used.

Advantages of PI-based regimens include excellent anti-viral activity, a relatively high barrier for development of drug resistance (i.e. requires multiple mutations) 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 (RTV) to boost exposure through inhibition of CYP3A-mediated metabolism, which adds to the potential for DDIs to occur.

About the product

Elvitegravir (EVG; JTK-303, GS-9137) blocks HIV-1 replication by inhibiting the strand transfer activity of the HIV-encoded enzyme integrase and as such is an Integrase Strand Transfer Inhibitor (InSTI).

Integration of the viral genome is an essential and characteristic step in the life cycle of all retroviruses including HIV-1. The virally-encoded protein integrase is one of three HIV-1 enzymes required for viral replication and it is the only protein known to be required to catalyse each of the specific steps necessary for integration including:

1. assembly of a stable complex with the viral DNA,
2. endonucleolytic processing of the viral DNA ends (the U3 and U5 LTRs),
3. strand transfer or joining of the viral and cellular DNA.

In HIV-1 infected cells, the specific interaction between integrase and the viral DNA end results in the formation of a stable pre-integration complex. The uncoupled strand transfer assay has been shown to be a good surrogate for integration assays using pre-integration complexes isolated from HIV-1

infected cells. Raltegravir has been shown to inhibit integrase-mediated strand transfer using staged biochemical assays and purified recombinant HIV-1 integrase. Co-administration of EVG with RTV was shown to result in considerable increases in the EVG plasma levels and changed the plasma profile. Further development of EVG has focussed on its co-administration with the pharmaco-enhancer cobicistat (COBI), as part of QUAD STR and on co-administration with RTV-boosted PIs, in which case the RTV affects the PK profiles of both the EVG and the companion PI in parallel.

The EVG 85 mg and 150 mg single tablets are intended for once daily dosing in adults who are infected with HIV-1 without known mutations associated with resistance to elvitegravir, in combination with one of the following ritonavir (RTV)-boosted protease inhibitors (PIs): darunavir (DRV), fosamprenavir (FPV), atazanavir (ATV) or lopinavir (LPV). The choice of dose of EVG depends on the co-administered protease inhibitor (see Table below).

Table 1. Proposed recommended dosing regimens

Dose of elvitegravir	**Dose of co-administered ritonavir-boosted protease inhibitor**
85 mg once daily	atazanavir/ritonavir 300/100 mg once daily
	lopinavir/ritonavir 400/100 mg twice daily
150 mg once daily	darunavir/ritonavir 600/100 mg twice daily
	fosamprenavir/ritonavir 700/100 mg twice daily

Due to the integrated nature of the EVG, COBI and QUAD STR development programmes this application includes studies that were conducted with:

- EVG alone and in conjunction with PIs,
- COBI-boosted elvitegravir (EVG/COBI),
- QUAD STR (EVG/COBI, tenofovir, emtricitabine).

This assessment report focuses on presenting and discussing the data most relevant to the use of EVG in conjunction with the RTV-boosted PIs specifically mentioned in the proposed SmPC. Data generated with each of EVG/COBI or with the QUAD STR are described only where considered essential to support this application.

Type of Application and aspects of development

The application has been made via the centralised procedure according to Regulation (EC) No 726/2004, within mandatory scope for a new active substance.

The application contains a single pivotal Phase 3 efficacy study GS-US-183-0145. The current application contains a report on data to Week 96. This study was conducted in treatment-experienced HIV-infected subjects and directly compared EVG/RTV with RAL when each was given in conjunction with an optimised background regimen (OBR). EVG and RAL were used in regimens that included RTV-boosted PI plus one other agent (NRTI or T20 or maraviroc).

This Phase 3 study is supported by a Phase 2 study plus a rollover follow-on study (GS-US-183-0105 and 0130) in which treatment-experienced subjects were initially randomised to EVG/RTV or a PI/RTV, each with OBR and then offered open label EVG/RTV as a follow-on. It is also supported by the efficacy data derived from COBI-boosted EVG administered with TDF/FTC as Stribild (STB, QUAD STB).

The following sections focus on the data pertaining to manufacture of EVG 85 and 150 mg tablets and the non-clinical and clinical studies performed with EVG when not incorporated into STB. While the

clinical safety and efficacy data relating to STB have some implications for this application and a few of the Phase 1 studies with STB provide data not available for EVG alone (with COBI as the pharmaco-enhancer and not RTV), the clinical data specific to EVG/RTV are regarded to be the most critical.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 85 mg or 150 mg of elvitegravir as active substance. Vitekta has the following composition:

Tablet core:

Croscarmellose sodium

Hydroxypropyl cellulose

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulfate

Film-coating:

Indigo carmine (FD&C blue #2) aluminium lake (E132)

Polyethylene glycol (Macrogol)

Polyvinyl alcohol

Talc (E553B)

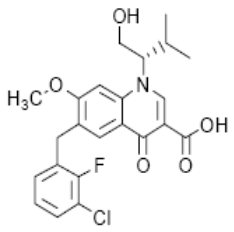
Titanium dioxide (E171)

Iron oxide yellow (E172)

The product is available in high density polyethylene (HDPE) bottles with a child-resistant closure.

2.2.2. Active Substance

The chemical name of elvitegravir is 6-(3-Chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and has the following structure:



The molecular formula is $C_{23}H_{23}ClFNO_5$ and its relative molecular mass 447.9 g/mol.

Elvitegravir appears as a white to pale yellow crystalline non-hygroscopic powder, sparingly soluble in methanol and ethanol and practically insoluble in water and aqueous solutions at pH 2.0 to 8.3. Its pKa is 6.6 and the distribution coefficient LogD 4.5 (at pH 6.8).

Elvitegravir exhibits polymorphism and appears in three polymorphs. The most thermodynamically stable polymorphic form has been determined and the crystallisation process is designed to consistently deliver this form. It contains a single asymmetric centre at C-11. The absolute configuration was established by single crystal X-ray crystallography and has been determined to be of "S" configuration. Enantiomeric purity is controlled routinely by chiral HPLC.

Manufacture

Elvitegravir is manufactured in six well defined synthetic steps using commercially available starting materials. Three sites are involved in the manufacture of this active substance. 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. Information about the formation, presence, origin and fate of impurities during manufacture has been satisfactorily discussed.

Representative batch analysis data provided for all three proposed manufacturing sites produced with the proposed synthetic route show that the active substance can be manufactured reproducibly.

Specification

The active substance specification includes tests and limits for appearance (visual inspection), identity (UV, IR, HPLC), water content (KF), assay (HPLC, UPLC), impurities (HPLC), enantiomeric purity (chiral HPLC), residual solvents (GC), residue on ignition (Ph. Eur.), heavy metals (ICP-MS), particle size (laser light scattering) and polymorphic form (DSC-Ph. Eur.)

Impurities, including genotoxic impurities, have been evaluated and qualified where necessary. The proposed limits are found to be acceptable from a safety point of view and therefore they are considered justified.

A microbial limit test for the active substance is not required in accordance with ICH Q6A because the latter steps of the active substance manufacturing process conducted in aqueous organic solvent mixtures and are expected to limit microbial content. In addition confirmatory testing demonstrated that elvitegravir is moderately to completely inhibitory to microbial growth.

The analytical methods have been well described and validated according to ICH Q2 (R1) and are suitable to control the quality of the active substance.

Batch analysis data on 23 commercial scale batches of the active substance manufactured by all three proposed manufacturers have been provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process regardless of the manufacturing site.

Stability

Stability studies have been conducted for three commercial scale batches from the first manufacturer and one batch from the secondunder ICH long term (25 °C/60% RH) and accelerated conditions (40 °C/75% RH) in the proposed packaging. Results at long term conditions for three batches were

submitted for up 36 months and for one batch for up to 12 months. Results under accelerated conditions were submitted for up to 9 months.

Long term and accelerated stability samples were tested for appearance, assay, impurity content, and water content. The enantiomeric purity and polymorphic form were tested annually during the long term studies. Enantiomeric purity was determined for one batch, at the beginning and end of the accelerated study and polymorphic form was tested at the end of the accelerated study. The analytical methods used are stability indicating.

All parameters remained within the specification limits under both conditions over the duration of study for all four batches. The data show no discernible trends for assay, total impurity content, individual specified impurities, degradation products or any other tested parameter.

In addition, a photostability study of elvitegravir has been assessed as per the ICH Q1B Guideline on one batch from the second manufacturer. No significant difference was observed between the control sample and exposed sample in appearance, assay, impurity content, polymorphic form and enantiomeric purity. The data indicate that elvitegravir 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

Vitekta is an immediate-release film-coated tablet developed in two strengths, 85 mg and 150 mg.

The principal factors considered during the pharmaceutical development were:

- Developing an immediate-release tablet formulation
- Optimizing the biopharmaceutical performance of elvitegravir
- Developing a robust and scalable formulation and manufacturing process

The film-coated immediate release tablet was chosen as the pharmaceutical form for its physical properties and suitable shelf-life. The small physical dimension of the tablets was pursued to enhance dosing compliance as Vitekta will be administered at the same time as a ritonavir-boosted protease inhibitor

The oral bioavailability of elvitegravir is limited by solubility and dissolution; therefore, various formulation and process development strategies were implemented to improve the manufacturing process and the biopharmaceutical performance of elvitegravir.

All the excipients used in this formulation are commonly used and meet the standards defined in the current Ph. Eur. monographs used in coating which is tested according to in-house standards based on compendial requirements.

During clinical studies, compatibility studies between the active substance and excipients were carried out between two formulations, dispersion and tablet. Modifications to the excipient matrix were made to the tablet and it was determined that the bioavailability from the conventional tablet was sufficient to achieve efficacy when co-administered with food and when ritonavir was used as a pharmacoenhancing agent.

The proposed commercial formulation and manufacturing process were optimised to identify the critical process parameters, critical quality attributes and to define the manufacturing operating ranges. Design of experiments was used to establish proven acceptable ranges (PARs) and normal acceptable ranges (NORs) within the operating ranges, with a focus on the fluid-bed granulation of elvitegravir and the following variables were studied: spray rate, inlet air temperature and quantity of water in the binder solution. PARs and NORs for the tablet compression, and aqueous film-coating processes have also been established. Moving inside the PARs would be acceptable without regulatory post approval change assessment. However, it is reminded that in case of excursion of one process parameter out of its normal operating range, but within the proven acceptable range, the other process parameters should be maintained at their target/ normal operating value.

Process analytical technology was incorporated into the analysis using an at-line Focused Beam Reflectance Measurement (FBRM) to monitor the granule growth throughout the granulation process.

The formulation and the manufacturing process used to prepare primary stability and clinical batches are identical to the proposed commercial formulation and manufacturing process, except for differences in the subclass of three types of equipment (fluid-bed processors, tumble blenders and pan coaters) required to accommodate a larger batch size.

Bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation.

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

Adventitious agents

Among excipients present in the finished product only lactose is of animal origin. It has been confirmed that lactose is produced from milk from healthy animals in the same conditions as those used to collect milk for human consumption and that lactose has been prepared without use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

Manufacture of the product

The manufacturing process of the film-coated tablets involves the following steps: blending, granulation, drying, blending, compression and film coating.

The process is considered to be a standard manufacturing process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for the manufacturing of a film coated tablet.

PARs and NORs for the granulation, tablet compression and film-coating steps have been established. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

Product specification

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

The non-compendial analytical procedures have been validated according to ICH Q2A guidelines.

Batch analysis results are submitted for 14 clinical batches used throughout development. The batch analysis data are within the set specification limits and show that the Vitekta tablets can be manufactured reproducibly.

Stability of the product

Stability data of one production scale batch of finished product stored under long term conditions during 48 months and of two production scale batches stored during 36 months at long term conditions 25 ºC / 60% RH and under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Additional stress studies at high temperature and humidity conditions were performed at 50 °C/ambient humidity and at 25 °C/80% RH for six weeks.

Samples were also tested for microbial contamination and to assess the in-use stability.

Vitekta tablets were also stored in open dishes at 25 °C/60% RH and 30 °C/75% RH for six weeks.

In addition, two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

The batches of Vitekta are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical procedures used are stability indicating and no degradation was observed in the tablets when stored at any condition.

Based on available stability data, the shelf-life with no special storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design space was claimed for the manufacturing process of the finished product. PARs have been defined for the following steps: dry granulation, tablet compression and film-coating. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.3. Non-clinical aspects

2.3.1. Introduction

The dossier included *in vitro* PD and PK studies. Results from a series of safety pharmacology studies have been provided. *In vivo* pharmacokinetics, toxicokinetics, distribution, metabolism and excretion of EVG were assessed primarily in the CD-1 mouse, Sprague Dawley rat, and beagle dog. The toxicology data were provided from single-dose oral toxicity studies in rats and dogs; 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 developmental and reproductive toxicity programme. Two-year oral carcinogenicity studies in mice and rats have also been provided.

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 are regarded as conducted to an appropriate scientific standard.

2.3.2. Pharmacology

Primary pharmacodynamic studies

EVG belongs to the new class of HIV-1 integrase strand transfer inhibitors, which inhibit the insertion of the viral genome into the DNA of the host cell. *In vitro*, EVG inhibited viral replication in laboratory strains and various clinical isolates of HIV-1 with mean EC_{50} values of 0.35 nM to 0.62 nM and also showed some activity against HIV-2. Primary pharmacodynamics are further discussed in the clinical part of the report.

Secondary pharmacodynamic studies

During a screen for binding and/or activity at a total of 32 secondary targets (receptors, enzymes and cell-based assay systems), no significant inhibition was observed at a concentration which is 333-fold higher than the clinical C_{max} (free) at proposed doses.

Elvitegravir did not inhibit the activity of human topoisomerase I and II enzymes up to 50 and 150 µM, respectively. As the observed effect on HIV-1 occurred primarily in the nanomolar range, these data suggest that elvitegravir does not inhibit HIV viral replication via effects on topoisomerases I and II.

EVG was weakly cytotoxic to human macrophages, primary T lymphocytes, primary PBMCs and primary moncocytes/macrophages (CC_{50} 25.6 to >500 µM). Specifically, in a [^{3}H]thymidine incorporation assay, following exposure to PBMCs for 7 days, EVG was cytotoxic, whereby the CC_{50} was 9.7 µM and 170 µM in the absence and presence of human serum. Selectivity indices (CC_{50}/EC_{50}) for EVG with and without human serum were high: 48,500 and 113,400, respectively. In addition, in HepG2 hepatoma cells, EVG had no significant effect on the content of mitochondrial DNA following exposure for 14 days.

Safety pharmacology programme

Single oral doses of EVG at up to 2000 mg/kg had no effects on the central nervous system in the rat. The corresponding C_{max} at the no-effect level was 43.5 ug/mL, which is approximately 23-fold higher than that observed clinically.

In vitro electrophysiology studies indicated that EVG inhibited the hERG potassium current at the maximum concentration tested (10 µM) and the major metabolites, M1 and M4 inhibited the hERG potassium current with IC_{50} values of 81 µM and >100 µM, respectively. The effective concentrations or the IC_{50} values were substantially above those observed clinically. EVG (at up to 3 µM) had no effect on action parameters in isolated papillary muscle and *in vivo*, had no effect on cardiovascular (or respiratory) parameters at up to 100 mg/kg; where the corresponding C_{max} was ~4.2-fold higher than that observed clinically. Overall, these data do not suggest a potential for QT prolongation.

Ex vivo, EVG at 30 µM caused a slight inhibition of single contractions induced by histamine, acetylcholine and barium chloride; however, *in vivo*, EVG had no effect on gastrointestinal transport at up to 2000 mg/kg. In addition, in the rat, similar doses of EVG had no effect on the urine volume or urinary excretion of electrolytes or the central nervous system. The corresponding C_{max} at the no-effect level of 2000 mg/kg was 43.5 µg/mL, which is approximately 23-fold higher than that observed clinically.

Pharmacodynamic drug interactions

The potential for pharmacodynamic drug interactions is discussed in the Clinical section of the report.

2.3.3. Pharmacokinetics

A series of method validation, absorption, distribution, metabolism, excretion and pharmacokinetic drug interaction studies have been conducted with EVG.

Absorption

In male animals, the absolute oral bioavailability for EVG was moderate and was estimated to be 30 to 35% in the rat and 26 to 33% in the dog. The systemic clearance in the rat was low relative to hepatic blood flow and intermediate in the dog, which indicates a low extent/degree of hepatic first pass metabolism following oral absorption. In general, following single or repeated oral administration in the mouse, rat and/or dog, systemic exposures increased in a dose-related manner and exposures to EVG did not appear to change significantly over time. Moreover, hepatic microsomal fractions from rats treated with EVG for up 3 months showed no notable change in activity, which confirms a lack of evidence for auto induction of CYP3A in these species. Nevertheless, there is evidence to suggest that EVG is a modest inducer of CYP3A in man (*in vitro* and *in vivo*). In the mouse and rat (but not in the dog), exposures were higher in females. This is consistent with the known gender difference in CYP3A expression (i.e. higher expression in males) in rodents.

The applicant suggested that EVG exposures were higher when EVG was co-administered with cobicistat. However, close examination of the toxicokinetic report and the actual data reveal that following co-administration with COBI (30 mg/kg/day), exposures to EVG were similar in females and only slightly increased in males (when compared to that observed when EVG was administered alone). The applicant clarified that co-administration with cobicistat increased exposures to EVG on Day 1, that the magnitude of pharmacokinetic enhancement is sex-dependent (males > females) and that the enhancement effect is reduced upon repeated dosing, due to COBI's ability to induce EVG metabolism

in rodents. There was a difference in the increase in EVG exposures observed in the mouse (up to 7-fold) when compared to the rat (1 to 3-fold) when co-administered with ritonavir/cobicistat. However, it is noted that although EVG is metabolised via a combination of oxidation and glucuronidation; in the mouse, EVG oxidation by CYP3A may play a greater role.

Distribution

The binding to plasma proteins (*in vitro*) was considered to be high (fraction unbound in the rat, dog, monkey and human was 0.1, 0.8, 1.5 and ~0.7 %, respectively) and there is evidence to suggest that albumin is the major plasma binding protein. The distribution to red blood cells (*in vitro* and *in vivo*) was low. Following single oral administration of radiolabeled-EVG to the Sprague Dawley rat, drug related radioactivity was rapidly distributed within 0.25 hours post-dose to the highly perfused organs (liver, adrenal gland, kidney, heart, lung and pancreas), with relative exclusion from the eye and brain. The tissue:plasma concentration ratios were generally <1, with the exception of the liver and gastrointestinal tract, which correlates with the route of elimination and the principal findings from the toxicity studies. The tissue concentrations of radioactivity largely declined in parallel with those of the plasma, reaching undetectable or trace levels by 96 hours post-dose. Pre-treatment of the CYP3A inhibitor, ritonavir, increased the blood and tissue concentrations of drug related material, but had no effect on the overall pattern of distribution. The placental transfer of EVG and its distribution into foetal tissues have not been evaluated. Data from a pre/post-natal study in the rat indicate that low levels of EVG distribute into the milk of lactating rats, with a milk:plasma ratio of 0.1. Given the potential for serious adverse reactions in nursing infants and the potential for HIV transmission, Section 4.6 of the SmPC indicates that women should not to breastfeed during treatment with EVG, which is supported.

Metabolism

The *in vitro* and *in vivo* studies indicate that EVG is extensively metabolized by oxidation, glucuronidation and combinations of the two. The most abundant metabolites the p hydroxylated metabolite (M1, GS-9202); the acyl glucuronide (M4, GS-9200) and M5 (rabbit) were generally common between mouse, rat, rabbit, dog, and human.

Excretion

Following administration of radiolabeled-EVG to the rat and dog, parent compound accounted for the majority of radioactivity in plasma and the predominant metabolite was M1 with lesser amounts of M4 and M7 (glucuronide of M1). Small amounts of the glucuronides, M4 and M7, were detected in urine but these metabolites were more abundant in bile. However, parent compound and the oxidative metabolites, M1 and M2, were the most abundant in the faeces, with no detectable glucuronide, which suggests that biliary glucuronide metabolites are cleaved within the intestine before being excreted via the faeces.

Pharmacokinetic interactions

The oxidative metabolism of EVG is catalysed primarily by CYP3A4 (with minor contributions from CYP3A5 and CYP1A1), which makes EVG a suitable partner for a pharmacokinetic enhancer, such as ritonavir (RTV) or with cobicistat (when administered as QUAD STR), which inhibit CYP3A enzymes. The applicant has investigated the effects of a number of medicinal products on EVG oxidation. The CYP3A4 inhibitor, ketoconazole was the most potent inhibitor (IC50 = 0.099 µM), followed by the protease inhibitors ritonavir, indinavir, nelfinavir, amprenavir, lopinavir and saquinavir (IC50 values

ranged from 0.079 µM to 4.5 µM). The conjugative metabolism (glucuronidation) of EVG is catalysed primarily by UGT1A1 and to a lesser extent UGT1A3. Both atazanavir and ketoconazole inhibited EVG glucuronidation with IC50 values of 0.4 µM and 9.6 µM, respectively. The SmPC captures some of these potential pharmacokinetic interactions and clarifies whether they are of clinical relevance or whether dose adjustments are necessary. Given the observed inhibitory effects of indinavir (IC50 0.51 µM), nelfinavir (IC50 1.1 µM) and saquinavir (IC50 4.5 µM) a pharmacokinetic interaction would be expected; however, the relevant interaction studies have not been performed in man. Section 4.5 of the SmPC has been amended and does not recommend the co-administration of saquinavir, nelfinavir or indinavir with EVG.

The potential to inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, UGT1A1, UGT1A3 and UGT2B7 was investigated in human hepatic microsomes. The data suggest that EVG should not cause any clinically significant pharmacokinetic drug interactions via inhibition of any of these enzymes at therapeutic concentrations, since the unbound mean C_{max} of EVG (0.03 µM) is substantially below the observed IC50 values (≥14 µM).

Studies were conducted to evaluate the potential of EVG to cause pharmacokinetic interactions via enzyme induction. In vivo (humans), repeated co-administration of EVG/COBI had no effect on the pharmacokinetics or pharmacodynamics of the CYP2B6 substrate, methadone. In vitro, EVG did not activate human aryl hydrocarbon receptor (AhR; <2-fold increase in CYP1A2 activity) in human hepatocytes, but showed some potential to induce enzymes such as CYP3A (up to 10.6-fold) and to a lesser extent CYP2C9 (up to 2.72-fold), which are controlled by pregnane X receptor (PXR), at concentrations within range of those observed clinically. In clinical practice, the effect of the co-administered pharmacokinetic enhancer would appear to blunt induction of CYP3A. There are clinical data to suggest that exposures to atazanavir are reduced upon co-administration with EVG and RTV and it is likely that this is due to the induction of CYP3A4 (by EVG) upon repeated administration. However, the magnitude of the observed effect is small; hence, the overall net effect will depend upon the induction liability of the pharmacokinetic enhancer itself and the other co-administered products.

Elvitegravir was earlier identified as a P-gp/MDR1 substrate; however, there was no evidence of saturation of intestinal efflux transport in vivo. EVG also shows weak inhibition of this efflux transporter (IC50 >30 µM); however, systemic concentrations would be insufficient to inhibit transporter activity. High concentrations of EVG present relatively briefly in the intestinal lumen during drug absorption can inhibit intestinal efflux transporters, such as P-gp. However, the effect on these transporters will most likely be limited by the poor solubility of EVG and hence, the potential for a clinically relevant interaction at the level of the small intestine is unlikely.

Elvitegravir is a weak inhibitor of OATP1B1 and a more potent inhibitor of OATP1B3 (IC50 values of >2 µM and 0.4 µM, respectively). The observed inhibition of OATP transporters is consistent with results of a clinical drug interaction study in which, after dosing with 150 mg COBI and 150 mg EVG (which inhibit both transporters), there was a modest increase in exposure of the OATP substrate, rosuvastatin and these data feature within Section 4.5 of the SmPC. The Applicant has also provided data to suggest that the potential for a clinically relevant interaction at the level of the BCRP, OAT1, OAT3, OCT2 or MATE-1 transporter is low.

2.3.4. Toxicology

Single dose toxicity

Following single oral administration in the rat and dog, no mortality or changes in body weight/food consumption were observed at up to 2000 mg/kg and 1000 mg/kg respectively. Emesis was observed

in the dog and this was considered to be a direct effect on the digestive tract as no emesis was observed at comparable exposures following intravenous administration.

Repeat dose toxicity

The repeated-dose studies demonstrated that EVG is well tolerated for up to 6 months in the rat and 9 months in the dog at doses producing systemic exposure levels that are 25.2 to 45.7-fold higher (rat) and 3- to 3.6-fold higher (dog) than those observed clinically. None of the observed findings as reported during the single- or repeated-dose non-clinical studies with EVG were considered to be adverse.

Treatment-related effects included changes in caecum weights, dilation of the caecum, and the presence of lipid vacuoles in the lamina propria of the upper small intestines of rats and dogs. In these species, changes in the caecum were not accompanied by any histological changes or gastrointestinal (GI) adverse events. In the rat, increased caecal weight and/or dilatation of the caecum was observed at ≥300 mg/kg/day where the systemic exposures (AUC) were at least 12.6-fold higher than that observed clinically. In the dog, dilation of the caecum was observed at exposures that were 3.6-fold higher than that observed clinically.

The incidence and severity of lipid vacuoles in the upper small intestines did not appear to increase with repeated dosing of EVG. The applicant maintains that the severity and the incidence of the vacuolization did not increase with dose, but it is noted that results from the 13-week rat study for example suggest otherwise. However, there was no evidence of toxicity or other histopathological correlate associated with these vacuoles. The vacuolization is considered related to the high local EVG concentrations to which the GI epithelium was exposed. These effects were not considered adverse and in most cases, these minor effects were slowly reversible after a recovery period. It is noted that this finding occurred at exposures similar and in excess to those observed clinically.

Combination studies where EVG was co-administered with RTV or COBI did not result in any additive or unexpected toxicity. Based upon the clinical data provided, the potential for additive toxicities is low when EVG is used in combination with darunavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir or lopinavir/ritonavir.

Genotoxicity

In vitro, EVG caused a slight increase in chromosomal aberrations with a 6-hour treatment in the absence of S9 in Chinese hamster lung (CHL) cells at 55 to 75 µg/mL. However, EVG did not cause any chromosomal aberrations in the presence of S9 or following incubation for 24 hours without S9. Moreover, in a bacterial reverse mutation test and in a rat micronucleus assay, EVG was not considered to be mutagenic. The exposures observed in the rat micronucleus assay were estimated to be similar to the effective concentrations for the chromosomal aberration assay and at least 3-fold higher than that observed clinically.

Carcinogenicity

In the mouse, following repeated oral administration for 104 weeks, EVG was not carcinogenic at up to 2000 mg/kg/day. On the basis of AUC_{0-t} the corresponding exposures were 1.7- to 4.7-fold higher than those observed clinically. In combination studies where EVG is co-administered with RTV and the exposures to EVG were higher than those observed with EVG alone, the combination of EVG and RTV was not carcinogenic. In the rat, following repeated oral administration for up to 88 weeks in males

and 90 weeks in females, EVG was not carcinogenic at up to 2000 mg/kg/day. On the basis of AUC, the corresponding exposures were 10.7- to 34.6-fold higher than that observed clinically.

Reproduction Toxicity

No adverse effects on male or female fertility and reproductive performance were observed at up to 2000 mg/kg/day, where the corresponding exposures (AUC) are approximately 21-38-fold higher than that observed clinically. In the rat, there were no treatment-related effects on embryofoetal development, reproduction or viability and growth of the offspring at systemic exposures that were ~22 to 29-fold higher than that proposed clinically. In addition, when EVG was administered in combination with RTV, no effects on embryofoetal development were observed; the exposures at the no-effect level were also higher than those observed clinically. During a preliminary embryofoetal development study in the rabbit, increased resorptions were noted at ≥300mg/kg/day and the number of live foetuses was reduced at 600 mg/kg/day. In the definitive study, the no-effect level for embryofoetal development was 450 mg/kg/day; the corresponding exposures were below that observed clinically and this is reflected in the SmPC.

Other toxicity studies

Elvitegravir was not phototoxic or immunotoxic and did not demonstrate the potential to cause hypersensitivity or irritancy to the skin/eye.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant has conducted environmental risk assessment and the data provided are summarised in the table below.

Table 2. Summary of studies submitted in support of the Environmental risk Assessment for Elvitegravir

Substance (INN / Invented Name): EVG			
PBT assessment		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow} BCF	OECD117 OECD 305	3.39-4.33	< 4.5; Not Bioaccumulative
Persistence	OECD 308	Not readily biodegradable	Persistent
Toxicity		Generally NOEC values >0.01 mg/L	Not overtly toxic
PBT-statement	The compound is not considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$ default or refined (e.g. prevalence, literature)	For Fpen (1%) **0.75** For refined Fpen (0.28%): **0.21**	µg/L	PEC_{sw} > 0.01 µg/l. Progress to Phase II
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	**OECD 106**	K_{oc} soil: 25500-104000 L/Kg Kd sludge: 10400 L/Kg	K_{oc} >10000 L/Kg Progress to Phase IIb
Ready Biodegradability Test	**OECD 301**	28 days: 0 – 2.5% mineralisation	EVG is not biodegradable.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	**OECD 308**	System DT_{50} 6-53 days Water DT_{50} 2-3 days Sediment DT_{50} (degradation) >100 days >10% associated with sediment from Day 7.	> 10% radioactivity associated with sediment at Day 14 or beyond. Progress to Sediment-dwelling studies

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae Growth Inhibition *Pseudokirchneriella subcapitata*)	**OECD 201**	NOEC	**162**	**µg/L**	
Daphnia sp. Reproduction Test	**OECD 211**	NOEC	**390**	**µg/L**	
Fish, Early Life Stage Toxicity	**OECD 210**	NOEC	**206**	**µg/L**	
Activated Sludge	**OECD 209**	NOEC	**>500**	**mg/L**	
Phase IIb Studies					
Bioaccumulation	**OECD 305**	BCF	**<10**		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 points for further investigation:

- As sediment shifting of the drug substance was demonstrated (sediment shifting > 10%), it is recommended to investigate the effects on sediment organisms (to what the Applicant has agreed). A statement to declare its persistence in the environment is included in Section 5.3 of the SmPC.
- The results of the adsorption/desorption study indicate an affinity of the drug substance to bind to sewage sludge; hence, it is recommended to conduct an environmental risk assessment for the terrestrial compartment (to what the applicant has agreed).

The additional studies along with a revised environmental risk assessment are expected to be provided by Q2 2015.

2.3.6. Discussion on non-clinical aspects

EVG inhibited viral replication in laboratory strains and various clinical isolates of HIV-1 and also showed some activity against HIV-2. The data from secondary pharmacology studies suggest that the potentials for interaction at the range of secondary targets evaluated and to cause cytotoxicity and mitochondrial toxicity are low. The observed margins between the no-effect concentrations/effective concentrations in safety pharmacology studies and those observed clinically are considered acceptable and the pharmacology package is considered adequate from a non-clinical point of view.

Data on absorption, distribution, metabolism, excretion and pharmacokinetic drug interactions of EVG have been provided. Given that EVG is to be used in combination with darunavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir or lopinavir/ritonavir (and possibly others), the potential for additive effects at the level of the enzymes and transporter systems has been investigated. It is acknowledged that the interaction at the level of the CYP and UGT enzymes appear to be primarily responsible for the observed interactions, although interaction at the level of the transporter may also play a contributory role. The interactions which result in clinically significant interactions/ those which warrant dose adjustment are reflected within the SmPC. Overall, the package of pharmacokinetic studies are considered adequate to support the marketing authorisation of EVG.

None of the observed findings as reported during the single- or repeated-dose non-clinical studies with EVG were considered to be adverse. After single dose emesis was observed in the dog, considered a result of direct effect on the digestive tract. Treatment-related effects after repeat doses included changes in caecum weights, dilation of the caecum, and the presence of lipid vacuoles in the lamina propria of the upper small intestines of rats and dogs. Similar changes in the caecum have been reported with antibacterial quinolones which affect the GI microflora. Elvitegravir has a quinolone moiety and was confirmed to have antibacterial activity in the reverse mutation assay. Although the

activity was much weaker than that of the antibacterial quinolones, the changes in the caecum were considered to be due to the anti-bacterial activity of high local concentrations of EVG in the GI tract.

Interestingly, in man, there was an increase in the incidence of diarrhoea when EVG was co-administered with a protease inhibitor, while there was no excess of diarrhoea in the QUAD STR (EVG/COBI/FTC/TDF) groups *vs*. comparators during the Phase 3 studies. The CHMP recommends conducting additional studies to determine the EVG MIC for common bacteria in the human gut and assess MICs in light of estimated intra-colonic concentrations, to which the applicant has agreed and intends to provide the results by March 2014. Performing these additional studies alone is not expected to confirm what effects long-term oral dosing with EVG may have on gut flora (and whether EVG could select for fluoroquinolone-resistant organisms), however, once the results of these are provided then the potential need to recommend conducting additional studies can be revisited. In absence of evidence of toxicity and clinical findings, this is deemed acceptable.

There was no evidence of toxicity or other histopathological correlate associated with lipid vacuoles in the upper small intestines, and in the 2-year rat carcinogenicity study there were no notable findings in the upper small intestine, further suggesting that the presence of the vacuoles was not of toxicological significance.

During a preliminary embryofoetal development study in the rabbit, increased resorptions were noted at ≥300mg/kg/day and the number of live foetuses was reduced at 600 mg/kg/day, and in the definitive study, the no-effect level for embryofoetal development was 450 mg/kg/day. There were no other adverse findings in reproduction toxicity studies.

Other toxicity studies indicated that the potential to cause genotoxicity in man is low, that EVG does not pose a carcinogenic risk to humans and that EVG was not phototoxic or immunotoxic and did not demonstrate the potential to cause hypersensitivity or irritancy to the skin/eye.

The applicant has conducted environmental risk assessment. The CHMP made recommendations for further investigations.

2.3.7. Conclusion on the non-clinical aspects

Overall, the nonclinical aspects have been sufficiently studied, information has been reflected appropriately in the proposed Product Information and there are no objections to the approval of this application from the nonclinical point of view. The CHMP recommends addressing minor outstanding issues regarding impact of EVG on gut flora and regarding the environmental risk assessment.

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.

Overview of clinical studies

Table 3. Overview of phase 1 studies

PK and DDI	
EVG	XAX1-1 safety and PK of EVG after single oral administration
	XAX1-2 safety and PK of EVG after single oral administration of solid dispersion formulation of EVG
	GS-US-183-0152 steady-state PK; confirmed dose of EVG/r in HIV-1 infected ARV-experienced adolescents
	GS-US-183-0126 mass-balance study of EVG/r
	GS-US-183-0103 evaluated PK of EVG, FTC or TFV on co-administration of EVG/r and TVD
	GS-US-183-0104 multiple-dose DDI EVG/r and zidovudine (ZDV)
	GS-US-183-0111 multiple-dose DDI EVG/r and didanosine (ddI) or d4T
	GS-US-183-0112 multiple-dose DDI EVG/r and etravirine
	GS-US-183-0115 multiple-dose DDI EVG/r and abacavir (ABC) sulfate
	GS-US-183-0118 multiple-dose DDI EVG/r and maraviroc
	GS-US-183-0146 effect of a second, potent CYP3A (and UGT1A1) inhibitor (ketoconazole) on boosted EVG
	GS-US-183-0125 multiple-dose DDI EVG and rifabutin
	GS-US-183-0119 effect of acid-reducing agents on EVG
	GS-US-183-0102 EVG 100 mg after single and multiple oral dosing +/- RTV 100 mg
	GS-US-183-0113 dose response of RTV on CYP3A activity and EVG PK
	GS-US-183-0109 multiple-dose DDI boosted EVG and lopinavir (LPV/r)
	GS-US-183-0116 multiple-dose DDI EVG/r and LPV/r
	GS-US-183-0114 multiple-dose DDI EVG/r and tipranavir (TPV/r)
	GS-US-183-0123 multiple-dose DDI EVG/r and fosamprenavir (FPV)/r
	GS-US-183-0120 multiple-dose DDI EVG/r and darunavir (DRV)/r
	GS-US-183-0147 multiple-dose DDI EVG and ATV
	GS-US-183-0106 and -0108 effect of ATV/r on boosted EVG
EVG and COBI	**GS-US-201-0104 evaluated the PK of EVG and COBI when co-administered with DRV**
	GS-US-216-0116 EVG administered with 2 formulations of COBI
	GS-US-216-0123 evaluated unboosted ATV, rosuvastatin and dose-reduced rifabutin on EVG and COBI.
	GS-US-216-0120 and -0122 evaluated the effect of acid-reducing agents on EVG and EVG/COBI.
QUAD STR	GS-US-236-0106 evaluated the drug-drug interaction of the QUAD STR and hormonal contraceptives.
Special Populations	
EVG and COBI	GS-US-183-0133 evaluated the PK of EVG/COBI in subjects with moderate hepatic impairment.
	GS-US-216-0124 evaluated the PK of EVG/COBI in subjects with varying degrees of renal impairment.

Food Effect (see also XAX-1 above)	
QUAD STR	GS-US-236-0105 effect of food on EVG, COBI, FTC, and TFV when administered as the QUAD STR.
Biopharmaceutics	
EVG	GS-US-183-0140 multiple-dose relative bioavailability of a test formulation of EVG/r.
	GS-US-183-0121 relative bioavailability of various formulations of EVG/r.
Secondary PD	
EVG	GS-US-183-0128 effect of EVG/RTV at therapeutic and supratherapeutic doses on the QTcF interval

The studies shown in bold involved co-administration of EVG with RTV and with the PIs proposed for co-administration

In addition, results of A Phase 1 Study Evaluating the Drug Interaction Potential Between Once-Daily Cobicistat-Boosted Elvitegravir and Methadone or Buprenorphine/Naloxone (GS-US-216-0125) were provided.

Table 4. Tabular Summary of Phase 2 and 3 Clinical Studies

Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects by Treatment	Study Population / Entry Criteria
GS-US-183-0145	Assess the noninferiority of EVG versus RAL, each administered with a BR containing a fully active PI/r and a second agent in HIV-1 infected, antiretroviral treatment-experienced adults. Additionally, the efficacy, safety, and tolerability of the 2 treatment regimens, EVG and RAL, are being evaluated.	Phase 3, double-blind, double-dummy, multicentre, randomized, active-controlled study	Treatment Group (TG) 1: EVG 150 mg once daily (EVG 85 mg once daily for subjects taking ATV/r or LPV/r as part of their BR) + RAL placebo twice daily + BR TG 2: RAL 400 mg twice daily + EVG placebo once daily + BR	Blinded Phase: 96 weeks until unblinding Open-Label Extension Phase: 96 weeks, 96 weeks + 30 days or until EVG development is terminated (UK), or until commercially available	Randomized: 724 TG 1: 361 TG 2: 363 Received Study Drug: 712 TG 1: 354 TG 2: 358 Continuing Study Drug at Week 96: TG 1: 208 TG 2: 208 Continuing in Study at Week 96: TG 1: 216 TG 2: 223	Antiretroviral treatment-experienced, HIV-1 infected adults ≥ 18 years old and life expectancy ≥ 1 year with plasma HIV-1 RNA levels ≥ 1000 copies/mL who had documented resistance from 2 or more different classes of antiretroviral agents or at least 6 months experience before screening with at least 1 antiretroviral agent and were fully sensitive to the selected PI
GS-US-183-0105	Assess noninferiority of EVG/r relative to CPI/r, both in combination with a background ARV regimen	Phase 2, randomized, partially blinded (EVG dose), multicenter, multiple dose, active-controlled, dose-finding study	CPI/r (A) EVG/r 20/100 mg QD (B) EVG/r 50/100 mg QD (C) EVG/r 125/100 mg QD (D) CPI/r switch to EVG (blinded dose of 20, 50, or 125 mg) or EVG 125 mg open label (E)	48 weeks	Randomized: 297 Treated : 278 Completed: 211 Safety Analysis Set: A: 63 B: 71 C: 71 D: 73 E: 30	HIV-1 infected, treatment-experienced subjects on a stable ARV regimen
GS-US-	Investigate safety,	Phase 1/2,	EVG 200 mg BID PO	10 days per cohort	Randomized: 48	HIV-1 infected, ARV

Study Number	Study Objective(s)	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects by Treatment	Study Population / Entry Criteria
183-0101	tolerability, antiviral activity, and PK/PD of EVG	randomized, double-blind, multicentre, multiple-dose, placebo controlled, proof-of concept, sequential cohort, dose-ranging study	(A) EVG 400 mg BID PO (B) EVG 800 mg QD PO (C) EVG 800 mg BID PO (D) EVG 50 mg + RTV 100 mg QD PO (E) Placebo, BID or QD PO (F) Placebo + RTV 100 mg QD PO (G)		Treated: 40 Completed: 40 Safety Analysis Set: A: 6 B: 6 C: 6 D: 6 E: 6 F: 8 G: 2	Treatment naïve or treatment experienced adult subjects who were not currently receiving ARV therapy
GS-US-183-0130	Observe the long-term safety of EVG/r in combination with other ARV agents in subjects who have completed a prior EVG/r treatment study	Phase 2, rollover, open-label, multicentre, multiple-dose, single-arm extension study	EVG/r 85/100 mg QD PO EVG/r 150/100 mg QD PO EVG/r 300/100 mg QD PO (substudy; subjects from EVG 150 mg group)	Until EVG becomes commercially available or study terminated by sponsor	Enrolled: 192 Treated : 192 Ongoing: 113 Substudy: 40 enrolled and treated	HIV-1 infected adult and adolescent subjects

Results of several other studies from the development programmes of QUAD STB and COBI have been provided in the application.

2.4.2. Pharmacokinetics

The pharmacokinetic properties of EVG were assessed in Phase 1 studies with EVG alone, on co-administration with RTV or COBI and as a component of QUAD STB (i.e. with COBI plus TDF/FTC). Phase 2 and 3 studies of efficacy included intensive sampling sub-studies and sparse sampling. A population PK analysis was conducted. PK data were also collected in some PD studies.

Phase 1 studies mostly used conventional tablets of various sizes (early formulations). In Phase 3 (GS-US-183-0145) the commercial formulation (F2) tablets containing 85 mg or 150 mg EVG were used. The 150 mg tablet was shown to be bioequivalent to the 125 mg early formulation reference tablet.

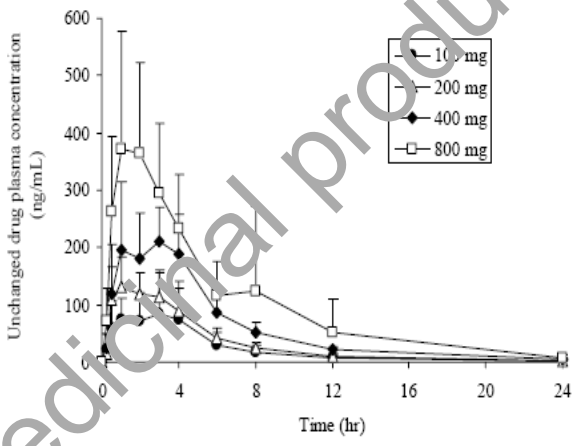
The original EVG bioanalytical method involved solid phase extraction from human plasma followed by LC-MS/MS with positive ionisation. For the fully validated bioanalytical method calibration curves for EVG and metabolites M4 and M1 the range was from 20-10,000 ng/mL. A similar assay method applied to urine samples gave calibration curves that ranged from 32.5 (LLQ) to 1300 ng/mL.

Absorption

The absolute bioavailability of EVG, with or without RTV, has not been determined.

In an early study (XAX1-1) single unboosted doses of EVG (100-800 mg; early formulation) were administered in the fasting state. There was rapid conversion of some of the EVG dose to M4 but AUC_{inf} was always < 10% of EVG exposure. The EVG dose proportionality constants (β) were 0.723 (95% CI, 0.544 to 0.902) for C_{max} and 0.789 (95% CI, 0.582 to 0.995) for AUC_{inf}.

Figure 1. EVG concentrations in study XAX1-1



In GS-US-183-0102 EVG 100 mg (early formulation) and EVG/RTV (100/100 mg) were given twice daily for 10 days in the fed state.

Without RTV the EVG steady-state (D10) mean AUC_{tau} was ~ 20% lower vs. a single dose on D1 (AUC_{inf}), indicating auto-induction of its metabolism. Non-linear RTV PK occurred on dosing to steady state, most likely due to its time-dependent, mechanism-based inhibition of CYP3A.

Table 1. PK parameters in study GS-US-183-0102

Plasma PK Parameter	EVG Alone (N = 12)		EVG + RTV (N = 12)	
	Day 1 (Single Dose)	Day 10 (Multiple Dose)	Day 11 (Single Dose)	Day 20 (Multiple Dose)
EVG				
AUC (ng•h/mL)[a]	908.1 (28.3)	719.3 (26.2)	6167.3 (29.1)[b]	14,302.1 (23.7)
C_{max} (ng/mL)	200.1 (30.4)	164.1 (28.8)	795.3 (38.4)	1826.4 (26.4)
C_{tau} (ng/mL)[c]	19.2 (52.5)	12.4 (63.7)	543.3 (30.4)	1035.6 (32.0)
$T_{½}$ (h)	3.1 (2.2, 4.8)	3.5 (2.2, 4.1)	18.2 (9.0,42.6)[b]	9.5 (5.9, 78.2)
RTV				
AUC (ng•h/mL)[d]	—	—	4979.4 (57.8)[e]	9402.5 (46.9)
C_{max} (ng/mL)	—	—	616.3 (53.5)	1686.5 (46.5)
C_{tau} (ng/mL)[c]	—	—	219.8 (61.8)	544.8 (44.3)
$T_{½}$ (h)	—	—	5.1 (2.2, 8.3)[e]	4.8 (4.3, 6.9)

After the first dose of EVG/RTV (D11) there were higher EVG plasma concentrations that remained at plateau through 12 h, resulting in an 8.58-fold increase in exposure vs. D10 of EVG alone. This large increase in EVG exposure was attributed to improved oral bioavailability resulting from decreased first pass metabolism and reduced systemic clearance.

Administration of EVG/RTV to steady state (D20) resulted in an 11-fold increase in C_{max} and a greater than predicted (20-fold) increase in AUC_{tau}. There was an increase in T½ (9.5 h EVG/r vs. 3.5 h EVG alone) and some drug accumulation due to net inhibition of EVG metabolism by RTV. These observations underlined the importance of conducting the DDI studies with EVG/RTV at steady-state.

GS-US-183-0113 evaluated co-administration of RTV (oral solution, mixed with 25 mL Ensure) doses from 20-200 mg with 125 mg EVG, each given once daily for 10 days in the fed state. Midazolam (MDZ) 1 mg intravenous was given in the afternoon on Days 1, 11 and 21. The increases in EVG C_{max}, AUC_{tau} and C_{tau} observed with RTV doses from 20 mg to 200 mg were less than RTV-dose proportional. The apparent clearance of EVG decreased and T½ increased with RTV dose with a plateau around 100 mg suggesting near maximal inhibition of CYP3A between 50-100 mg RTV.

Table 2. Statistical Comparisons of Pharmacokinetic Parameters for EVG with Increasing Doses of Ritonavir (PK Analysis Set)

Test Versus Reference Comparison of GS-9137 Plasma PK Parameters[a]	Geometric Least Squares Mean Ratio (GMR%, 90% CI)		
Test: GS-9137 +	**50-mg RTV**	**100-mg RTV**	**200-mg RTV**
Reference: GS-9137 + 20-mg RTV			
AUC_{tau} (ng•h/mL)	160.89 (128.49, 201.46)	206.85 (173.69, 246.34)	209.28 (167.14, 262.06)
C_{max} (ng/mL)	117.46 (90.01, 153.29)	143.20 (117.57, 174.40)	152.02 (116.49, 198.38)
C_{tau} (ng/mL)	400.21 (285.58, 560.84)	586.39 (444.40, 773.75)	658.03 (469.56, 922.15)
Test: GS-9137 +	**20-mg RTV**	**100-mg RTV**	**200-mg RTV**
Reference: GS-9137 + 50-mg RTV			
AUC_{tau} (ng•h/mL)	nc	128.57 (102.68, 160.99)	130.08 (108.30, 156.24)
C_{max} (ng/mL)	nc	121.91 (93.42, 159.09)	129.42 (105.24, 159.14)
C_{tau} (ng/mL)	nc	146.52 (106.13, 202.29)	164.42 (125.33, 215.71)
Test: GS-9137 +	**20-mg RTV**	**50-mg RTV**	**200-mg RTV**
Reference: GS-9137 + 100-mg RTV			
AUC_{tau} (ng•h/mL)	nc	nc	101.17 (80.[illegible]0, 1[illegible]6.69)
C_{max} (ng/mL)	nc	nc	106.1[illegible] (81.[illegible]5, 138.[illegible]3)
C_{tau} (ng/mL)	nc	nc	112.2[illegible] (8[illegible].28, 154.93)

Plasma levels of the EVG metabolite M1 (GS-9202; chlorofluorophenyl group hydroxide) were BLLQ at most time points. Plasma exposure to M4 (GS-9200; acyl glucuronide conjugate) increased with RTV dose in a similar fashion to EVG. M4 concentrations were < 10% of parent drug with a fairly constant ratio maintained, suggesting that RTV did not affect the formation or elimination of M4.

Mean MDZ plasma concentrations increased with increasing doses of RTV but not in a dose-proportional fashion. The dose-response curve ED50 for hepatic CYP3A4 (as assessed using intravenous MDZ) was 12.2 mg. Plasma levels of 1′-OH MDZ were BLLQ at most time points.

It was concluded that RTV doses of 50 mg and 100 mg provided near maximal CYP3A4 inhibition, supporting further evaluation of EVG/r 125/100 mg once daily. The mean clearance (CL/F) of EVG when given with RTV 100 mg was 0.119 L/min, which is ~ 7.9 % of hepatic blood flow, supporting the hypothesis that RTV-boosted EVG is a very low clearance compound.

In GS-US-216-0116 EVG/COBI 150/150 mg (F2) and EVG/r 150/100 mg were each given for 10 days. EVG concentrations demonstrated bioequivalence between EVG/COBI and EVG/RTV.

Table 3. PK parameters in study GS-US-216-0116

Cohort 2	EVG/co	EVG/r	
EVG (n=22)			
AUC_{tau} (ng•h/mL)	22,246.5 (18.2)	20,270.3 (23.1)	110.67 (104.47, 117.23)
C_{tau} (ng/mL)	379.4 (40.7)	397.2 (38.0)	93.73 (81.40, 107.93)
C_{max} (ng/mL)	2253.0 (18.4)	2048.3 (24.1)	111.26 (103.30, 119.85)

EVG plasma exposures on Day 10 resembled those reported after 10 days dosing with EVG/RTV 125/100 mg in GS-US-183-0113 (AUC_{tau} 20,236 ng.h/mL, C_{max} 1830 ng/mL, C_{tau} 380 ng/mL). On this basis it was concluded that near maximal inhibition of CYP3A4-mediated EVG metabolism (F2, 150 mg) was achieved with RTV 100 mg or COBI 150 mg.

GS-US-183-0140 compared the bioavailability of the EVG 125 mg tablet used in the Phase 2 study (GS-US-183-0105) with the 150 mg F2 tablet (commercial) administered in the Phase 3 study (GS-US-183-0145). EVG was administered daily with 100 mg RTV within 5 minutes of a standard breakfast. The EVG results on Day 10 met the BE criteria (AUC_{tau}, C_{max} and C_{tau}). The comparisons of RTV exposures on co-administration with the two EVG formulations also fell within the bounds of 80% to 125%.

Table 4. Statistical Comparisons of Elvitegravir Steady-State Pharmacokinetic Parameters for Test versus Reference Treatment in study GS-US-183-0140 (PK Analysis Set).

Elvitegravir PK Parameters	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test[a] (N = 24)	Reference[a] (N = 24)		
C_{max} (ng/mL)	1997.7	1896.0	105.4	98.8, [illegible]
AUC_{tau} (ng•h/mL)	21086.1	19396.5	108.7	[illegible]
C_{tau} (ng/mL)	397.2	360.7	110.1	[illegible]2.6

The effect of food on the EVG commercial formulation was not studied. Unboosted EVG 400 mg early formulation tablets administered in the fed state (575 kcal, 33% fat) gave ~3-fold higher C_{max} and AUC_{inf} compared to the fasted state. There was a similar effect of food on plasma levels of M4 but the AUC was still < 10% that of EVG.

Table 5. Effect of food on EVG PK

	Pharmacokinetic parameter	Fed / Fasted		
		Geometric least-squares mean ratio	90% confidence interval	
			Lower limit	Upper limit
Unchanged drug	C_{max}	3.30	2.27	4.80
	$AUC_{0\text{-}inf}$	2.69	2.16	3.36
Metabolite M4	C_{max}	3.13	2.38	4.13
	$AUC_{0\text{-}inf}$	2.72	2.31	3.21

GS-US-236-0105 evaluated the effect of food (fasted, light [373 kcal, 20% fat] and high-fat [800 kcal, 50% fat] meal) when a single dose of the F1 formulation of STB (EVG 150 mg, COBI 150 mg, FTC 200 mg, TDF 300 mg) was administered. Maximum increases in EVG exposure vs. fasted state were seen following a high-calorie/high-fat meal (AUC_{inf} 87%, AUC_{last} 91% and C_{max} 56%). Modest increases in EVG exposure occurred with a light meal vs. fasted state (AUC_{inf} 34%, AUC_{last} 36%, and C_{max} 22%).

The %CV was similar under fed conditions regardless of meal type. There was slightly greater variability in the fasted state, consistent with solubility-limited dissolution of EVG.

Table 6. GS-US-236-0105: Mean (%CV) EVG PK after a single dose of STB

PK Parameter (N)	Meal Condition	AUC_{inf} (ng•h/mL)	C_{max} (ng/mL)	C_{last} (ng/mL)
EVG	HC/HF Meal	28800 (22)	2230 (27)	95.1 (75)

(N = 24)	Light Meal	21100 (28)	1760 (32)	82.0 (115)
	Fasted	16400 (39)	1490 (40)	79.3 (95)

HC, high calorie; HF, high fat; Data are mean (%CV) and are shown to 3 significant digits.

Based on these data EVG was administered with food (type unspecified) in Phase 2 and 3 studies to achieve a high mean EVG IQ_{95} (~ 10).

Distribution

Equilibrium dialysis studies using plasma from HIV-1 infected patients, healthy subjects and subjects with renal or hepatic impairment showed that EVG was ~98% to 99% bound to human plasma proteins regardless of concentration, with preferential binding to albumin over AAG. After a single oral 50 mg dose of RTV-boosted [14C] EVG (GS-US-183-0126) the blood-to-plasma ratio of total 14C-radioactivity was time-independent and ~ 0.73, indicating that EVG and its metabolites are predominantly distributed to plasma relative to the cellular components of the blood.

Elimination

Excretion

In GS-US-183-0126, using RTV 100 mg and [14C] EVG 50 mg, the T½ of the administered radioactivity from pooled plasma samples was similar to that observed for EVG (9.64 vs. 9.59 hours). The combined faecal and urinary recovery accounted for 101% of the administered radioactive dose, which was almost exclusively recovered in faeces (94.8% of the radioactive dose).

EVG and M1 accounted for 30.8% and 33.9%, respectively, of the total quantitated radioactive dose in pooled faeces. Low levels of minor hydroxylation products were also observed (M9, M13 and M15). The total amount of EVG in faeces likely resulted from a combination of unabsorbed drug, biliary secretion of EVG itself and biliary secretion of M4 converted back to EVG by the β-glucuronidases in the intestinal microflora. Renal elimination accounted for 6.7% of the administered dose, mostly as glucuronidated metabolites and with no unchanged EVG. The radioactivity recovered in pooled urine was present as the glucuronide of EVG (M4) or as glucuronides of EVG hydroxylation products (M7, M19 and M20) in roughly equal proportions.

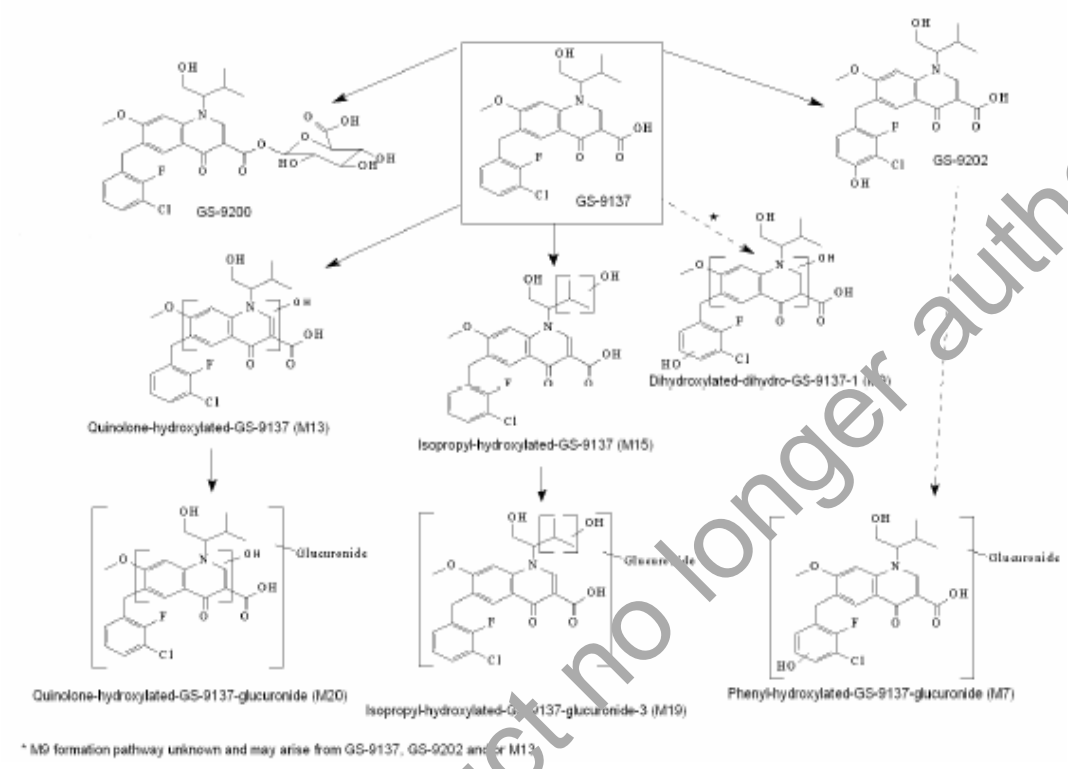
Metabolism

In-vitro studies indicated that biotransformation of EVG is primarily via CYP-mediated aromatic and aliphatic hydroxylation and/or primary or secondary glucuronidation. Human liver microsome studies in the presence of NADPH indicated that EVG was primarily metabolised to M1 (GS-9202 - a chloroquinolophenyl group hydroxide) and also to small amounts of M5 and M8. Similar studies in the presence of UDPGA resulted in formation of the acyl glucuronide conjugate M4 (GS-9200).

In-vitro studies showed that EVG was metabolised by CYP1A1, CYP3A4 and CYP3A5 at rates of metabolism of 0.9, 9.4 and 0.4 pmol/min/pmol P450, respectively, but was not metabolised by other isoenzymes tested (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A5). The main metabolite formed in human liver microsomes (M1) was produced by these CYP isoenzymes and the highest formation rate occurred with CYP3A4. Among the minor metabolites M2 was produced by CYP1A1 while M5 and M8 were only produced by CYP3A4.

In GS-US-183-0126 on dosing with EVG/r the predominant circulating species in plasma was EVG (~ 94% of radioactivity). Metabolic profiling showed that M1, M4, M7 and M19 accounted for the non-EVG-associated radioactivity in plasma. All observed metabolites constituted < 10% relative systemic exposure (AUC_{tau}) to EVG. Taking into account all of the above, the proposed biotransformation pathway in man is summarised as shown below.

Figure 2. Proposed Biotransformation Pathway for [^{14}C] EVG



Dose proportionality and time dependencies

Multiple-dose data showed less than proportional increases in EVG exposure with increasing doses, which is thought to be most likely due to solubility-limited dissolution. Doubling the dose from 125 mg to 250 mg resulted in ~ 40% increase in mean EVG trough concentrations in healthy subjects. Administration of EVG/r 300/100 mg in HIV-1 infected subjects resulted in ~17% increase in EVG trough concentrations compared to EVG/r 150/100 mg.

Intra- and inter-individual variability

GS-US-236-0105 using the F1 QUAD STB formulation generally gave smaller CV% values for EVG AUC and C_{max} in the fed vs. fasting state. The smallest CV% was observed with the high fat/high calorie meal. CV% values were numerically higher in the small numbers of HIV-infected subjects who underwent intensive sampling (n = 12-19) than in healthy subjects but the population PK estimations of %CV were low and were comparable between HIV-1 infected subjects and healthy subjects.

Intra-subject variability for EVG cannot be estimated from Phase 3 data because intensive sampling was on a single occasion. Intra-subject variability for C_{max}, AUC and C_{tau} in the Phase 1 study GS-US-183-0140 was estimated at 12%, 13% and 22%, respectively.

Population PK analysis

The population PK report specific to use of EVG/r used pooled data from 19 studies in healthy subjects and three in HIV-infected subjects. A two-compartment PK model with first-order absorption rate constant and absorption lag-time provided a good description of the pharmacokinetics of EVG in healthy and HIV-infected subjects. No differences in EVG exposures were observed between healthy and HIV-1 infected subjects based on population PK modelling.

Body surface area (BSA) had a statistically significant effect on EVG clearance and affected inter-compartmental clearance. However, the BSA effect was modest and the resulting decrease in the inter-individual variability term associated with EVG clearance was only 25%.

The 85 mg dose was identified as a covariate for EVG clearance. Subjects who received 85 mg EVG in combination with ATV/r or LPV/r had a 28% lower EVG clearance compared with subjects who received EVG 150 mg, resulting in similar EVG AUC and C_{max} and slightly higher C_{trough} across the two EVG dose levels. These results were in line with the inhibitory effect of ATV/r or LPV/r on UGT1A1 and supported dose reduction to 85 mg with these PI/r combinations (see PK interaction studies).

A statistically significant relationship was observed between RTV AUC and EVG bioavailability but the effect at the clinically relevant RTV dose was not considered to be clinically meaningful.

PK data obtained from HIV-infected subjects

In the monotherapy PK/PD study (GS-US-183-0101) EVG was administered alone and as EVG/r 50/100 mg once daily for 10 days in the fed state. EVG dosing alone at 200, 400 and 800 mg BID gave 31%, 23% and 52% lower exposures, respectively, at steady state vs. a single dose, consistent with auto-induction of CYP3A. The EVG AUC_{tau} on Day 10 of dosing with EVG/r was ~2-fold the $AUC_{0\text{-}last}$ 4615 ng.h/mL on Day 1. The EVG T½ increased from ~3h unboosted to ~9h with RTV.

Table 7. GS-US-183-0101: Summary of EVG Steady-State PK Parameters (PK Analysis Set)

EVG Steady-State PK Parameter[a]	EVG 200 mg BID (N = 6)	EVG 400 mg BID (N = 6)	EVG 800 mg QD (N = 6)	EVG 800 mg BID (N = 6)	EVG 50 mg QD + RTV 100 mg (N = 6)
AUC_{tau} (ng•h/mL) Mean (%CV)	1954.65 (46.35)	3535.30 (54.52)	5512.87 (53.59)	3566.35 (36.83)	8843.50 (25.46)
C_{max} (ng/mL) Mean (%CV)	479.03 (42.58)	906.87 (77.58)	939.92 (54.31)	835.53 (48.20)	744.65 (20.40)
C_{tau} (ng/mL) Mean (%CV)	30.73 (39.78)	48.68 (64.84)	13.62 (68.64)	47.98 (32.65)	135.00 (36.55)
$T_{½}$ (h) Median (min, max)	2.82 (1.51, 4.75)	3.08 (2.48, 5.02)	3.80 (3.02, 4.60)	2.53 (2.14, 3.03)	8.86 (6.10, 10.91)

In the Phase 2 study GS-US-183-0105 EVG/r was administered initially at 20/100 mg, 50/100 mg and 125/100 mg, each with OBR. The Week 8 intensive PK sub-study showed that EVG exposures increased in a less than dose proportional manner between 50 and 125 mg (~ 2-fold higher AUC_{tau} over a 2.5-fold dose increase). The CV% decreased as dose increased.

Table 8. EVG PK parameters in study GS-US-183-0105

EVG Plasma PK Parameter [a]	EVG/r 20/100 mg (N = 11)	EVG/r 50/100 mg (N = 12)	EVG/r 125/100 mg (N = 12)
C_{max} (ng/mL) Mean (%CV)	265.79 (72.77)	753.71 (30.10)	1442.20 (33.97)
AUC_{tau} (ng•h/mL) Mean (%CV)	3029.25 (84.58)	8701.86 (40.84)	16,789.54 (33.06)
C_{tau} (ng/mL) Mean (%CV)	67.28 (176.31)	211.03 (77.51)	262.99 (52.13)
T_{max} (h) Median (Q1, Q3)	3.98 (3.00, 5.75)	4.00 (2.38, 4.75)	4.01 (2.96, 4.87)
$T_{1/2}$ (h) Median (Q1, Q3)	6.88 (6.14, 7.47)[b]	9.14 (8.62, 12.28)[b]	8.11 (7.31, 10.07)

Plasma M1 concentrations were BLLQ in all subjects. Plasma M4 increased in a less than dose proportional manner while the AUC_{tau} ratios vs. EVG were in the range from 14% to 2[illegible]%. RTV peak and overall exposures were comparable across the 50 mg and 100 mg EVG doses.

In study GS-US-183-0130 increasing the dose to EVG/RTV 300/100 mg gave a [illegible]% higher C_{tau} relative to EVG/RTV 150/100 mg. In comparison to data obtained in GS-US-183-0145 at the 300/100 mg dose the C_{max} and AUC_{tau} were increased by 33% and 31%, respectively. Thus, the data showed a markedly less than dose-proportional increase in plasma EVG exposure, consistent with a solubility-limited absorption profile. Based on this data subjects in the PK sub-study reverted to 150/100 mg dose.

In the Phase 3 study GS-US-183-0145 there was a PK sub-study in small numbers that generated intensive PK profiles at Week 2. The steady-state mean EVG AUC_{tau} and C_{max} were comparable following administration of 85 mg EVG (with LPV/r or ATV/r) or 150 mg EVG (with DRV/r, TPV/r or FPV/r).

Table 9. EVG PK parameters in PK sub-study of study GS-US-183-0145

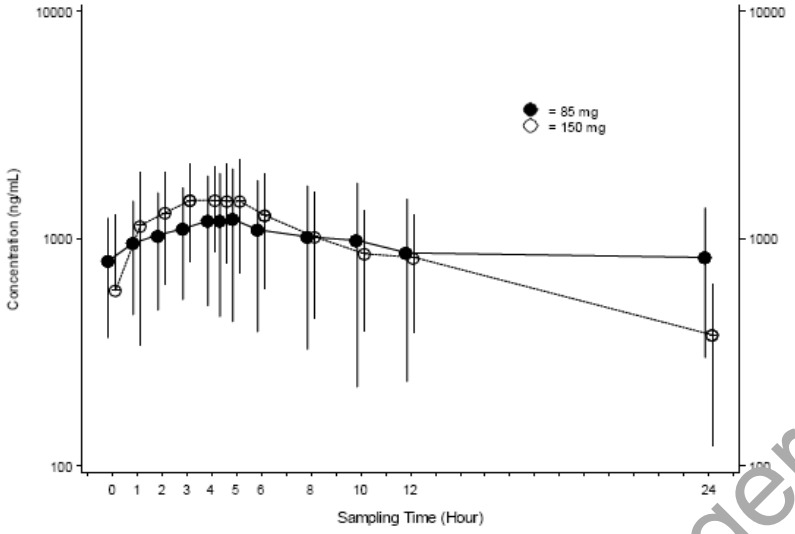
EVG Steady-State PK Parameter[a]	EVG 200 mg BID (N = 6)	EVG 400 mg BID (N = 6)	EVG 800 mg QD (N = 6)	EVG 800 mg BID (N = 6)	EVG 50 mg QD + RTV 100 mg (N = 6)
AUC_{tau} (ng•h/mL) Mean (%CV)	1954.65 (46.35)	2[illegible]35.3[illegible] (54.52)	5512.87 (53.59)	3566.35 (36.83)	8843.50 (25.46)
C_{max} (ng/mL) Mean (%CV)	479.03 (42.[illegible]8)	606.87 (77.58)	939.92 (54.31)	835.53 (48.20)	744.65 (20.40)
C_{tau} (ng/mL) Mean (%CV)	[illegible]0.[illegible]3 (3[illegible].9[illegible])	48.68 (64.84)	13.62 (68.64)	47.98 (32.65)	135.00 (36.55)
$T_{½}$ (h) Median (min, max)	2.82 (2.51, 4.75)	3.08 (2.48, 5.02)	3.80 (3.02, 4.60)	2.53 (2.14, 3.03)	8.86 (6.10, 10.91)

Table 10. EVG Summary Statistics of PK Parameters at Week 2 by EVG Dose in study GS-US-183-0145 (PK Substudy Analysis Set)

EVG PK Parameter[a]	EVG Dose: 85 mg (n = 12)	EVG Dose: 150 mg (n = 19)
AUC_{tau} (ng•h/mL), Mean (%CV)	21,918.1 (56.4)	20,298.1 (51.5)
C_{max} (ng/mL), Mean (%CV)	1514.4 (49.7)	1721.5 (43.3)
C_{tau} (ng/mL), Mean (%CV)	759.6 (73.3)	378.2 (67.4)
T_{max} (h), Median (Q1, Q3)	4.75 (1.50, 9.09)	3.00 (1.17, 4.50)
$T_{½}$ (h), Median (Q1, Q3)	13.72 (8.69, 17.20)[b]	8.67 (7.10, 13.75)

C_{tau} was higher with the 85 mg vs. 150 mg dose (see figure below) but following either dose the mean trough level was ~ 8.5- to 17.1-fold above the protein binding-adjusted IC_{95} (45 ng/mL).

Figure 3. EVG Plasma Concentrations (Mean and SD) at Week 2 by EVG Dose in study GS-US-183-0145 (PK Substudy Analysis Set)



Concentrations of M4 were clearly and consistently lower following administration of EVG 85 mg vs. 150 mg, which was thought to reflect inhibition of UGT1A1 by the co-administered PIs (i.e. ATV and LPV). The AUC_{tau} ratios for M4 vs. EVG were 10.8% with the 85 mg dose and 21.2% with the 150 mg dose.

During the study the sparse sampling showed that:

- Mean EVG 85 mg trough concentrations were 9.7- to 12.0-fold above the IC95-target between Week 2 and Week 48 (n = 57 to 111)
- Mean EVG 150 mg trough concentrations were 6.9- to 9.2-fold above the IC95-target between Week 2 and Week 48 (n = 58 to 186).

Dosing with EVG/r 150/100 mg (EVG F2 formulation) in healthy (GS-US-183-0140) and HIV-1 infected subjects (GS-US-183-0145) showed that:

- In GS-US-183-0140 the EVG C_{max} was 1998 ng/mL, AUC_{tau} was 21086 ng.h/mL and C_{tau} was 397 ng/mL.
- In GS-US-183-0145 the corresponding values were 1722 ng/mL, 20298 ng.h/mL and 378 ng/mL.

RTV levels were stated to be consistent with historical (published) data, with a reference to ATV/RTV and LPV/RTV as measured during the CASTLE study. US-GS-183-0145 did not generate any data on the other PI drug levels.

Special populations

Impaired renal function

GS-US-216-0124 evaluated EVG/COBI 150/150 mg given once daily in the fed state for 10 days to subjects with severe renal impairment (eGFR < 30 mL/min; not on dialysis) and controls (eGFR ≥ 90

mL/min) matched by age, sex, BMI. The actual mean eGFRCG values at baseline were 23.5 mL/min and 97.2 mL/min in respective groups.

The EVG AUC_{tau}, C_{max}, and C_{tau} were lower (by 25%, 33% and 31%, respectively) in subjects with severe renal impairment vs. controls. However, EVG exposure in controls on Day 7 was substantially higher than in previous clinical studies with EVG/co at these doses and exposures in subjects with severe renal impairment were higher than usually observed in normal controls. The EVG mean (SD) % free fraction on Day 7 was 1.42 (0.17) in renally impaired subjects and 1.16 (0.16) in controls.

Table 11. Statistical Analysis of EVG Pharmacokinetic Parameters on Day 7 Between Severely Renally Impaired and Normal Subjects in study GS-US-183-0124 (EVG PK Analysis Set).

	Geometric Least-Squares Mean		
EVG PK Parameter	Test Severe Renal Impairment $eGFR_{CG}$ < 30 mL/min (N = 12)	Reference Normal Renal Function $eGFR_{CG}$ ≥ 90 mL/min (N = 11)	Geometric Least-Squares Means Ratio (%) (90% CI)
AUC_{tau} (ng•h/mL)	25316.69	33530.63	75.50 (62.82, 90.75)
C_{max} (ng/mL)	2154.03	3200.46	67.30 (54.78, 82.68)
C_{tau} (ng/mL)	491.26	711.29	69.07 (51.82, 92.06)

Impaired hepatic function

GS-US-183-0133 evaluated EVG/co 150/150 mg once daily for 10 days in the fed state in subjects with moderate hepatic impairment (CPT B; actual scores 7-9) and healthy controls matched by age, sex, BMI. Mean creatinine clearance was 98.7 ml/min and 116.8 ml/min in respective groups.

The steady-state AUC_{tau}, C_{tau} and C_{max} of EVG were 35%, 80% and 41% higher, respectively, in subjects with moderate hepatic impairment. It was proposed that the increase in C_{max} with moderate hepatic impairment may have reflected higher oral bioavailability. The mean (SD) % free fraction EVG was 1.15 (0.14) in the control group and 1.22 (0.23) in the CPT B group, indicating the lack of effect of hepatic impairment on EVG protein binding.

Table 12. Mean (%CV) EVG PK Following EVG/co or STB in Healthy and HIV-1 Infected Subjects

Study No.	Subject Population (N)	EVG PK Parameter AUC_{tau} (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)
GS-US-183-0133	Moderate Hepatic Impaired Subjects (N = 10)	29,800 (41)	2820 (34)	741 (65)
	Matched Healthy Control Subjects (N = 10)	21,300 (28)	1950 (30)	370 (44)
GS-US-236-0110	Healthy Subjects (N = 36)	22,500 (27)	1920 (24)	508 (41)
GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104[a]	HIV-1 Infected Subjects (N = 419)	23,000 (33)	1730 (23)	451 (58)

Population PK analyses: All the STB-treated subjects in GS-US-236-0103 and GS-US-236-0104 and all the STB-treated subjects who participated in the PK sub-study in GS-US-236-0102 were included.

Other intrinsic factors

In the population PK analysis for EVG/r age, gender, race, health status (HIV-infected vs. healthy), body weight, BMI, RCMIN, eGFR, formulation, background treatment and HBV and/or HCV co-infection were not found to have significant effects on any of the model parameters.

There are no data in children or the elderly with the exception of the PK data from GS-US-183-0152 in which EVG 85 mg or 150 mg was administered in the fed state to HIV-1 infected subjects aged 12-17 years taking a PI/r-containing background regimen.

The initial PK study involved dosing for 10 days with EVG 85 mg (ATV/r or LPV/r) or 150 mg (other protocol-specified PIs). Mean EVG AUC_{tau} and C_{max} were slightly higher and mean C_{tau} significantly higher with 85 mg vs. 150 mg EVG, consistent with data from adults.

Adolescents showed slightly higher exposures vs. HIV-infected adults. Comparisons for adolescents vs. healthy adults for the 150 mg dose showed that the AUC_{tau} ratio was 93.43 % [75.21, 115.14]. The 85 mg dose in adolescents also gave modestly higher AUC_{tau} and C_{max} vs. adult data. The mean C_{tau} in adolescents was 7- to 13-fold above the in-vitro protein binding-adjusted IC95 (4[illegible] ng/mL). Consistent with data from adult studies, M4 was a minor metabolite with low exposures relative to EVG. M1 levels were BLLQ.

Pharmacokinetic interaction studies

Drug-drug interactions

In vitro

EVG showed no detectable inhibition of human hepatic microsomal CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 activity. The IC50 value for CYP3A4 (testosterone substrate) was 28.32 µg/mL (63.19 µmol/L), suggesting weak inhibition. For other isoforms the IC50 values were more than 30 µg/mL (67.0 µmol/L).

At clinically relevant concentrations EVG was considered to be a weak inducer of CYP3A. EVG did not induce CYP1A2 but it had some ability to induce CYP2C9 at 1 and 10 µg/mL.

The metabolism of EVG to M1 in human liver microsomes in the presence of NADPH was decreased by approximately 97% with 2 µmol/L of ketoconazole. In human liver microsomes the IC50 values of tested agents for conversion of EVG to M1 were: amprenavir 1.1 µmol/L; indinavir sulfate 0.51 µmol/L; ketoconazole 0.099 µmol/L; lopinavir 3.1 µmol/L; nelfinavir 1.1 µmol/L, ritonavir 0.079 µmol/L; saquinavir 4.5 µmol/L. For efavirenz, nevirapine and zidovudine the inhibition ratio was lower than 50% even at 50 or 100 µmol/L.

Sulfaphenazole (CYP2C9 inhibitor) and quinidine (CYP2D6 inhibitor) showed no inhibitory effect on EVG metabolism.

EVG is a substrate for and weak inhibitor of human P-gp/MDR1 but there was no evidence of saturation of intestinal efflux transport. Co-administration with inhibitors or inducers of MDR1 is not expected to affect EVG plasma levels.

EVG was not predicted to affect the absorption of P-gp substrates. The reference theoretical intestinal concentration for EVG was 10 × 150 mg/250 mL (13.4 mM) but the IC_{50} of EVG for inhibition of Pgp was > 30 µM.

The absorption phases of EVG and RTV will overlap. Since Pgp will be inhibited by RTV, the presence of EVG is unlikely to result in additional inhibition of any clinical relevance.

EVG is a substrate for and a weak inhibitor of human OATP1B1 (40% inhibition at 2 µM) and human OATP1B3 (IC50 0.44 µM). Since the OATP-independent permeability of EVG is so high it is not likely to be affected by pharmacogenetic variability or by inhibitors of these transporters. Inhibition of OATP by EVG was assessed in the DDI study with rosuvastatin.

Formation of M4 was extensively inhibited by atazanavir (ATV), a selective UGT1A1 inhibitor *in vitro*. This was investigated in the clinical DDIs with ketoconazole (inhibitor of CYP3A and UGT1A1), ATV/r and LPV/r (both of which inhibit UGT1A1).

Chelating of EVG via pharmacophore binding can occur with high concentrations of divalent and trivalent cations, as found in some antacid preparations.

In vivo

HIV protease inhibitors

Atazanavir

In GS-US-183-0108 co-administration of 300/100 mg ATV/r with EVG 200 mg once daily in the fed state for 14 days was associated with lower plasma exposures to ATV vs. ATV/r alone and the ATV T½ decreased from 17.75 h to 12.65 h.

Table 13. Statistical Comparisons of PK Parameters for Atazanavir Between Treatments (PK Analysis Set).

Test versus Reference Comparison of Atazanavir Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test (Mean)	Reference[b] (Mean)		
GS-9137 + Atazanavir/r vs. Atazanavir/r				
C_{max} (ng/mL)	5232.73	6206.36	84.31	78.19, 90.92
AUC_{tau} (ng•h/mL)	47,672.02	60,188.71	79.20	73.57, 85.27
C_{tau} (ng/mL)	863.95	1319.17	65.49	59.08, 72.60

Plasma concentrations of RTV when administered with ATV or with ATV + EVG tended to be higher than the values observed after administration of EVG/r.

Compared to EVG/r given alone, the EVG AUC_{tau}, C_{max} and C_{tau} were significantly increased (~2-fold AUC_{tau} and C_{max}; ~3-fold C_{tau}) on co-administration of EVG 200 mg with ATV/r. Since an additional effect of ATV on RTV inhibition of the CYP3A4-mediated metabolism of EVG was unlikely, the increase in EVG plasma levels was ascribed to inhibition of UGT1A1 by ATV.

Table 14. Statistical Comparisons of PK Parameters for GS-9137 Between Treatments (PK Analysis Set)

Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
GS-9137 + Atazanavir/r vs. GS-9137/r				
C_{max} (ng/mL)	5495.35	2971.72	184.92	168.52, 202.92
AUC_{tau} (ng•h/mL)	57497.82	28821.05	199.50	184.58, 215.62
C_{tau} (ng/mL)	1461.21	507.69	287.81	253.26, 327.08

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, once-daily; atazanavir/r = 300 mg of atazanavir + 100 mg of ritonavir, once-daily, CI = confidence interval

a N = 33 per treatment with the exception of C_{tau} in Reference Treatment when N = 32; the pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment = GS-9137 + atazanavir/r, Reference Treatment = GS-9137/r, each treatment given for 14 days

There was a marginal increase in plasma levels of the glucuronide metabolite M4 on co-administration, which was less than proportional than the increase in EVG exposure.

GS-US-183-0106 compared EVG/r 150/100 mg with EVG 85 mg plus ATV/r 300/100 mg and with ATV/r alone, all given once daily for 10 days. The comparisons of EVG C_{max} and AUC_{tau} indicated that 85 mg EVG + ATV/r would provide similar AUC_{tau} and C_{max} vs. 150/100 mg EVG/r and a slightly higher C_{tau}.

Table 15. Statistical Comparisons of PK Parameters for EVG Between Treatments (PK analysis Set)

Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
85 mg GS-9137 + Atazanavir/r vs. 150/100 mg GS-9137/r				
C_{max} (ng/mL)	1367.24	1505.37	90.91	81.38, 101.57
AUC_{tau} (ng•h/mL)	18640.07	17394.64	107.16	95.09, 120.76
C_{tau} (ng/mL)	473.51	343.73	138.08	118.30, 161.16

AUC_{tau} and C_{max} of the glucuronide metabolite M4 were lower on co-administration of 85 mg EVG with ATV/r (GMRs 68% and 56%, respectively, vs. EVG/RTV alone), which resulted in a lower mean M4:EVG ratio (3.7% vs. 6.0%). This was consistent with study 0108 in which the ratios were 3.5% for EVG + ATV/r and 5.7% with EVG/r alone.

The ATV C_{max}, AUC_{tau} and C_{tau} were somewhat lower when ATV/r was co-administered with 85 mg EVG (lower bound below 80 and entire 90% CI below 1.0 for AUC_{tau} and C_{tau}) vs. ATV/r alone.

Table 16. Statistical Comparisons of PK Parameters for Atazanavir Between Treatments (PK Analysis Set)

Test versus Reference Comparison of Atazanavir Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
85 mg GS-9137 + Atazanavir/r vs. Atazanavir/r				
C_{max} (ng/mL)	4894.88	5066.21	96.62	86.58, 107.82
AUC_{tau} (ng•h/mL)	44720.94	50211.66	89.06	79.98, 99.18
C_{tau} (ng/mL)	836.41	1008.60	82.93	72.14, 95.32

ATV increased plasma exposures to RTV regardless of EVG but the RTV AUC_{tau} and C_{max} were slightly lower after co-administration with 85 mg EVG vs. ATV/r alone.

GS-US-183-0147 compared EVG/r 300/100 mg once daily with EVG 300 mg plus ATV 400 mg once daily over 10 days. Oral midazolam 5 mg was administered on Day 10. EVG C_{max} and AUC were slightly lower when it was given with RTV rather than with ATV but trough values were comparable. Plasma exposures to the glucuronide metabolite M4 were ~37% lower with EVG/r + ATV vs. EVG/r alone with respective M4: EVG ratios of 2.7% and 4.4%.

Lopinavir

GS-US-183-0116 compared EVG/r 125/100 mg once daily, EVG 125 mg once daily plus LPV/r 400/100 mg twice daily and LPV/r at this regimen alone over 14 days. Co-administration with LPV/r gave significant increases in EVG and M4 AUC_{tau}, C_{max} and C_{tau} compared to EVG/r but the ratios of plasma M4 to EVG with both treatments were < 10% (AUC_{tau} and C_{tau}).

Table 17. Statistical Comparisons of PK Parameters for EVG between Treatments (PK Analysis Set)

Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Square Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
GS-9137 + Lopinavir/r vs. GS-9137/r				
C_{max} (ng/mL)	2741.7	1806.9	151.74	128.76, 178.82
AUC_{tau} (ng•h/mL)	31,693.9	18,112.6	174.98	149.67, 204.57
C_{tau} (ng•h/mL)	879.8	369.6	238.06	180.95, 313.18

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir once daily; lopinavir/r = 400 mg of lopinavir +100 mg of ritonavir twice daily; CI, confidence interval

a N = 14/treatment. Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

b Test Treatment = GS-9137 + lopinavir/r, Reference Treatment = GS-9137/r; each treatment given for 14 consecutive days

Table 18. Statistical Comparisons of PK Parameters for M4 between Treatments (PK Analysis Set)

Test versus Reference Comparison of M4 Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
GS-9137 + Lopinavir/r vs. GS-9137/r				
C_{max} (ng/mL)	210.7	121.9	172.91	141.93, 210.65
AUC_{tau} (ng•h/mL)	2492.3	1186.0	210.14	176.61, 250.03
C_{tau} (ng•h/mL)	90.1	27.6	326.93	249.39, 428.59

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir once daily; lopinavir/r = 400 mg of lopinavir +100 mg of ritonavir twice daily; CI, confidence interval

a N = 14/treatment with the exception of C_{tau}; Test Treatment n = 12; Reference treatment n = 10; Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

b Test Treatment = GS-9137 + lopinavir/r, Reference Treatment = GS-9137/r, each treatment given for 14 consecutive days

LPV AUC_{tau} and C_{max} were unaltered in the presence of EVG. There was only a marginal decrease in C_{tau} while $T_{1/2}$ increased from 12.8 h to 17.9 h without an effect on AUC.

Table 19. Statistical Comparisons of PK Parameters for Lopinavir Between Treatments (PK Analysis Set)

Test versus Reference Comparison of Lopinavir Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
GS-9137 + Lopinavir/r vs. GS-9137/r				
C_{max} (ng/mL)	16,275.5	16,405.6	99.21	87.99, 111.85
AUC_{tau} (ng•h/mL)	145,661.1	150,844.0	96.56	85.32, 109.29
C_{tau} (ng•h/mL)	9625.8	10,423.8	92.34	78.73, 108.32

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir once daily; lopinavir/r = 400 mg of lopinavir + 100 mg of ritonavir once daily; CI, confidence interval

a N = 13/treatment. Subjects 9, 11, 15, 19, and 21 did not have evaluable PK for a treatment pair and were excluded from the PK analysis set and summary statistics.

b Test Treatment = GS-9137 + lopinavir/r, Reference Treatment = lopinavir/r, each treatment given for 14 consecutive days

Table 20. Statistical Comparisons of PK Parameters for Ritonavir Between Treatments (Group 2 PK Analysis Set)

Test versus Reference Comparison of Ritonavir Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
Lopinavir/r + GS-9137 vs. lopinavir/r				
C_{max} (ng/mL)	1483.3	1305.7	113.60	86.89, 148.52
AUC_{tau} (ng•h/mL)	7645.0	7459.8	102.62	86.99, 121.06
C_{tau} (ng/mL)	262.4	297.0	88.34	74.39, 104.90

GS-9137 = 125 mg once daily; lopinavir/r = 400 mg of lopinavir + 100 mg of ritonavir twice daily; CI, confidence interval

a N = 13/lopinavir/r + GS-9137 vs. lopinavir/r treatment

b Test Treatment = GS-9137 + lopinavir/r, Reference Treatment = lopinavir/r, each treatment given for 14 consecutive days

Tipranavir

GS-US-183-110 compared EVG/r 200/100 mg once daily with EVG 200 mg once daily plus TPV/r (500/200 mg) twice daily, each for 14 days.

The addition of TPV/r twice daily gave a reduction in EVG AUC and C_{tau} compared to EVG/r alone. In contrast, M4 exposures (C_{max}, AUC_{tau}, and C_{tau}) were higher by 32.8%, 32.5% and 49.2%, respectively when EVG was given with TPV/r vs. EVG/r alone.

Table 21. Statistical comparisons of Pharmacokinetic Parameters for EVG Between Treatments (PK Analysis Set).

Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
GS-9137 + Tipranavir/r vs. GS-9137/r				
C_{max} (ng/mL)	3084.1	2909.3	106.0	89.4, 125.7
AUC_{tau} (ng•h/mL)	25,835.3	27,962.2	92.4	78.7, 108.4
C_{tau} (ng•h/mL)	462.4	511.7	90.4	69.8, 116.9

Co-administration did not produce any significant changes in TPV C_{max} and AUC based on ratios and 90% CI but means were numerically lower in the presence of EVG. Mean C_{tau} was also lower. Addition of EVG had no effect on RTV AUC vs. TPV/r while C_{max} and C_{tau} were slightly higher.

Table 22. Statistical Comparisons of Pharmacokinetic Parameters for Tipranavir Between Treatments (PK Analysis Set)

Test versus Reference Comparison of Tipranavir Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
GS-9137 + Tipranavir/r vs. GS-9137/r				
C_{max} (ng/mL)	79,439.0	86,759.5	91.6	83.8, 100.1
AUC_{tau} (ng•h/mL)	584,651.5	657,751.4	88.9	80.0, 98.8
C_{tau} (ng•h/mL)	27,141.3	30,544.6	88.9	77.4, 102.0

a N = 26/treatment; the pharmacokinetic analysis set excludes Subjects 4, 14, 15, 16, 19, 25, 26, and 33 because they did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment = GS-9137 + tipranavir/r, Reference Treatment = tipranavir/r, each treatment given for 14 consecutive days

GS-9137/r = 200 mg of GS-9137 + 100 mg of ritonavir, once-daily; tipranavir/r = 500 mg of tipranavir + 200 mg of ritonavir, twice-daily, CI = confidence interval

Darunavir

GS-US-183-0120 compared EVG/r 125/100 mg once daily and DRV/r 600/100 mg twice daily with EVG 125 mg once daily plus DRV/r (600/100 mg) twice daily. EVG C_{max} and AUC were slightly higher when given with DRV/r vs. EVG/r alone but the upper bound of the 90% CI fell within 125% while that for the C_{tau} ratio was 131.4%. M4 levels were also higher in the presence of DRV/r but were still < 10% of those of EVG. The greater effect of DRV on M4 compared to EVG was proposed to reflect inhibition of M4 biliary elimination by DRV.

Table 23. Statistical Comparisons of PK Parameters for EVG Between Treatments (PK Analysis Set)

Test versus Reference Comparison of GS-9137 Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test[b] (Mean)	Reference[b] (Mean)		
GS-9137 + Darunavir/r vs. GS-9137/r				
C_{max} (ng/mL)	2150.80	1905.23	112.89	102.65, 124.15
AUC_{tau} (ng•h/mL)	21426.63	19511.96	109.81	99.09, 121.69
C_{tau} (ng/mL)	452.82	383.72	118.01	106.01, 131.37

GS-9137/r = 125 mg of GS-9137 + 100 mg of ritonavir, once-daily; darunavir/r = 600 mg of darunavir + 100 mg of ritonavir, twice-daily, CI = confidence interval

a The pharmacokinetic analysis set includes 21 subjects for each treatment.

b Test Treatment = GS-9137 + darunavir/r, Reference Treatment = GS-9137/r, each treatment given for 14 consecutive days

DRV exposures were lower when EVG was co-administered vs. DRV/RTV alone with 90% CI around the ratios for C_{max} and AUC within limits of 80 – 125 % but not including 100%. C_{tau} was 17% lower when EVG was added, with 90% CI 74 - 93%. The comparison of RTV C_{max} and AUC indicated lower exposures when EVG was added vs. DRV/RTV alone, with lower bounds of 90% CI all below 80%.

Fosamprenavir

GS-US-183-0123 compared EVG/r 125/100 mg once daily and FPV/r 700/100 mg twice daily with EVG 125 mg once daily plus FPV/r 700/100 mg twice daily. The comparison of EVG PK parameters indicated

no additional effect of FPV on PK EVG vs. EVG/r and no effect on M4. There was also no appreciable effect of co-administration with EVG 125 mg on PK amprenavir (APV). Addition of EVG to FPV/r resulted in a slightly lower RTV C_{max} (90% CI 75, 107%) but comparable AUC and C_{tau}, indicating no appreciable effect of EVG.

Other types of antiretroviral agents

Co-administration of zidovudine (ZDV) 300 mg twice daily with EVG/r 200/100 mg had no appreciable effect on PK of ZDV, on zidovudine glucuronide formation or on EVG and RTV plasma levels.

Neither didanosine (ddI) 400 mg nor stavudine (d4T) 40 mg affected PK of EVG (given as EVG/r 200/100 mg) except that C_{tau} was 24% higher on co-administration with d4T. Plasma exposure to ddI was slightly lower (~15% reduction in AUC and C_{max} and lower bound of 90% CI below 80%) on co-administration with EVG/r but the ddI median $T_{½}$ values were 1.64 vs. 1.77 h. The d4T AUC_{inf} and $AUC_{0\text{-}last}$ were slightly higher with EVG/r but 90% CI fell within 80, 125.

Etravirine (ETV 200 mg once daily) did not affect PK EVG (given as EVG/r 150/100 mg once daily) although plasma exposures to EVG were slightly higher. The RTV AUC and C_{tau} were slightly lower on co-administration but only for C_{tau} did the 90% CI fall outside 80 - 125% interval (64, 78). EVG/r did not affect PK of ETV.

Abacavir (ABC) 600 mg did not affect PK EVG (given as EVG/r 200/100 mg once daily). Co-administration with EVG/r did not affect ABC.

Tenofovir/emtricitabine co-administration with EVG/r 50/100 mg had no effect on PK of EVG, FTC or TFV.

Maraviroc (MVC) 150 mg twice daily did not affect PK EVG (given as EVG/r 150/100 mg once daily). RTV was also essentially unaffected. Co-administration with EVG/r resulted in 2-4-fold increases in MVC C_{max}, AUC and C_{tau} due to CYP3A4 and P-gp inhibition by RTV. The recommended dose of maraviroc in the absence of a potent CYP3A inhibitor is 300 mg twice daily.

Table 24. Statistical Comparisons of PK Parameters for Maraviroc Between Treatments (PK Analysis Set, study GS-US-183-0118)

Test versus Reference Comparison of Maraviroc Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% Confidence Interval
	Test[b] (Mean)	Reference[b] (Mean)		
Maraviroc + GS-9137/r vs. Maraviroc Alone				
C_{max} (ng/mL)	885.50	412.16	214.84	171.43, 269.26
AUC_{tau} (ng•h/mL)	2653.40	927.68	286.03	232.93, 351.23
C_{tau} (ng/mL)	76.01	17.96	423.33	347.21, 516.13

Maraviroc 150 mg twice daily when administered alone or with GS-9137/r; GS-9137/r, 150 mg of GS-9137 + 100 mg of ritonavir once daily

a N = 11 per treatment; the pharmacokinetic analysis set excludes subjects who did not have evaluable pharmacokinetic profiles for the treatment pair.

b Test Treatment, maraviroc + GS-9137/r; Reference Treatment, maraviroc alone; each treatment given for 10 days

Other medicinal products

Co-administration of EVG/r 50/100 mg with magnesium/aluminium-containing antacid was associated with marked reductions (ratios ~ 50 – 60%) in C_{max} and AUC EVG.

Table 25. Statistical Comparisons of PK Parameters for EVG with and without co-administration of antacid (PK Analysis Set, study GS-US-183-0103)

Test versus Reference Comparison of Plasma PK Parameters[a]	Geometric Least-Squares Means		Geometric Least-Squares Mean Ratio (%)	90% CI
	Test (Mean)	Reference (Mean)		
Antacid + GS-9137/r vs.GS-9137/r[c]				
C_{max} (ng/mL)	664.1	1250.6	53.1	46.8, 60.2
C_{tau} (ng/mL)	184.4	311.8	59.1	52.0, 67.2
AUC_{tau} (ng•h/mL)	8561.5	15,550.7	55.1	50.4, 60.2

This was further investigated by comparing administration of EVG/r 50/100 mg alone and after food once daily with groups that received Mg/Al-containing antacid 2 or 4 h before and after dosing. EVG/r was also given as 50/100 2 h after 40 mg omeprazole for 5 days. On dosing EVG/r with a 4 h interval before/after antacid and at 2 h after a daily dose of omeprazole there was no significant effect on EVG exposures. Dosing with a 2 h interval before or after 20 mL antacid gave lower EVG exposures with 90% CI around ratios that did not span zero. The highest RTV exposures occurred when EVG/r was given 2 or 4 h before antacid and the lowest when it given with omeprazole. However, for each comparison with EVG/r alone the 90% CI fell within limits of 80 – 125% and spanned 100 except for omeprazole (which almost spanned 100).

Rifabutin dosed at 150 mg every other day did not affect EVG exposures vs. EVG/r 300/100 mg once daily alone. RTV plasma levels were elevated in the presence of rifabutin (e.g. AUC ratio 124.5% [90% CI 109 – 142%]). The rifabutin C_{max} and C_{tau} at 24 h post rifabutin 300 mg once daily alone and at 48 h post rifabutin co-administered with EVG/r were comparable. Median $T_{½}$ increased from 10.43 h to 24.4 h following co-administration. The estimate derived from 2 × AUC_{0-24} for rifabutin alone was comparable to AUC_{0-48} during co-administration. In contrast, 25-O-desacetyl rifabutin AUC_{0-48}, C_{max} and C_{tau} increased 9.5-, 5.4- and 19.4-fold, respectively, on co-administration. The total antimycobacterial activity (calculated from total concentration in µM for rifabutin plus 25-O-desacetyl rifabutin) was increased by 50% during co-administration.

Co-administration of EVG/r 150/100 mg once daily with ketoconazole (KTZ) 200 mg twice daily gave KTZ PK values that were comparable with those reported during co-administration with DRV/r. RTV exposures increased on co-administration with KTZ (e.g. AUC ratio 162% [90% CI 143, 184%]). KTZ resulted in increases in EVG plasma concentrations, especially for AUC and C_{tau}. The EVG T1/2 were comparable (11.8 h vs. 12.0 h with KTZ) but clearance (CL/F) and CL/F/kg showed reductions by about one third in the presence of KTZ.

Table 26. Statistical Comparisons of EVG PK Parameters after Administration of EVG/r Alone or EVG/r Plus Ketoconazole (PK Analysis Set)

Test versus Reference Comparison PK Parameter	Geometric Least-squares Means		Geometric Least-squares Means Ratio (%)	90% Confidence Interval
	Test[a] (Mean)	Reference[b] (Mean)		
Elvitegravir/r + Ketoconazole versus Elvitegravir/r				
C_{max} (ng/mL)	2260.2	1926.3	117.3	103.8, 132.6
AUC_{tau} (ng•h/mL)	32286.0	21766.3	148.3	136.2, 161.6
C_{tau} (ng/mL)	804.8	482.9	166.7	148.2, 187.5

There was also a modest increase in M4 (GS-9200) plasma levels when KTZ was added to EVG/r.

In the same study, co-administration of MDZ (5 mg PO) with EVG/r resulted in markedly increased MDZ exposures and there was a further but more modest increase in AUC_{inf} and C_{last} when KTZ was added. Co-administration with EVG/r resulted in significant decreases in 1′-OH MDZ exposure but there were increases on addition of KTZ.

EVG boosted with COBI

Co-administration of DRV 800 mg with EVG 150 mg and COBI 150 mg for 10 days resulted in DRV mean C_{tau} (1045.7 ng/mL) that was lower than observed in other studies in which DRV 800 mg daily was co-administered with COBI 150 mg (1332.7 ng/mL) or RTV 100 mg (1866.7 ng/mL) without EVG. Also, the EVG C_{max} (2091 ng/mL), AUC_{tau} (18,067 ng.h/mL) and C_{tau} (242 ng/mL) were slightly lower than observed in another study with EVG/r 125/100 mg alone or EVG 125 mg plus DRV/r 600/100 mg twice daily.

Co-administration of EVG/co 150/150 mg with omeprazole (20 mg) or famotidine (40 mg) over 7 days showed no effect on PK of EVG (or COBI) when each was given 12 h after EVG/co. When omeprazole was given 2 h before EVG/co the plasma levels of EVG increased slightly with 90% CI for C_{max} and C_{tau} that exceeded 125% but the AUC ratio was 110 [102, 119]. Co-administration of EVG/co 150/150 mg with famotidine 40 mg once daily showed no discernible effects on PK EVG.

Co-administration of EVG/co 150/150 mg with ROS 10 mg showed no effect on PK EVG. The ROS C_{max} and AUC were greater (89% and 38%, respectively) when given with EVG/co but the overall concentration-time profile and T½ were comparable vs. ROS alone.

Co-administration of EVG/co 85/150 mg with ATV 300 mg did not affect the EVG AUC_{tau} while C_{max} was lower (~ 15%) and C_{tau} was higher vs. EVG/co 150/150 mg alone. The ATV AUC_{tau} was lower (10-12%) when given with EVG/co vs. ATV/r. C_{max} was ~ 21-24% lower and C_{tau} was ~ 20-35% lower although it was above the DHHS target (140 ng/mL) in all subjects.

Co-administration of EVG/co 150/150 mg with rifabutin 150 mg every other day did not affect the EVG C_{max} but the AUC_{tau} was ~ 20% lower and C_{tau} markedly (~ 63%) lower with an associated shorter T½ vs. EVG/co alone. COBI exposures were substantially lower only at 18 and 24 h following co-administration with rifabutin and an associated shorter T1/2. The AUC_{tau}, C_{max} and C_{tau} rifabutin were comparable between the EVG/co + 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. Co-administration with EVG/co resulted in large increases in AUC_{tau}, C_{max} and C_{tau} of 25-*O*-desacetylrifabutin vs. rifabutin alone.

GS-US-216-0125 evaluated methadone PK in HIV-1 uninfected subjects on a stable dose following once-daily co-administration of EVG/co and methadone vs. methadone alone. R-methadone (active enantiomer) and S-methadone exposures were unchanged on co-administration with EVG/co vs. methadone alone. The 90% CIs were within 80% to 125% with the exception of R-methadone C_{tau} (127-132%).

Table 27. GS-US-216-0125: Methadone Pharmacokinetics

PK Parameter	Test Mean (%CV)	Reference Mean (%CV)	GLSM Ratio (%)	90% Confidence Interval
R-Methadone: EVG/co + Methadone (Test) vs Methadone (Reference), (N = 11)				
AUC_{tau} (ng•h/mL)	6211.6 (43.7)	5547.6 (21.3)	106.98	(96.06, 119.16)
C_{max} (ng/mL)	336.9 (46.4)	316.4 (21.4)	101.41	(90.75, 113.32)
C_{tau} (ng/mL)	234.0 (55.7)	196.6 (25.0)	110.00	(94.84, 127.58)
S-Methadone: EVG/co + Methadone (Test) vs Methadone (Reference), (N = 11)				
AUC_{tau} (ng•h/mL)	7542.1 (56.1)	7036.3 (39.8)	100.17	(89.38,112.26)
C_{max} (ng/mL)	452.4 (51.9)	445.8 (35.1)	95.92	(86.03,106.23)
C_{tau} (ng/mL)	260.0 (71.0)	229.8 (49.5)	102.19	(89.24,117.01)

Studies with Stribild

One DDI study was conducted with STB and an oral contraceptive containing norgestimate and ethinyl oestradiol (0.025 mg). Co-administration was for 9 days in subjects at least in the second dosing cycle and resulted in increases in norelgestromin AUC_{tau}, C_{max} and C_{tau} but decreases in ethinyl oestradiol (EE) AUC_{tau} and C_{tau}. EVG and COBI levels were in the expected range. Serum progesterone remained unchanged while FSH decreased to a similar extent and LH showed a larger decrease on co-administration.

Table 28. GS-US-236-0106: Statistical Comparisons of Norelgestromin Pharmacokinetic Parameters (NGMN PK Analysis Set)

NGMN PK Parameter	Geometric Least-squares Means		Geometric Least-squares Means Ratios (Test/Reference) (%)	90% Confidence Intervals
	NGM/EE Reference (N=15)	NGM/EE + EVG/COBI/FTC/TDF Te (N=15)		
AUC_{tau} (h·pg/mL)	21084.51	47642.85	225.96	(215.13, 237.34)
C_{tau} (pg/mL)	497.64	1326.57	266.57	(243.06, 292.35)
C_{max} (pg/mL)	2126.10	4420.00	207.98	(199.74, 216.57)

NGM/EE = Ortho Tri-Cyclen Lo

NGM/EE + EVG/COBI/FTC/TDF = Ortho Tri-Cyclen Lo plus a fixed-dose combination tablet containing EVG 150 mg, COBI 150 mg, FTC 200 mg, and TDF 300 mg.

Cobicistat (COBI) is the new generic name for GS-9350.

Note: The statistical model included treatment as a fixed effect and subject as a random effect.

Table 29. GS-US-236-0106: Statistical Comparisons of Ethinyl Estradiol Pharmacokinetic Parameters (EE PK Analysis Set)

EE PK Parameter	Geometric Least-squares Means		Geometric Least-squares Means Ratios (Test/Reference) (%)	90% Confidence Intervals
	NGM/EE Reference (N=15)	NGM/EE + EVG/COBI/FTC/TDF Test (N=15)		
AUC_{tau} (h·pg/mL)	1002.29	751.44	74.97	(69.41, 80.98)
C_{tau} (pg/mL)	21.72	12.27	56.48	(51.88, 61.49)
C_{max} (pg/mL)	101.24	95.25	94.09	(85.54, 103.50)

NGM/EE = Ortho Tri-Cyclen Lo

NGM/EE + EVG/COBI/FTC/TDF = Ortho Tri-Cyclen Lo plus a FDC tablet containing EVG 150 mg, COBI 150 mg, FTC 200 mg, and TDF 300 mg.

Cobicistat (COBI) is the new generic name for GS-9350.

Note: The statistical model included treatment as a fixed effect and subject as a random effect.

2.4.3. Pharmacodynamics

Mechanism of action

EVG specifically inhibits HIV-1 integrase strand-transfer activity and the integration of viral DNA into host cell chromosomal DNA in cell culture.

Primary pharmacology

EVG inhibited DNA strand-transfer with an IC50 value of 8.8 nM. It inhibited laboratory strains and various clinical isolates of HIV-1 with an EC50 of 0.38 nM (range, 0.02 to 1.3 nM) in human PBMCs. Activity was shown against multiple subtypes of HIV-1 and against HIV-2.

The EC95 value in the presence of HSA and AAG was 100 nM (44.8 ng/mL) in HIV-1 infected human PBMC cultures, representing an 89-fold loss in antiviral activity.

In-vitro ARV combination studies showed additive to synergistic interactions with the NRTIs FTC and TFV (as well as others tested), with NNRTIs (EFV, nevirapine and etravirine) and with a range of PIs. In-vitro assays with T-20, RAL and maraviroc also demonstrated additive to synergistic interactions.

In-vitro, EVG selected for 3 primary resistance mutations in HIV-1 integrase - T66I/A/K, E92Q/G or Q148R. These conferred 15-, 36- and 109-fold reduced susceptibility, respectively.

Additional secondary IN mutations selected by EVG were H51Y, F121Y, S147G, S153Y, E157Q and R263K. These mutations further decreased susceptibility to EVG when they occurred in addition to T66I or E92Q mutations.

Elvitegravir did not inhibit replication of HBV or HCV *in vitro*.

There were no measurable changes in the content of mtDNA and therefore the potential for mitochondrial toxicity is considered low.

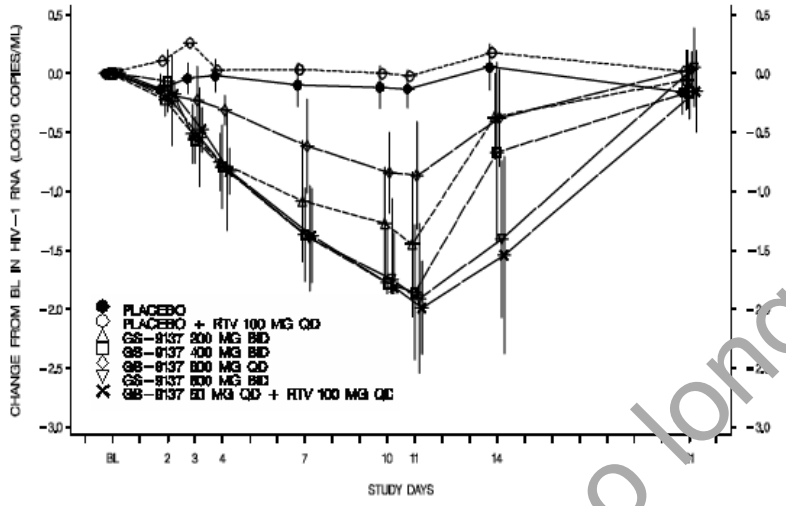
In MT-2 cells the M4 and M1 metabolites showed HIV-1 antiviral activity that was 6.7- and 9.3-fold lower than EVG. However, M4 and M1 selected for EVG-associated resistance mutations.

The EVG dose-escalation studies of selection of resistance-associated mutations were of different methodologies. However, they indicated that T66I could be selected by passage 7 whereas E92Q

emerged at passage 30. Using the viral breakthrough method Viruses with IN resistance mutations were observed at EVG concentrations corresponding to 10-fold the EC50 (T66I/T) and 40- and 80-fold the EC50 (Q148R). Viruses with emergent IN resistance mutations were also observed for RAL at concentrations corresponding to 5-fold the EC50 (N155H) and 40-fold the EC50 (Q148K).

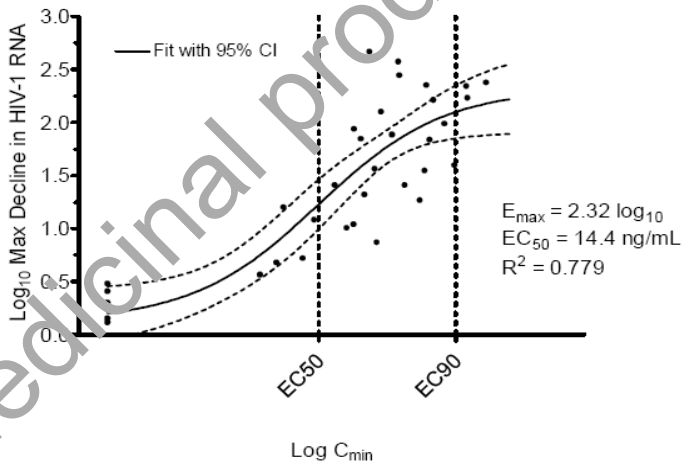
In GS-US-183-0101 EVG monotherapy at 200, 400 or 800 mg twice daily, at 800 mg once daily or 50 mg + RTV 100 mg once daily for 10 days significantly reduced HIV-1 RNA levels vs. placebo but maximal and comparable mean/median changes were observed with 400 or 800 mg twice daily and 50 mg + RTV 100 mg once daily.

Figure 4. Mean Change in HIV-1 RNA Through Day 21



EVG C_{tau} values fitted well to a simple E_{max} (maximum PD effect) model with an EC50 value at 14.4 ng/mL and an E_{max} of 2.32 log10 copies/mL reduction from baseline.

Figure 5. Pharmacokinetic/Pharmacodynamic Dose-Response Relationship for EVG



The estimated inhibitory quotients (IQ; calculated as the observed mean C_{tau} divided by the protein binding-adjusted in-vitro IC50 of 7.17 ng/mL) were 5.9, 6.7 and 18.8 at 400 mg twice daily, 800 mg twice daily and 50 mg + RTV once daily, respectively. EVG trough concentrations at these doses exceeded the protein binding-adjusted in vitro IC95 (45 ng/mL; 100 nM) for the entire dosing interval.

In the Phase 3 study GS-US-183-0145 EVG (85 or 150 mg) was compared with twice-daily raltegravir (RAL), each administered with a fully active PI/r in the OBR. A pure virological failure (PVF) analysis showed virological response rates ~65% in both treatment groups at Week 48. Exploratory PK/PD evaluations indicated that virological response spanned the observed PVF-based efficacy for all 3 quantile-based analyses (i.e. quartiles, quintiles or octiles of EVG C_{trough} for 85 mg and 150 mg doses). Lower response rates were observed in the lowest quantile that may reflect the influence of observations below the LLQ.

Table 30. GS-US-183-0145: Summary for EVG Trough Concentration and Pure Virologic Response at Week 48 (HIV-1 RNA < 50 copies/mL) by EVG C_{tau} Quartile Subgroups for EVG 85-mg and 150-mg Doses (PK/PD Analysis Set).

	EVG C_{tau} Quartile			
	Q1	Q2	Q3	Q4
EVG 85 mg				
Median EVG C_{tau} Within Quartile (ng/dL)	124.2	316.2	482.7	866.8
Pure Virologic Response, n/N (%)	15/26 (57.7%)	21/26 (80.8%)	19/26 (73.1%)	18/26 (69.2%)
EVG 150 mg				
Median EVG C_{tau} Within Quartile (ng/dL)	88.8	243.8	368.0	700
Pure Virologic Response, n/N (%)	21/41 (51.2%)	29/41 (70.7%)	32/41 (78.0%)	31/ 2 (3.8%)

Secondary pharmacology

The TQT study GS-US-183-0128 evaluated the effects of EVG/RTV 125/100 and 250/100 mg on QTc. Moxifloxacin showed the expected positive control effect with a difference in QTcF vs. placebo that was generally between 5 and 10 ms and with an upper limit of the 90% CI > 10 ms at multiple time points. For the QTcF change from baseline in Part 2 of the study the upper limits of the 2-sided 90% CI for the difference in LSMs (EVG/r vs. placebo) were all < 10 ms. Actual differences in LSMs were < 5 ms at all time points for both EVG/r groups. Consistent results were obtained from similar analyses conducted for QTcB, QTcI and QTcN. The categorical analyses were unremarkable. The linear correlations between QTcF, QTcB, QTcN and QTcI and plasma concentrations of EVG and GS-9200 were very weak.

2.4.4. Discussion on clinical pharmacology

The oral bioavailability of EVG when administered alone was estimated to be low (< 25%) and increased in a less than dose-proportional manner. Multiple dosing with unboosted EVG showed auto-induction of metabolism.

The effect of food on the final formulation was not studied. However, based on the food effect studies using early formulation of EVG or QUAD STR, in all subsequent studies EVG was administered with food.

The large increase in EVG exposure on co-administration with a single dose of RTV 100 mg was attributed to improved oral bioavailability due to decreased first pass metabolism and to reduced systemic clearance. On multiple dosing of EVG/RTV there were further increases in EVG plasma exposures, including C_{tau}, with a greater than predicted steady-state AUC. Plasma RTV concentrations were higher after multiple dosing with non-linear PK on dosing to steady state, most likely due to its time-dependent, mechanism-based inhibition of CYP3A. These observations underline the importance of conducting the DDI studies with EVG and RTV at steady-state.

Plasma concentrations of M1 were below LLQ with RTV 100 mg doses. Concentrations of M4 increased with RTV dose in a non-linear fashion with a ratio M4:EVG maintained < 10%, suggesting that RTV did not affect M4 formation.

The cross-study comparison following multiple-dose administration of EVG/RTV 150/100 mg in healthy (GS-US-183-0140) and HIV-1 infected subjects (GS-US-183-0145) indicated comparable mean exposures based on C_{max}, C_{tau} and AUC.

The results in subjects with renal impairment are difficult to interpret given the overall higher exposures in this study vs. other in healthy subjects. Despite the limitations of the study, less than 8% of EVG is excreted in urine and the free EVG fraction remained just over 1% in patients with severe renal impairment. Therefore, it is supported that no dose adjustment is needed.

Taking into account the mean (%CV) EVG exposure parameters AUC_{tau}, C_{max}, and C_{tau} across studies GS-US-183-0133 and GS-US-236-0110 as well as the population PK analyses derived from the STB Phase 2 and 3 studies (GS-US-236-0102, 0103 and 0104) the higher EVG AUC observed in subjects with moderate hepatic impairment is not considered to merit dose adjustment taking into account also the available safety data with EVG.

RTV, ATV and EVG share a common pathway for systemic clearance – primarily CYP3A-mediated oxidation. ATV, which is known to inhibit RTV clearance, resulted in higher RTV exposure regardless of whether or not EVG was also given. Addition of EVG to ATV/r had some negative effect on RTV plasma levels vs. ATV/r alone. It appeared that not only did ATV inhibit formation of M4 via its effect on UGT1A1 but also it inhibited elimination of M4. It seems that M4 is a substrate for MRP2 and it was proposed that decreased M4 elimination could reflect altered MRP2-mediated biliary clearance since RTV is known to inhibit this transporter and ATV may also be an inhibitor (since other PIs have this effect).

EVG inhibits OATP1B1 and OATP1B3 but the IC50 values (IC50 2.2 µM and 0.44 µM, respectively) exceed unbound plasma EVG (free fraction ~1%, mean C_{max} 4.45 µM) so that a strong inhibitory effect on OATP1B1 and OATP1B3 was not expected.

Co-administration of 200 mg EVG with ATV/r increased the EVG exposures vs. EVG/r 200/100 mg given alone most likely because of CYP3A inhibition by ATV. Dose adjustment to EVG 85 mg when co-administered with ATV/r was aimed at matching EVG plasma levels observed with RTV-boosted EVG 150 mg and providing exposures corresponding to antiviral activity with mean C_{tau} values (overall and by EVG dose) that exceed the protein binding adjusted IC95 (by ~8 to 9-fold).

Co-administration of ATV/r + EVG 200 mg gave lower ATV and RTV plasma levels vs. ATV/r alone (all 90% CI below 100). On co-administration with 85 mg EVG there were also lower ATV and RTV plasma levels (90% CI for AUC and C_{tau} entirely < 100) vs. ATV/r alone. In contrast to the apparent effect of EVG on RTV when given with ATV, there was no depression of plasma RTV when EVG was added to LPV/r, IDV/r or FPV/r and only a very slight depression with DRV/r vs. each of these PI/r combinations given alone. The explanation of the observed effect of EVG on ATV/r remains unclear. Nevertheless, in light of the actual ATV plasma levels observed and the effects of other drugs on ATV plasma levels, as well as the efficacy data, the PK findings were not considered to preclude co-administration of ATV/r 300/100 mg once daily with EVG 85 mg. For example, ATV exposures were similar to therapeutically effective concentrations reported in the literature and in the prescribing information for ATV/r. Additionally, mean ATV trough concentrations in subjects receiving ATV/r plus EVG 85 mg were substantially above (~36 to 62-fold) the protein-binding adjusted IC_{90} for wild type HIV-1 (14 ng/mL).

EVG 125 mg did not have a notable effect on plasma LPV or RTV vs. LPV/r alone but co-administration with LPV/r increased the EVG AUC by 75% compared to EVG/r alone. A reduced dose of 85 mg EVG was selected through PK simulation and was estimated to provide high trough concentrations and an

equivalent AUC to EVG/r 150/100 mg. The adequacy of EVG exposures for HIV-1 infected subjects receiving EVG 85 mg (with ATV/r [n = 15] or LPV/r [n = 10]) vs. EVG 150 mg (with other PI/r) was assessed in the intensive PK sub-studies in GS-US-183-0145 (adults) and GS-US-183-0152 (adolescents). The steady-state mean EVG AUC_{tau} and C_{max} were comparable following administration of 85 mg EVG vs. 150 mg EVG when each was given with the specified PI/r combinations. The EVG C_{tau} (C_{trough}) was higher with the 85 mg dose vs. the 150 mg dose. Further assessment of the adequacy of EVG exposures to support antiviral efficacy was based on population PK modelling after co-administration of EVG 85 mg with LPV/r in GS-US-183-0145. The mean EVG C_{tau} values were 7.6-fold above the protein binding-adjusted IC_{95}. Finally, the efficacy of EVG 85 mg with LPV/r was documented in GS-US-183-0145 (see the results presented according to EVG dose and specific PI/r).

GS-US-183-0120 indicated lower C_{tau} DRV in the presence of EVG vs. DRV/r alone and 90% CI for C_{max} and AUC that did not span 100. However, the largest subset of patients in the efficacy study received EVG with twice daily DRV/r with response rates at least as good as those achieved with this regimen in the RAL group. On this basis, co-administration of EVG with twice daily DRV/RTV can be accepted. It is important to note that the data cannot support use of EVG with once daily DRV/r 800/100 mg.

GS-US-183-0123 suggested no important effect of FPV/r on EVG (90% CI for the EVG AUC ratio fell just below 100%) and addition of EVG did not affect plasma levels of amprenavir or RTV. On this basis co-administration can be accepted.

In GS-US-183-0110 EVG 200 mg once daily and TPV/r 500/200 mg twice daily gave a lower EVG AUC and C_{tau} vs. EVG/r alone and lower TPV C_{tau} vs. TPV/r alone. Population PK modelling taking into account PK data obtained on co-administration of EVG 150 mg with TPV/r in GS-US-183-0145 indicated that the mean EVG C_{tau} values were 6.3-fold above the protein binding-adjusted IC_{95}. For TPV the lower bound for the C_{tau} comparison was < 80% but the TPV trough concentrations with both treatments were > 330-fold above the IC_{90} for HIV-1 (96 ng/mL). Nevertheless, there were too few subjects that received EVG with TPV/r in the Phase 3 study to provide support based on efficacy data (3/6 in the EVG group failed) and no TPV PK data were obtained. There remains concern that this combination may not be appropriate and it is not recommended in the SmPC.

The available data indicate that plasma EVG concentrations may increase when co-administered with a PI/r and with an agent that inhibits UGT1A1/3 (which may be the PI). In particular, co-administration of EVG with ATV/r or LPV/r increased EVG plasma levels vs. EVG/r alone, which was ascribed to UGT inhibition by the PI in the presence of near maximal inhibition of CYP3A by RTV. Addition of KTZ (a strong inhibitor of CYP3A4) to EVG/r provided only a small increment in isoenzyme inhibition vs. RTV based on the effects on co-administered MDZ. Taking into account the MDZ data from this study, a maximum increase in EVG AUC of approximately 25% was anticipated due to additional CYP3A inhibition by KTZ. However, the actual increase in EVG AUC was ~ 48% when given with RTV and KTZ and the total increment was ascribed mainly to the additional effect of inhibition of UGT1A1 by KTZ.

Since a need has been established for EVG dose reduction when it is given with RTV and an agent that inhibits UGT (hence 85 mg is given with ATV/r and LPV/r), the effects of giving EVG with any of the proposed PI/r combinations plus another drug that is a strong inhibitor of UGT1A1/3 should be carefully considered. The potential net affect could be expected to depend on which PI/r is being co-administered with EVG. Co-administration of EVG with medicines that inhibit UGT seems rather less of a concern if the PI/r has already achieved near maximal UGT inhibition. In contrast, addition of a strong UGT inhibitor to 150 mg EVG plus DRV/r, TPV/r or FPV/r might increase EVG plasma levels by at least the same extent as ATV or LPV.

Studies have been conducted on possible interactions between EVG and other medicinal products, and the results have been reflected in the SmPC.

The in-vitro activity of EVG has been adequately investigated and is clearly demonstrated.

There is incomplete cross-resistance between EVG and RAL. For example, viruses carrying only T66I remain susceptible to RAL whereas viruses carrying N155H and/or Q148K show resistance to RAL and EVG. The results of the in-vitro studies suggest that the genetic barrier to resistance of EVG is relatively low, as is that of RAL.

The applicant concluded that 85 mg and 150 mg EVG doses, administered with the selected RTV-boosted PIs, provided EVG exposures corresponding to the plateau of the dose-response relationship and were associated with antiviral efficacy. Nevertheless, it has to be noted that the PK/PD analysis presented based on GS-US-183-0145 and using EVG 85 or 150 mg depending on the PI are difficult to interpret due to the various regimens and PIs that were allowed and the recognised contribution of boosted PIs to overall efficacy.

The TQT study with up to EVG/RTV 250/100 mg delivered supra-therapeutic exposures compared to anticipated plasma levels achieved with 150 mg EVG in the presence of RTV and did not suggest clinically important effects on QTc.

2.4.5. Conclusions on clinical pharmacology

EVG is clearly active against HIV *in vitro.*

The PK interactions with PIs/r proposed for coadministration and other medicines likely to be administered in combination have been studied appropriately. However, since EVG is to be co-administered with a PI/r, due to the PK properties of EVG itself and the various PI/r regimens that may be administered with EVG, the ability to assess and predict the total risk of possible interactions is limited.

EVG has been evaluated in PK studies with DRV/RTV or LPV/RTV only given twice daily. In addition, the few data available from study 0145 strongly point against using EVG with once daily DRV/RTV. Off-label use of EVG with these regimens would therefore constitute a major concern and corresponding warning against use of elvitegravir with other PIs or dosing frequencies than those explicitly recommended has been included in the SmPC.

2.5. Clinical efficacy

Data to support the efficacy of EVG when co-administered with an RTV-boosted PI and the EVG doses proposed for use with individual PIs were generated in:

- DDI studies with EVG plus RTV-boosted PIs (DRV, LPV, ATV, FPV, TPV; see section on PK)
- The short-term EVG monotherapy study in HIV-infected subjects GS-US-183-0101 (see section on PD)
- A Phase 2 study with an open-label follow-up phase (GS-US-183-0105 and 0130, see Dose Response studies and supportive studies).
- A single pivotal Phase 3 study GS-US-183-0145 (data reported to Week 96).
- Supportive data for EVG boosted with COBI in combination with TDF/FTC from the Phase 2/3 studies with QUAD STR, which are not discussed in this Assessment Report[1].

[1] for more information, see CHMP Assessment Report / European Public Assessment Report for Stribild

2.5.1. Dose response studies

The 150 mg QD dose of EVG was selected by the Applicant based on results from study GS-US-183-0101 (see section on PD), supported by results from Phase 2 study GS-US-183-0105 (see below), and a Phase 1 biopharmaceutics/formulation study (GS-US-183-0140). Drug-drug interaction studies on EVG with RTV-boosted PIs were conducted to identify whether dose adjustment of EVG was required (see section on PK).

Study GS-US-183-0105

This was a randomised, partially blinded, multicentre study to assess non-inferiority of EVG/RTV vs CPI/RTV when administered with an OBR. Treatment-experienced subjects with plasma HIV-1 RNA levels ≥ 1,000 copies/mL with documented presence of at least one of the protease gene mutations (as defined by the IAS–USA 2005 Guidelines) were eligible to enter the study.

Subjects were initially randomised to once-daily EVG/RTV 20/100, 50/100 or 125/100 mg or to an investigator-selected RTV-boosted PI, each administered with OBR.

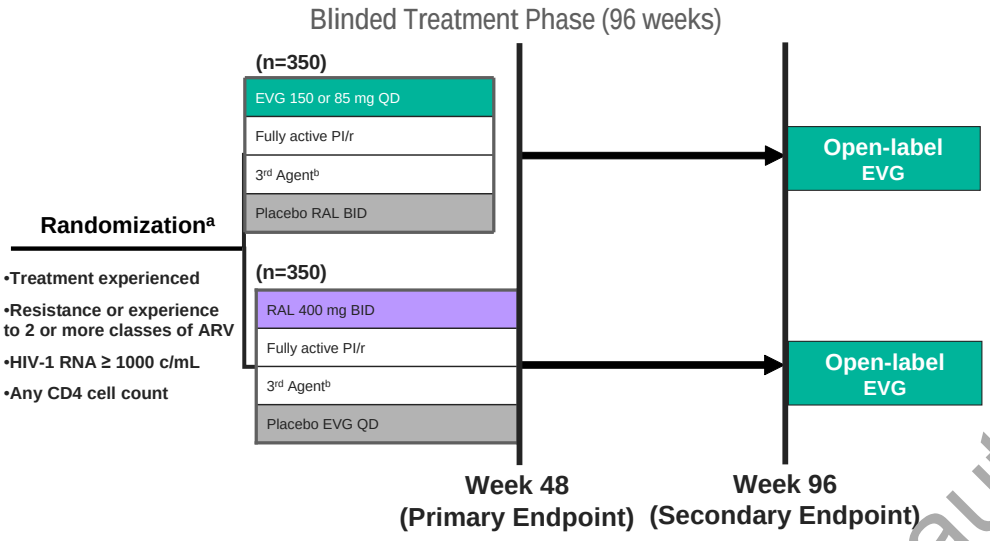
The 20/100 mg group was discontinued due to lower than expected responses by Week 8 and subjects switched to 125/100 mg. Due to this and other protocol amendments (e.g. allowance of using DRV or TPV was added by amendment) the virological data are difficult to interpret, especially after Week 16. The Week 24 responses in those who then switched to open label 125/100 mg were comparable with those who started the study on this dose. Maintaining viral suppression was strongly dependent on at least one fully active agent in the OBR and there was a marked effect of co-administering EVG/r with first use of T-20. Subjects with evidence of virological failure developed known INSTI resistance mutations; the most common was E92Q.

2.5.2. Main study (GS-US-183-0145)

Methods

This Phase 3, double-blind, double-dummy, multicentre, randomized, active-controlled study was a merger of two Phase 3 studies (0144 and 0145) that were consolidated by protocol amendment due to slow enrolment. The study report containing data out to Week 96 was included in this dossier.

Figure 6. Outline of study design for study 183-0145



a. Stratification by screening HIV-1 RNA (≤ vs. > 100,000 copies/mL) and the 3rd agent (NRTI vs other classes)
b. 3rd Agent: NRTI, ETR, MVC, T-20 (If M184V/I, may add 3TC, or FTC)

Study Participants

Eligible subjects were to have no prior treatment with an integrase inhibitor and:

- Plasma HIV-1 RNA ≥ 1000 copies/mL assessed using the COBAS Amplicor HIV-1 Monitor Ultrasensitive Test (Version 1.5; range 50 – 100,000 copies/mL).
- A stable ARV regimen for at least 30 days prior to screening and baseline.
- A screening HIV-1 genotype report that showed documented resistance (IAS-USA definitions) OR at least 6 months exposure to ≥ 2 classes of ARVs. In this regard, it has to be noted that the CSR stated: Subjects may have had virus resistant to 1 class and at least 6 months experience prior to screening with a second class OR virus resistant to 2 classes OR at least 6 months experience with ≥ 2 classes OR virus resistant to and/or at least 6 months experience with ≥ 3 classes.

At screening, the protease/reverse transcriptase (PR/RT) genotype and phenotype were determined using PhenoSense GT (Monogram Biosciences, South San Francisco, CA). Integrase resistance testing was also performed by Monogram Biosciences. Repeat testing was performed for viruses obtained in cases of primary failure or rebound.

Those completing at least 96 weeks blinded treatment were eligible for the post-Week 96 extension.

Ongoing or perceived need for therapy with any of a lengthy list of potentially interacting medications precluded study participation.

Treatments

Prior to the Baseline/Day 1 visit and pre-randomisation, the investigator selected each subject's OBR based on ARV drug history and viral resistance profile. The PI had to be predicted to be fully active against the individual's virus based on phenotyping. Randomisation was to treatment with EVG (see doses below) or RAL 400 mg twice daily. Within the EVG group subjects were dosed according to the selected RTV-boosted PI as follows:

Table 31. GS-US-183-0145: Total Daily Dose of Elvitegravir, Boosted PI, and Ritonavir

Elvitegravir + Protease Inhibitor Dosing (Total Daily Dose)	Ritonavir Dosing (Total Daily Dose)
Elvitegravir 85 mg once daily + atazanavir 300 mg once daily (300 mg)	100 mg once daily (100 mg)
Elvitegravir 150 mg once daily + darunavir 600 mg twice daily (1200 mg)[b]	100 mg twice daily (200 mg)
Elvitegravir 150 mg once daily + fosamprenavir 700 mg twice daily (1400 mg)	100 mg twice daily (200 mg)
Elvitegravir 85 mg once daily + lopinavir/r[a] 400/100 mg twice daily (800/200 mg)	Not applicable[a]
Elvitegravir 150 mg once daily + tipranavir 500 mg twice daily (1000 mg)	200 mg twice daily (400 mg)

a Since lopinavir is coformulated with ritonavir, no additional ritonavir doses were required.

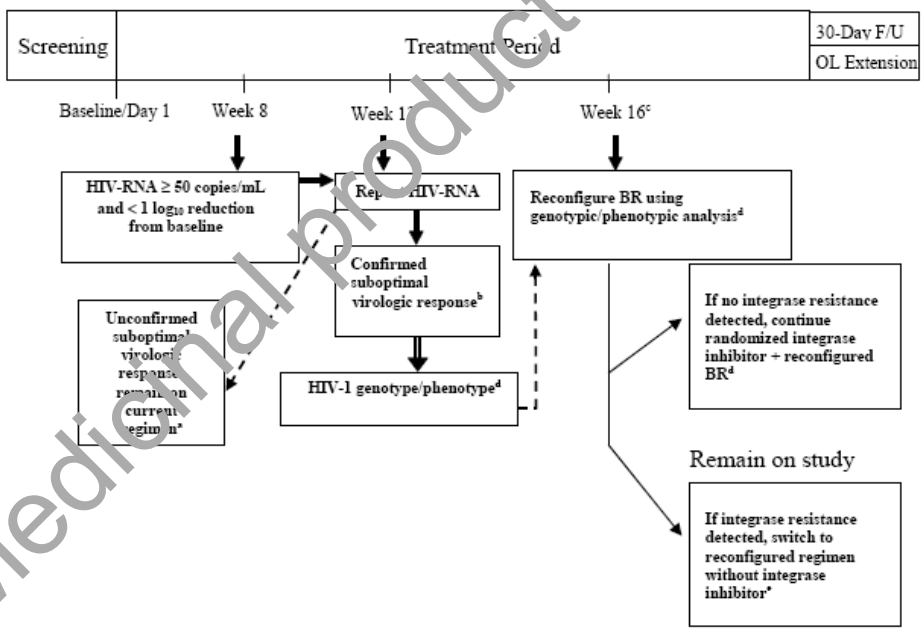
b Darunavir 800 mg once daily boosted with 100 mg ritonavir once daily was permitted if approved by applicable regulatory authorities.

Study drug was to be administered in a blinded fashion up to at least Week 96 and then beyond Week 96 until the unblinding visit.

Except for Spain, in which the second agent was to be fully active, the second agent in the OBR may or may not have been fully active and could have been one nucleoside or nucleotide RT inhibitor, etravirine, maraviroc or T-20. Use of any other integrase inhibitor, an NNRTI (due to unknown PK interactions) or FDCs (Atripla or Trizivir) was not allowed. If the M184V/I RT mutation was present on the screening genotype report and an NRTI was used as the second agent, then either FTC or 3TC could be added as a third agent in the OBR and appropriate FDCs were allowed.

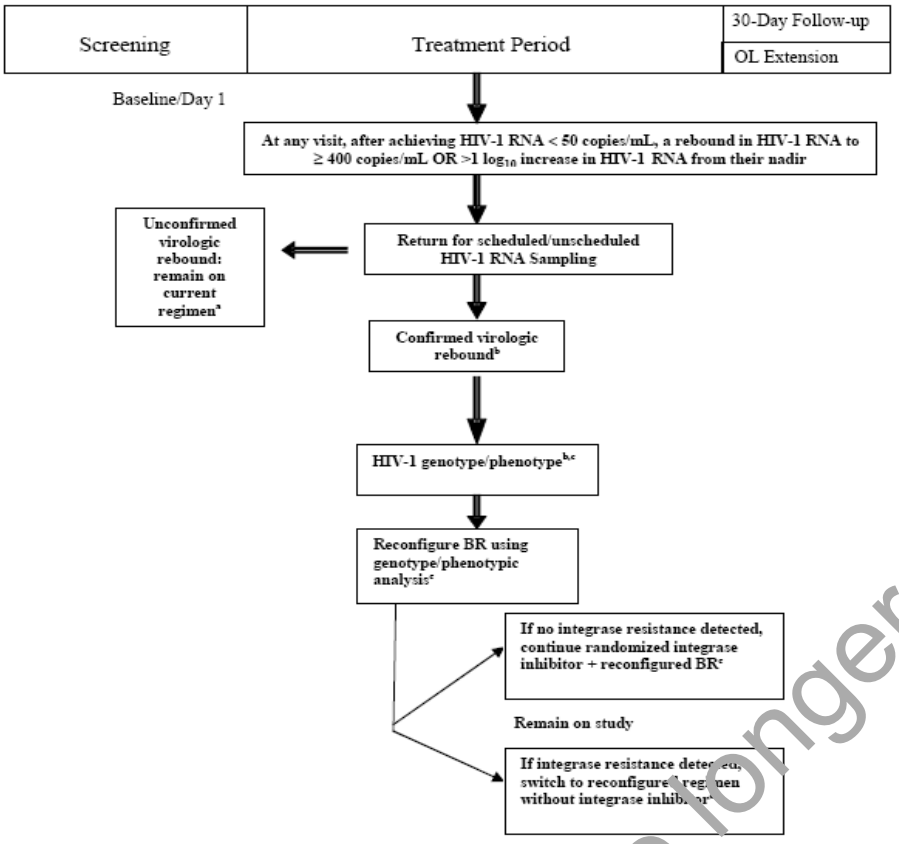
In case of suboptimal virological response (< 1 log10 reduction and ≥ 50 copies/mL at Week 8) subjects were managed according to the following algorithm, which allowed continuation of the assigned integrase inhibitor with a revised OBR if no integrase resistance was detected.

Figure 7. GS-US-183-0145: Suboptimal Virologic Response Schema-Blinded Phase



In case of virological rebound (drop to < 50 copies/mL followed by confirmed rebound to ≥ 400 copies/mL or > 1 log10 increase in HIV-1 RNA from nadir) subjects were managed according to the following algorithm, which allowed continuation of the assigned integrase inhibitor with a revised OBR if no integrase resistance was detected.

Figure 8. GS-US-183-0145: Virologic Rebound Schema – Blinded Phase



Objectives

The primary objective was to assess non-inferiority of a regimen containing RTV-boosted EVG versus RAL, each administered with OBR in HIV-1 infected, ARV-experienced adult subjects based on percentages achieving and maintaining HIV-1 RNA < 50 copies/mL through Week 48.

Outcomes/endpoints

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48, as defined by the TLOVR (time to loss of virologic response) algorithm.

Secondary efficacy endpoints were as follows:

- The percentage of subjects with HIV-1 RNA < 50 copies/mL and < 400 copies/mL at Weeks 48 and 96, as defined by the snapshot analysis algorithm
- The achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Week 96, as defined by TLOVR

  The achievement and maintenance of confirmed HIV-1 RNA < 400 copies/mL through Weeks 48 and 96, as defined by TLOVR
- The time to pure virologic failure (PVF) with HIV-1 RNA cut-off at 50 copies/mL up to Weeks 48 and 96
- The time to PVF with HIV-1 RNA cut-off at 400 copies/mL up to Weeks 48 and 96
- The change from baseline in log10 HIV-1 RNA (copies/mL) at Weeks 48 and 96

- The change from baseline in CD4 cell count at Weeks 48 and 96

Sample size

A sample size of 700 subjects was planned to provide at least 85% power to establish non-inferiority of EVG vs. RAL for Week 48 virological response rates (< 50 copies/mL). The pre-defined non-inferiority margin was -10%, assuming both treatments would give a response rate of 0.74. All efficacy analyses were stratified by baseline HIV-1 RNA level (≤/> 100,000 copies/mL) and class of the second agent (NRTI vs. other classes).

Randomisation

Randomisation was by IVRS or IWRS in a 1:1 ratio and was stratified by:

- Geographic areas US and Puerto Rico vs. Others (Australia, Canada, Europe and Mexico)
- Screening HIV-1 RNA level (≤ 100,000 copies/mL vs. > 100,000 copies/mL)
- Class of the second agent in the BR (NRTI vs. other classes)

Blinding (masking)

Blinding was preserved during the conduct of the study and access to unblinded data was limited to designated parties. The IDMC reviewed progress, efficacy and safety throughout study conduct but there were no formal stopping rules applied. Analyses of Week 12 and Week 48 data were conducted and the IDMC recommended that the study should continue with extension of the double-blind period to 96 weeks, as requested by the FDA.

Statistical methods

The Intent-to-Treat Analysis Set comprised all treated subjects except for site 4390 (see section on Conduct of the study). This was the primary analysis set for efficacy analyses. The Per Protocol Analysis Set comprised all ITT subjects with no major protocol violation. The PP analysis set was used for analyses of virological outcomes at week 48 (at < 400 and < 50 copies/mL) in the FDA TLOVR and snapshot algorithms.

The non-inferiority evaluation of proportions that achieved HIV-1 RNA < 50 copies/mL at Week 48 (FDA-defined TLOVR) was the pre-specified primary comparison. The primary analysis was initially conducted using the interim Week 48 data but was re-evaluated using the interim Week 96 data.

TLOVR was analysed using the Kaplan-Meier method, stratified by baseline HIV-1 RNA level (≤100,000 copies/mL vs >100,000 copies/mL) and the class of the second agent (NRTI vs other classes).

The virological responses at the < 50 and < 400 copies/mL levels were analysed applying the Missing = Failure (M = F) and Missing = Excluded (M = E) methods.

Subjects who met the following criteria were classified as pure virological responders (PVRs):

- Had achieved confirmed suppression (< 50 copies/mL) on or prior to the Week 48 visit
- Did not have a confirmed rebound (≥ 50 copies/mL) after a confirmed suppression

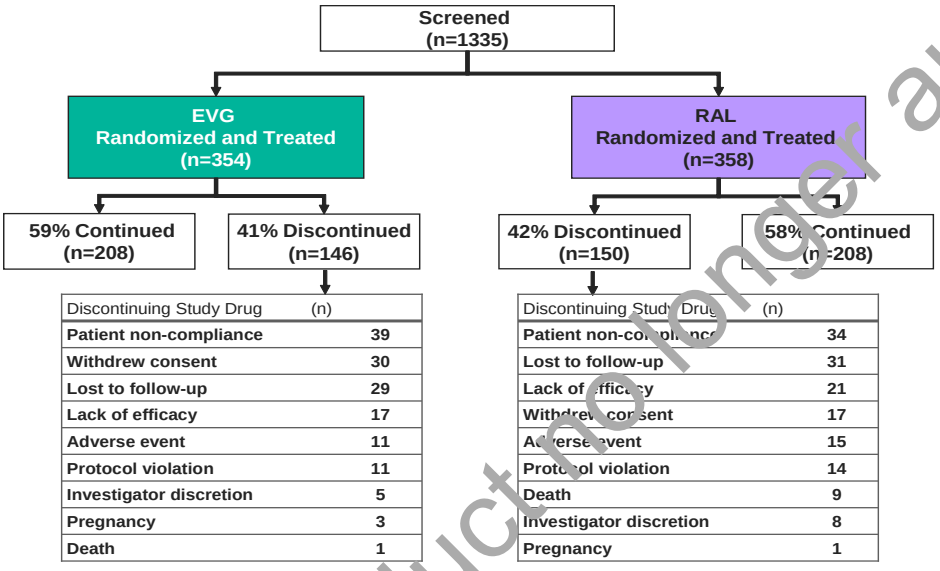
Subjects who did not achieve a PVF were assumed to have failed on Day 1. The relationship between PVF and discontinuation of study drug (DC) by Week 48 and 96 was investigated by classifying subjects according to PVR, PVF or DC alone or PVF + DC. Time to PVF was also analysed.

Results

Participant flow

The interim Week 96 CSR includes all CRF data captured up to 31 October 2011 when the last subject completed 96 weeks of assigned study therapy and all laboratory data up to 1 December 2011.

Figure 9. Subject disposition through week 96 in study 183-0145



Discontinuing Study Drug	(n)
Patient non-compliance	39
Withdrew consent	30
Lost to follow-up	29
Lack of efficacy	17
Adverse event	11
Protocol violation	11
Investigator discretion	5
Pregnancy	3
Death	1

Discontinuing Study Drug	(n)
Patient non-compliance	34
Lost to follow-up	31
Lack of efficacy	21
Withdrew consent	17
Adverse event	15
Protocol violation	14
Death	9
Investigator discretion	8
Pregnancy	1

Recruitment

The study enrolled subjects at 161 study sites including 86 in the US and 49 in the EU. Up to the data cut-off more than 40% of subjects in each treatment group had discontinued, the most common reasons being non-adherence to the protocol and LTFU.

Conduct of the study

After study initiation the protocol (dated 29 April 2008) was amended 5 times. The most important changes included:

- Amendment 1, dated 30 July 2008. Added Asia as a region for sites and Mexico as a participating country in North America. Added the criteria regarding the M184V/I RT mutation.
- Amendment 2, dated 18 February 2009. Unified GS-US-183-0144 and GS-US-183-0145. Added several secondary efficacy endpoints.
- Amendment 3, dated 05 August 2009. Changed the HIV-1 RNA reference assay from COBAS TaqMan 1.0 to the Amplicor Assay.
- Amendment 4, dated 06 July 2010. Added the optional 144-week open-label extension.

- Amendment 5, dated 04 February 2011. At the request from the FDA, the blinded part of the study was extended to 96 weeks.

There were 533 important protocol deviations reported for 320 subjects. Most (203/320) had a single important deviation and the majority concerned missing 2 or more consecutive days of study drug.

Subjects enrolled at site 4390 (3 EVG and 7 RAL) were excluded from the ITT and the PP efficacy analyses due to important protocol deviations identified at that site by the Sponsor.

In the original CSR subjects who discontinued study drug due to lack of efficacy were incorrectly classified within the TLOVR outcomes under 'Drug Discontinuation due to Other Reasons' instead of under 'Virologic Failure.' The Sponsor corrected this with an amendment to the CSR (dated 30 January 2012). The changes in efficacy results are shown in tables on treatment outcomes by TLOVR analysis.

Baseline data

The majority of subjects were white males with median age 45 years and homosexual. The following pertains to the ITT population in the Week 96 dataset.

Table 32. Subject demographics in study GS-US-183-0145 (ITT Analysis Set)

Characteristic	EVG (N=351)	RAL (N=351)	Total (N=702)	p-value[a]
Age (Years)				
N	351	351	70	0.036
Mean (SD)	44 (9.0)	45 (9.2)	5 (1)	
Median	44	45	4	
Q1, Q3	38, 50	40, 51	39, 50	
Min, Max	20, 78	19, 74	19, 78	
Sex				
Male	292 (83.2%)	284 (80.9%)	576 (82.1%)	0.43
Female	59 (16.8%)	67 (19.1%)	126 (17.9%)	
Race				
White	211 (60.1%)	226 (64.4%)	437 (62.3%)	0.61
Black or African American	125 (35.6%)	113 (32.2%)	238 (33.9%)	
Asian	9 (2.6%)	5 (1.4%)	14 (2.0%)	
American Indian or Alaska Native	2 (0.6%)	3 (0.9%)	5 (0.7%)	
Native Hawaiian or Other Pacific Islander	1 (0.3%)	0	1 (0.1%)	
Other	3 (0.9%)	4 (1.1%)	7 (1.0%)	
Ethnicity				
Hispanic or Latino	79 (22.5%)	73 (20.8%)	152 (21.7%)	0.86
Not Hispanic or Latino	271 (77.2%)	277 (78.9%)	548 (78.1%)	
Not Reported	1 (0.3%)	1 (0.3%)	2 (0.3%)	

About one quarter had > 100,000 copies/ml at baseline with mean/median ~ 4.3 log10 copies/ml.

Most subjects had HIV-1 subtype B (94%) while 22 had subtype A, 8 had G and 6 had C. The remaining 7 had other subtypes or recombinant forms of subtype B.

Baseline mutational resistance data are presented in the section on *Resistance Analysis*.

Co-infection with HBV occurred in 4.2% but 14% were co-infected with HCV.

In addition to EVG or RAL > 80% had at least two ARVs predicted to be active (GSS and/or PSS) against their virus in their initial OBR (taken for at least 28 days after baseline), assuming sensitivity for subjects previously naïve to maraviroc or T-20.

Table 33. Baseline characteristics in study GS-US-183-0145 (ITT Analysis Set)

Characteristic	EVG (N=351)	RAL (N=351)	Total (N=702)	p-value[a]
Baseline CD4 (cells/mm³)				
N	340	341	681	0.83
Mean (SD)	259.3 (204.44)	264.0 (207.92)	261.7 (206.05)	
Median	227.0	215.0	222.0	
Q1, Q3	100.0, 371.0	111.0, 381.0	106.0, 379.0	
Min, Max	2.0, 1374.0	1.0, 1497.0	1.0, 1497.0	
HIV Status				
Asymptomatic	170 (48.4%)	168 (47.9%)	338 (48.1%)	0.99
Symptomatic HIV Infections	51 (14.5%)	54 (15.4%)	105 (15.0%)	
AIDS	126 (35.9%)	125 (35.6%)	251 (35.8%)	
Unknown	4 (1.1%)	4 (1.1%)	8 (1.1%)	
HIV Risk Factors[b]				
Heterosexual Sex	126 (33.7%)	137 (35.8%)	263 (34.7%)	
Homosexual Sex	208 (55.6%)	182 (47.5%)	390 (51.5%)	
IV Drug Use	23 (6.1%)	26 (6.8%)	49 (6.5%)	
Vertical Transmission	0	2 (0.5%)	2 (0.3%)	
Other	5 (1.3%)	6 (1.6%)	11 (1.5%)	
Transfusion	4 (1.1%)	14 (3.7%)	18 (2.4%)	
Unknown	8 (2.1%)	16 (4.2%)	24 (3.2%)	
Baseline Genotypic Sensitivity Score Category[c]				
0	4 (1.1%)	1 (0.3%)	5 (0.7%)	0.6
1	50 (14.3%)	53 (15.1%)	103 (14.7%)	
2	284 (81.1%)	291 (82.9%)	575 (82.0%)	
3	12 (3.4%)	6 (1.7%)	18 (2.6%)	
Baseline Phenotypic Sensitivity Score Category[c]				
1	5 (1.4%)	4 (1.1%)	9 (1.3%)	0.41
1.5	23 (6.6%)	28 (8.0%)	5[illegible] ([illegible]%)	
2	306 (87.4%)	306 (87.4%)	6[illegible] (87.4%)	
2.5	2 (0.6%)	1 (0.3%)	[illegible] (0.4%)	
3	14 (4.0%)	10 (2.9%)	[illegible] (3.4%)	
3.5	0	1 (0.3%)	1 (0.1%)	

The majority of viruses had resistance to 2 or 3 classes of ARVs (436/702) and the majority of subjects had taken agents in 2 or 3 ARV classes in the 6 months prior to screening (649/702).

Table 34. GS-US-183-0145: Number of Subjects by Baseline Resistance and by Number of ARV Drug Classes Within 6 Months Prior to Screening (ITT Analysis Set)

ARV classes of agent received within 6 months prior to screening[b]	Baseline Resistance to Any of the 3 ARV Classes (NRTI, NNRTI, and PI)[a]				
	None (N = 120)	One (N = 146)	Two (N = 304)	Three (N = 132)	Total (N = 702)
None	[illegible]	0	1	0	1
One	[illegible]	17	21	9	52
Two	112	125	275	112	624
Three	3	4	7	11	25

a Four mutually exclusive groups of subjects were defined based on their baseline resistance: 1) Subjects had no resistance to all three classes of ARVs (NRTI, NNRTI, and PI); 2) Subjects had resistance to one of the three classes of ARVs; 3) Subjects had resistance to two of the three classes of ARVs; 4) Subjects had resistance to all three classes of ARVs.

b Four mutually exclusive groups of subjects were defined based on their ARVs within 6 months prior to screening: 1) Subjects had not taken any of the three classes of ARVs (NRTI, NNRTI, and PI); 2) Subjects had taken only one of the three classes of ARVs; 3) Subjects had taken only two of the three classes of ARVs; 4) Subjects had taken all three classes of ARVs.

The most commonly used PI was DRV while ~5% or less used either FPV or TPV and 69% used TDF.

Table 35. Background regimen in study GS-US-183-0145

Characteristic	EVG (N=351)	RAL (N=351)	Total (N=702)	p-value[a]

Type of PI in Background Regimen (Excluding Ritonavir)[c, d]				
Darunavir	202 (57.5%)	207 (58.8%)	409 (58.2%)	
Kaletra	68 (19.4%)	68 (19.3%)	136 (19.3%)	
Atazanavir	61 (17.4%)	51 (14.5%)	112 (15.9%)	
Fosamprenavir	14 (4.0%)	19 (5.4%)	33 (4.7%)	
Tipranavir	6 (1.7%)	7 (2.0%)	13 (1.8%)	
Type of NRTI in Background Regimen[c]				
Tenofovir DF	163 (46.0%)	171 (47.8%)	334 (46.9%)	
Truvada	91 (25.7%)	67 (18.7%)	158 (22.2%)	
Lamivudine	11 (3.1%)	13 (3.6%)	24 (3.4%)	
Abacavir	5 (1.4%)	12 (3.4%)	17 (2.4%)	
Epzicom	4 (1.1%)	8 (2.2%)	12 (1.7%)	
Combivir	6 (1.7%)	5 (1.4%)	11 (1.5%)	
Zidovudine	3 (0.8%)	6 (1.7%)	9 (1.3%)	
Didanosine	1 (0.3%)	5 (1.4%)	6 (0.8%)	
Emtricitabine	2 (0.6%)	2 (0.6%)	4 (0.6%)	

a P-values are estimated using a two-sided Cochran-Mantel-Haenszel test (categorical data) and the Wilcoxon rank sum test (continuous data).

b Subject may select more than one HIV-1 risk factors; therefore, percentages may add to more than 100.

c Baseline (BL) background regimen (BR) is defined as antiretrovirals (other than study drug) taken on or before Study Day 28 from BL for a minimum of 4 wks on/after BL. The GSS and PSS are calculated by summing up drug susceptibility values (1=sensitive; 0.5=partially sensitive; 0=resistance or reduced susceptibility) on all drugs in the BR. For subjects naive to T-20 (or maraviroc), a score of 1 is assigned for T-20 (or maraviroc).

d All subjects have one PI identified in the BR except Subject 0983-3150. This subject took darunavir on Days 1-4 and fosamprenavir on Days 6-11.

About 80% of subjects who received DRV/RTV were dosed twice daily. Small numbers in the ITT analysis set received LPV/RTV or FPV/RTV once daily.

Numbers analysed

About 75% of the Week 96 dataset were eligible for the PP population analysis.

Table 36. GS-US-183-0145: Analysis Sets (All Randomized Set, Week 96 Dataset)

Analysis Set[a]	EVG (N=361)	RAL (N=363)	Total (N=724)
Subjects in the Safety Analysis Set[b]	354 (98.1%)	358 (98.6%)	712 (98.3%)
Subjects in the ITT Analysis Set[c]	351 (97.2%)	351 (96.7%)	702 (97.0%)
Subjects in the Per Protocol Analysis Set[d]	270 (74.8%)	268 (73.8%)	538 (74.3%)
Subjects in the GS-9137 PK Analysis Set	341 (94.5%)	0	341 (47.1%)
Subjects in the GS-9137 PK Substudy Analysis Set	31 (8.6%)	0	31 (4.3%)
Subjects in the GS-9200 PK Substudy Analysis Set	31 (8.6%)	0	31 (4.3%)
Subjects in the GS-9202 PK Substudy Analysis Set[e]	0	0	0
Subjects in the RTV PK Substudy Analysis Set	30 (8.3%)	0	30 (4.1%)
Subjects in the PK/PD Analysis Set	269 (74.5%)	0	269 (37.2%)

a Denominator for percentages is the number of subjects in the all randomized set within the treatment group.
b Safety analysis set includes subjects randomized and treated with at least one dose of study drug.
c Intent-to-treat (ITT) analysis set includes subjects randomized and treated with study drug and not enrolled at Site 4390. Note that 10 subjects from Site 4390 were excluded from ITT analysis set due to critical and multiple protocol violations.
d Other protocol exclusion criteria are only defined for subjects in the ITT analysis set; a subject can meet more than one exclusion criteria.
e All GS-9202 concentrations were BLQ and none of PK parameters were estimable. This leads to 0 subject qualified for GS-9202 PK substudy analysis set.

While 72% of all subjects had an adherence rate ≥ 90% the rates were 78.3% for EVG and 65.3% for RAL although percentages with >80 to < 90% adherence were 10.7% and 20.7%, respectively, suggesting broadly comparable proportions with adherence < 80%.

Outcomes and estimation

The results of the primary analysis of outcomes at Week 48 were identical when using the Week 48 and the Week 96 datasets (ITT, using TLOVR algorithm) and demonstrated non-inferiority for EVG vs. RAL (95% CI -6%, 8.2%). While the rebound rate was lower in the EVG group the rate for primary failure (never suppressed) was slightly higher for EVG vs. RAL.

Table 37. GS-US-183-0145: Treatment Outcomes at Week 48 for HIV-1 RNA Cut-off at 50 copies/mL, TLOVR Analysis (ITT Analysis Set, Week 96 Dataset).

Treatment Outcome	EVG (N=351)	RAL (N=351)	EVG vs. RAL	
			p-value[a]	Prop Diff (95% CI)[b]
Responder[c]	207 (59.0%)	203 (57.8%)	0.76	1.1% (-6.0% to 8.2%)
Virologic Failure[d]	~~70 (19.9%)~~ **78 (22.2%)**	~~77 (21.9%)~~ **81 (23.1%)**		
Rebound	40 (11.4%)	56 (16.0%)		
Never Suppressed through Week 48	27 (7.7%)	18 (5.1%)		
Switched Background Regimen	3 (0.9%)	3 (0.9%)		
Drug Discontinuation due to Lack of Efficacy	**8 (2.3%)**	**4 (1.1%)**		
Death[d]	2 (0.6%)	7 (2.0%)		
Drug Discontinuation due to AEs[d]	6 (1.7%)	12 (3.4%)		
Drug Discontinuation due to Other Reasons[d]	~~66 (18.8%)~~ **58 (16.5%)**	~~52 (14.8%)~~ **48 (13.7%)**		
Investigator's Discretion	1 (0.3%)	2 (0.6%)		
~~Lack of Efficacy~~	~~8 (2.3%)~~	~~(1.1%)~~		
Lost to Follow-Up	17 (4.8%)	19 (5.4%)		
Pregnancy	2 (0.6%)	0		
Protocol Violation	6 (1.7%)	6 (1.7%)		
Subject Non-Compliance	18 (5.1%)	13 (3.7%)		
Withdrew Consent	4 (1.0%)	8 (2.3%)		

a The p-value is estimated from a 2-sided Cochran-Mantel-Haenszel test adjusted by baseline HIV-1 RNA level and the class of second agent. This is the superiority p-value.

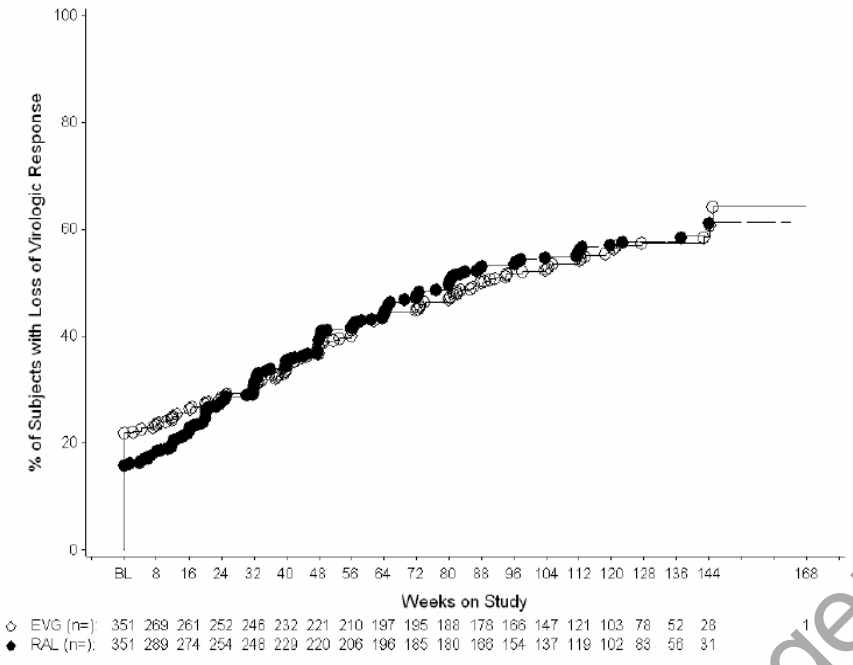
b The difference in proportions and its 95% CIs between randomized treatment groups are based on stratum-adjusted [by baseline HIV-1 RNA level (≤ 100,000 or > 100,000 copies/mL) and the class of second agent (NRTI or other classes)] Mantel-Haenszel (MH) proportions and normal approximation.

c Responders include subjects who achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48.

d If there is more than one event at the earliest time of failure, the order for classification is death, virologic failure, discontinuation due to adverse event and discontinuation due to other reasons.

The ITT TLOVR analysis at the cut-off < 50 copies/mL showed that the KM curves separated early. This reflected the subjects that never achieved < 50 copies/mL who were assumed to have failed at Day 1 in the analysis. In contrast, subjects with rebound were counted as failing at the time when this occurred. Total percentages with LOVR were comparable with Week 96 KM estimates of 52% for EVG and 55% for RAL. Median TLOVR was 617 days vs. 562 days (p = 0.86), respectively.

Figure 10. GS-US-183-0145: Time to Loss of Virologic Response with HIV-1 RNA Cut-off at 50 Copies/mL (ITT Analysis Set, Week 96 Dataset)



Event time for TLOVR responders was censored at the last HIV-1 RNA collection date. Event time for subjects who never achieved a confirmed response was 1 (ie, assumed to have failed on Day 1). Event time for the remaining subjects was the earliest time to death, discontinuation of study drug, first switch of background regimen, first occurrence of confirmed rebound (HIV-1 RNA ≥ 50 copies/mL), or nonconfirmed rebound followed by premature discontinuation of study drug.

The number of subjects listed below the x-axis is the number of subjects at risk per specified time point.

Non-inferiority for EVG vs. RAL at Week 48 for percentages achieving < 50 copies/mL was also demonstrated in the PP TLOVR analysis using the Week 96 dataset. Actual success rates were higher vs. the ITT population but the difference between treatments and the 95% CI were almost identical.

Table 38. Treatment outcomes at week 48 for HIV-1 RNA cutoff at 50 copies/mL, TLOVR Analysis PP Analysis Set

	EVG (N=270)	RAL (N=268)	EVG vs. RAL p-value	EVG vs. RAL Prop Diff (95% CI)
Responder	201 (74.4%)	197 (73.5%)	0.77	1.1% (-6.2% to 8.4%)
Virologic Failure	58 (21.5%)	65 (24.3%)		
Rebound	28 (10.4%)	47 (17.5%)		
Never Suppressed through Week 48	27 (10.0%)	17 (6.3%)		
Switched Background Regimen	3 (1.1%)	1 (0.4%)		
Drug Discontinuation due to AEs	0	1 (0.4%)		
Drug Discontinuation due to Other Reasons	11 (4.1%)	5 (1.9%)		
LACK OF EFFICACY	8 (3.0%)	4 (1.5%)		
LOST TO FOLLOW-UP	0	1 (0.4%)		
SUBJECT NON-COMPLIANCE	2 (0.7%)	0		
WITHDREW CONSENT	1 (0.4%)	0		

The percentages maintaining < 50 copies/mL at Week 96 (TLOVR analysis, ITT) were comparable between treatments. Virological failure was reported less frequently in the EVG group due to the lower rebound rate.

Table 39. GS-US-183-0145: Treatment Outcomes at Week 96 for HIV-1 RNA Cut-off at 50 copies/mL, TLOVR Analysis (ITT Analysis Set, Week 96 Dataset).

Treatment Outcome at Week 96	EVG (N=351)	RAL (N=351)	EVG vs. RAL p-value[a]	EVG vs. RAL Prop Diff (95% CI)[b]
Responder[c]	167 (47.6%)	158 (45.0%)	0.47	2.6% (-4.6% to 9.9%)
Virologic Failure[d]	~~80 (22.8%)~~ **93 (26.5%)**	~~96 (27.4%)~~ **103 (29.3%)**		
Rebound	69 (19.7%)	86 (24.5%)		
Never Suppressed through Week 96	8 (2.3%)	6 (1.7%)		
Switched Background Regimen	3 (0.9%)	4 (1.1%)		
Drug Discontinuation due to Lack of Efficacy	**13 (3.7%)**	**7 (2.0%)**		
Death[d]	2 (0.6%)	9 (2.6%)		
Drug Discontinuation due to AEs[d]	9 (2.6%)	15 (4.3%)		
Drug Discontinuation due to Other Reasons[d]	~~93 (26.5%)~~ **80 (22.8%)**	~~73 (20.8%)~~ **66 (18.8%)**		
Investigator's Discretion	4 (1.1%)	3 (0.9%)		
~~Lack of Efficacy~~	~~13 (3.7%)~~	~~7 (2.0%)~~		
Lost to Follow-Up	19 (5.4%)	24 (6.8%)		
Pregnancy	2 (0.6%)	0		
Protocol Violation	8 (2.3%)	7 (2.0%)		
Subject Non-Compliance	26 (7.4%)	20 (5.7%)		
Withdrew Consent	21 (6.0%)	12 (3.4%)		

Responses at the < 400 copies/ml level at Week 48 were identical using either the Week 48 or Week 96 datasets (TLOVR; ITT) and reflected the corresponding analyses based on the cut-off of < 50 copies/mL.

At Week 96 43% EVG and 44% RAL subjects had loss of virological response at the 400 copies/mL level with median TLOVR of 1014 vs. 1009 days, respectively. Percentages maintaining < 400 copies/mL at Week 96 were 57.0% EVG and 56.1% RAL (stratum-adjusted difference 0.9% and 95% CI −6.4% to 8.2%). In the NC analysis percentages maintaining < 400 copies/mL at Week 48 were 85.6% EVG and 85.4% RAL with a stratum-adjusted difference of 0.2% and 95% CI −5.8% to 6.2%.

In addition to TLOVR analysis the results were assessed also with snapshot analysis.

Using the Week 96 dataset, the percentages with < 50 copies/mL at Week 48 (snapshot analysis, ITT) were identical to those using the Week 48 dataset and comparable between treatments (EVG 59.8% vs. RAL 57.5%; stratum-adjusted difference 2.2%, 95% CI −5.0% to 9.3%).

Table 40. GS-US-183-0145: Snapshot Analysis of Subjects with HIV-1 RNA <50 copies/mL at Week 48 (ITT Analysis Set, Week 96 Dataset).

Virologic Response at Week 48	EVG (N=351)	RAL (N=351)	EVG vs. RAL	
			p-value[a]	Prop Diff (95% CI)[b]
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	210 (59.8%)	202 (57.5%)	0.55	2.2% (-5.0% to 9.3%)
Virologic Failure at Week 48	115 (32.8%)	112 (31.9%)		
HIV-1 RNA >= 50 copies/mL	56 (16.0%)	66 (18.8%)		
Discontinued Study Drug Due to Lack of Efficacy	9 (2.6%)	7 (2.0%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[c]	49 (14.0%)	37 (10.5%)		
HIV-1 RNA >= 50 copies/mL at Background Regimen Switch and HIV-1 RNA < 50 copies/mL at Week 48	1 (0.3%)	2 (0.6%)		
No Virologic Data in Week 48 Window	26 (7.4%)	37 (10.5%)		
Discontinued Study Drug Due to AE or Death	8 (2.3%)	18 (5.1%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	14 (4.0%)	17 (4.8%)		
Missing Data during Window but on Study Drug	4 (1.1%)	2 (0.6%)		

Comparability between treatments was maintained in the ITT snapshot analysis for percentages < 50 copies/mL at Week 96.

Table 41. GS-US-183-0145: Snapshot Analysis of Subjects with HIV-1 RNA <50 copies/mL at Week 96 (ITT Analysis Set, Week 96 Dataset)

Virologic Response at Week 96	EVG (N=351)	RAL (N=351)	EVG vs. RAL	
			p-value[a]	Prop Diff (95% CI)[b]
Virologic Success at Week 96				
HIV-1 RNA < 50 copies/mL	184 (52.4%)	186 (53.0%)	0.88	-0.5% (-7.9% to 6.8%)
Virologic Failure at Week 96	125 (35.6%)	109 (31.1%)		
HIV-1 RNA >= 50 copies/mL	40 (11.4%)	31 (8.8%)		
Discontinued Study Drug Due to Lack of Efficacy	15 (4.3%)	19 (5.4%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[c]	67 (19.1%)	57 (16.2%)		
HIV-1 RNA >= 50 copies/mL at Background Regimen Switch and HIV-1 RNA < 50 copies/mL at Week 96	3 (0.9%)	2 (0.6%)		
No Virologic Data in Week 96 Window	42 (12.0%)	56 (16.0%)		
Discontinued Study Drug Due to AE or Death	10 (2.8%)	24 (6.8%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c]	28 (8.0%)	30 (8.5%)		
Missing Data during Window but on Study Drug	4 (1.1%)	2 (0.6%)		

Using the Week 96 dataset and the PP analysis set the percentages with < 50 copies/mL at Week 48 (snapshot analysis) were 76.3% EVG and 72.8% RAL (difference 3.7%, 95% CI −3.6% to 10.9%). The corresponding analyses for percentages at < 400 copies/mL applying the snapshot analysis approach at Week 48 and Week 96 and in the ITT and PP populations gave very comparable findings to those reported above for < 50 copies/mL.

The KM curves for time to PVF using the cut-off 50 copies/mL separated early for the same reasons as in the primary analysis. At Week 96, the KM estimates for the percentages with PVF were 45% for the EVG group and 46% for the RAL group. The median time to PVF was 1014 days in the EVG group and 961 days in the RAL group (p = 0.99). The KM estimates for the time to PVF using the cut-off 400 copies/mL at Week 96 were comparable between treatments. At Week 96 the KM estimates for the percentages of subjects with PVF were 32% for the EVG group and 31% for the RAL group.

Comparable percentages in each treatment group:

- Were classified as PVR (Week 48 EVG 59.3% vs. RAL 58.1%; Week 96 47.9% vs. 45.3%).
- Had PVF alone (Week 48 EVG 16.5% vs. RAL 17.9%; Week 96 15.7% vs. 17.1%).
- Were considered failures due to DC alone (Week 48 EVG 4.6% vs. RAL 6.0%; Week 96 [illegible]% vs. 9.4%).
- Were considered failures due to a combination of PVF and DC (Week 48 EVG 19.[illegible]% vs. RAL 17.9%; Week 96 28.2% in each group).

The percentage of subjects with HIV-1 RNA < 50 copies/mL was comparable between treatment groups at each time point using M = F or M = E methods and the ITT analysis set. Similar findings resulted from corresponding analyses at the < 400 copies/mL cut-off.

Table 42. GS-US-183-0145: Subjects with HIV-1 RNA <50 copies/mL by Study Visit (Missing=Failure and Missing=Excluded) (ITT Analysis Set, Week 96 Dataset)

	EVG (N=351)	RAL (N=351)	EVG vs RAL Proportion Difference (95% CI)[a]
Missing = Failure[b]			
HIV-1 RNA < 50 at Baseline	5/351 (1.4%)	6/351 (1.7%)	-0.3% (-2.4% to 1.9%)
95% CI[c]	0.5% to 3.3%	0.6% to 3.7%	
HIV-1 RNA < 50 at Week 48	214/351 (61.0%)	213/351 (60.7%)	0.2% (-6.9% to 7.3%)
95% CI[c]	55.6% to 66.1%	55.4% to 65.8%	
HIV-1 RNA < 50 at Week 96	188/351 (53.[illegible]%)	198/351 (56.4%)	-2.9% (-10.2% to 4.4%)
95% CI[c]	48.[illegible]% to [illegible].9%	51.0% to 61.7%	
Missing = Excluded[d]			
HIV-1 RNA < 50 at Baseline	5/351 (1.4%)	6/351 (1.7%)	-0.3% (-2.4% to 1.9%)
95% CI[c]	0.5% to 3.3%	0.6% to 3.7%	
HIV-1 RNA < 50 at Week [illegible]	214/280 (76.4%)	213/291 (73.2%)	3.2% (-3.8% to 10.2%)
95% CI[c]	71.0% to 81.3%	67.7% to 78.2%	
HIV-1 RNA < [illegible] at Week 96	188/238 (79.0%)	198/238 (83.2%)	-4.2% (-11.3% to 2.9%)
95% CI[c]	73.3% to 84.0%	77.8% to 87.7%	

The change from baseline in plasma HIV-1 RNA levels was highly comparable between treatments. At Week 96, the mean (SD) decreases from baseline in HIV-1 RNA were −2.26 (1.078) log10 copies/mL in the EVG group and −2.31 (1.068) log10 copies/mL in the RAL group. The difference in least-squares means (LSM) was 0.05, and the 95% CI was −0.12 to 0.22.

Mean increases from baseline in CD4 cell counts were comparable between treatments at all time points. At Week 96 the mean increases from baseline in CD4 cell count were 205 cells/μL in the EVG group and 198 cells/μL in the RAL group. The difference in LSM was 7 (95% CI: -25, 39).

Subgroup analyses

Results according to class resistance at baseline: as only 53 of 702 subjects (7.5%) had received agents from none (1) or 1 ARV class (52) in the 6 months prior to screening, further analyses of efficacy by the various combinations of baseline resistance and treatment history were not considered meaningful.

The virological success rates at Week 48 were similar in the EVG and RAL treatment groups in each subgroup shown in the table.

Table 43. GS-US-183-0145: Virological success at week 48 by Baseline Resistance by Drug Class (Snapshot Analysis; ITT Analysis Set), n/N (%)

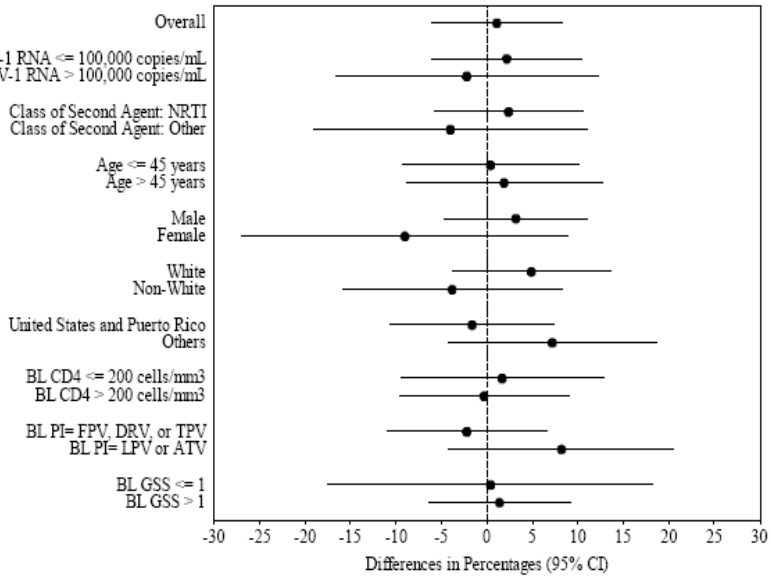
			EVG vs. RAL	
Baseline Resistance to ARV Classes	**EVG (N=351)**	**RAL (N=351)**	**p-value[a]**	**Difference in Percentages (95% CI)[b]**
None	31/63 (49.2%)	33/57 (57.9%)	0.48	-6.0% (-23.1% to 11.1%)
One	29/65 (44.6%)	32/81 (39.5%)	0.44	6.3% (-9.7% to 22.2%)
Two	111/163 (68.1%)	85/141 (60.3%)	0.24	6.5% (-4.3% to 17.2%)
Three	39/60 (65.0%)	52/72 (72.2%)	0.42	-6.5% (-22.7% to 9.6%)

a The p-value is estimated from a Cochran-Mantel-Haenszel (CMH) test for superiority.
b The difference in proportions and its 95% confidence intervals (CIs) between randomized treatment groups are based on stratum-adjusted (by baseline HIV-1 RNA level [≤ 100,000 or > 100,000 copies/mL]) Mantel Haenszel (MH) proportions and normal approximation.

Virological success rates were slightly higher in both treatment groups for those with resistance to 2 or 3 classes at baseline compared with no resistance or resistance to 1 class. These differences were mainly due to the rates of study drug discontinuation due to other reasons (noncompliance, lost to follow-up, withdrew consent, protocol violation, investigator's discretion, and pregnancy). These discontinuation rates for 2 or 3 class resistance were 14.8% in the EVG group (33/223) and 9.9% (21/213) in the RAL group. Rates for 0 or 1 class resistance were 23.4% in the EVG group (30/128) and 23.9% in the RAL group (33/138). It was hypothesised that subjects with more treatment options at baseline (0 to 1 class resistance) may have been less motivated to remain in the study than subjects with few options (2 or 3 class resistance) due to the availability of active agents outside of the study i.e. motivation to remain in the study may have been strongest for the most treatment-experienced patients failing current therapy.

Other subgroup analyses (see summary diagram below for Week 48) revealed generally comparable rates of virological success between treatments. Point estimates mostly favoured the EVG group.

Figure 11. GS-US-183-0145: Forest Plot of Treatment Difference and 95% CI by Subgroup for Virological response at Week 48, TLOVR outcome (ITT Analysis Set).



Relative to the vertical line at 0, differences on the right favor the EVG group and differences on the left favor the RAL group.

While sample sizes in many cases were small and the breadth of the 95% CI should be taken into account, some observations regarding response rates in various subgroups were as follows (Week 48 at < 50 copies/mL using snapshot approach and ITT analysis):

- While higher response rates were observed for those with ≤ 100,000 copies/mL at baseline (EVG 65.5% vs. RAL: 64.4%) vs. > 100,000 copies/mL (43.3% vs. 37.8%) and in those with baseline CD4 > 200 cells/µL (69.8% and 68.1% vs. 47.7% and 46.4%) it was unexpected that higher response rates occurred with baseline GSS ≤ 1 (EVG 75.9% vs. RAL 68.5%) compared to GSS > 1 (57.1% vs. 55.6%).
- Higher response rates were observed for those from outside the US and Puerto Rico (EVG 73.3% vs. RAL 64.2%) vs. those in the US and Puerto Rico (52.8% vs. 53.9%). Both treatments gave slightly lower responses in non-white (50.0% and 54.4%) vs. white subjects (66.4% and 59.3%).
- Among female subjects the response rate was lower in the EVG group (28/59; 47.5% vs. RAL 42/67; 62.7%). However, response rates among male subjects were 62.3% vs. 56.3%, respectively.
- Broadly comparable response rates were observed in subjects > 45 years of age (EVG: 63.3% vs. RAL 60.4%) vs. those aged ≤ 45 years (57.4% vs. 54.9%).
- Broadly comparable response rates occurred in subjects who were not taking an NRTI (EVG 66.2% vs. RAL 63.0%) compared to those taking an NRTI (58.2% vs. 56.1%).

Lower response rates in women were observed also at week 96.

Results according to the EVG dose and the PI used

Responses according to the EVG dose (85 mg or 150 mg) and the PI/r used revealed similar rates of virological success for EVG and RAL within each PI subgroup at Weeks 48 and 96. The 95% CIs for treatment differences in virological success included zero for all PI subgroups and supported similar efficacy of EVG and RAL in combination with a range of PIs.

Table 44. GS-US-183-0145: Virological Success by PI at Weeks 48 and 96 (Snapshot ITT)

HIV-1 RNA < 50 copies/mL, n/N (%)	EVG (N=351)	RAL (N=351)	EVG vs. RAL	
			p-value	Difference in Percentages (95% CI)
Virological Success at Week 48				
Darunavir	126/202 (62.4%)	122/207 (58.9%)	0.48	3.4% (-6.0% to 12.9%)
Lopinavir	39/68 (57.4%)	37/68 (54.4%)	0.73	2.9% (-13.7% to 19.6%)
Atazanavir	34/61 (55.7%)	28/51 (54.9%)	0.93	0.8% (-17.7% to 19.3%)
Fosamprenavir	8/14 (57.1%)	10/18 (55.6%)	0.93	1.6% (-33.0% to 36.2%)
Tipranavir	3/6 (50.0%)	5/7 (71.4%)	0.45	-21.4% (-73.6% to 30.7%)
Virological Success at Week 96				
Darunavir	105/202 (52.0%)	112/207 (54.1%)	0.67	-2.1% (-11.8% to 7.5%)
Lopinavir	36/68 (52.9%)	37/68 (54.4%)	0.86	-1.5% (-18.2% to 15.3%)
Atazanavir	33/61 (54.1%)	23/51 (45.1%)	0.34	9.0% (-9.5% to 27.5%)
Fosamprenavir	7/14 (50.0%)	11/18 (61.1%)	0.54	-11.1% (-45.7% to 23.4%)
Tipranavir	3/6 (50.0%)	3/7 (42.9%)	0.80	7.1% (-47.1% to 61.4%)

In the large subset given twice daily DRV the virological response rates were slightly numerically higher with EVG vs. RAL. In contrast, although once daily DRV+RAL gave response rates at least as good as with twice daily DRV there was a markedly lower response rate with EVG. The difference was ascribed mainly to the effect of rates of study drug discontinuation due to other reasons.

Table 45. GS-US-183-0145: Virological Outcomes by DRV Dosing Frequency at Week 48 (Snapshot Analysis; ITT Analysis Set)

Virological Outcome by DRV Dosing Frequency, Snapshot Analysis	**EVG**		**RAL**	
	DRV QD (N = 37)	**DRV BID (N = 165)**	**DRV QD (N = 41)**	**DRV BID (N = 166)**
Virological Success at Week 48				
HIV-1 RNA < 50 copies/mL	17 (45.9%)	109 (66.1%)	24 (58.5%)	98 (59.0%)
Virological Failure at Week 48	17 (45.9%)	45 (27.3%)	13 (31.7%)	48 (28.9%)
HIV-1 RNA >= 50 copies/mL	4 (10.8%)	24 (14.5%)	9 (22.0%)	31 (18.7%)
Discontinued Study Drug Due to Lack of Efficacy	1 (2.7%)	4 (2.4%)	0	2 (1.2%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[a]	11 (29.7%)	17 (10.3%)	4 (9.8%)	13 (7.8%)

Virological Outcome by DRV Dosing Frequency, Snapshot Analysis	EVG		RAL	
	DRV QD (N = 37)	DRV BID (N = 165)	DRV QD (N = 41)	DRV BID (N = 166)
HIV-1 RNA >= 50 copies/mL at Background Regimen Switch and HIV-1 RNA < 50 copies/mL at Week 48	1 (2.7%)	0	0	2 (1.2%)
No Virological Data in Week 48 Window	3 (8.1%)	11 (6.7%)	4 (9.8%)	20 (12.0%)
Discontinued Study Drug Due to AE or Death	0	5 (3.0%)	2 (4.9%)	12 (7.2%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[a]	3 (8.1%)	5 (3.0%)	2 (4.9%)	6 (3.6%)
Missing Data During Window but on Study Drug	0	1 (0.6%)	0	2 (1.2%)

a Discontinued study drug for other reason includes subjects who discontinued due to subject non-compliance, lost to follow-up, withdrew consent, protocol violation, investigator's discretion, and pregnancy.

A few subjects received EVG (n = 1) or RAL (n = 5) with LPV/r once daily. The subjects received 800/200 mg LPV/r per administration, which is the same total daily dose of LPV as 400/100 mg twice daily.

Resistance analysis

Viruses from all subjects screened were analysed for pre-existing resistance in the protease and RT portion of the pol gene using the PhenoSense GT assay. These pre-study isolates showed that the highest level of genotypic resistance observed was in the NAMs category (70%) and the M184V/I mutation was the most prevalent (57%). PI-R mutations were detected in 32%. Only 17% had no resistance mutations in protease or RT at baseline. Overall, 21% had genotypic resistance to a single class (one of PI, NNRTI or NRTI), 43% to two classes of antiviral agents, 64% to one or two classes and 19% to all three classes. Rates were comparable between treatment groups.

There were 180 subjects included in the Week 96 cumulative analysis population (RAP) (87 EVG and 93 RAL) and integrase genotypic data were available for 86 and 92, respectively. Development of INSTI-R mutations occurred at similarly low rates (EVG 6.6%, RAL 7.4%). The most frequent mutations observed in the EVG group were T66I/A and E92Q/G while the most frequent in the RAL group were N155H and Q148H. The mutations T66I/A, S147G, and Q148R were found exclusively in the EVG group, Y143R/H/C and Q148H were found exclusively in the RAL group while E92Q/G, T97A and N155H were observed in both treatment groups. Although development of integrase resistance at position Q148 was seen in both treatment groups there were distinct amino acid changes (EVG Q148R, RAL Q148H), suggesting that EVG and RAL may bind the HIV-1 integrase enzyme differentially near that residue.

Table 46. GS-US-183-0145: Development of HIV-1 Integrase Resistance Mutations (Week 96 Dataset).

Resistance Development Category	Number of Subjects (% Subjects; % RAP with Data)			
	Year 2 Analysis (Week 48 to Week 96)		Cumulative Analysis (Baseline to Week 96)	
	EVG (n = 351)	RAL (n = 351)	EVG (n = 351)	RAL (n = 351)
Resistance Analysis Population	43 (12.3%)[a]	37 (10.5%)[a]	87 (24.8%)	93 (26.5%)
Subjects with Data	42 (12%)	35 (10%)	86 (24.5%)	92 (26.2%)
Primary INSTI-R Mutations[b]	10 (2.8%; 23.8%)	13 (3.7%; 37.1%)	23 (6.6%; 26.7%)	26 (7.4%; 28.3%)
Other Integrase Mutation(s)	22 (6.3%; 52.4%)	15 (4.3%; 42.9%)	44 (12.5%; 51.2%)	49 (14%; 53.3%)
No Change from Baseline	10 (2.8%; 23.8%)	7 (2%; 20%)	19 (5.4%; 22.1%)	17 (4.8%; 18.5%)
INSTI-R[b] Breakdown:				
T66I/A	2 (0.6%; 4.8%)	0	8 (2.3%; 9.3%)	0
E92Q/G	2 (0.6%; 4.8%)	2 (0.6%; 5.7%)	7 (2%; 8.1%)	3 (0.9%; 3.3%)
T97A	3 (0.9%; 7.1%)	2 (0.6%; 5.7%)	4 (1.1%; 4.7%)	4 (1.1%; 4.3%)
Y143R/H/C	0	0	0	1 (0.3%; 1.1%)
S147G	1 (0.3%; 2.4%)	0	4 (1.1%; 4.7%)	[illegible]
Q148R	1 (0.3%; 2.4%)	0	4 (1.1%; 4.7%)	0
Q148H	0	3 (0.9%; 8.6%)	0	7 (2%; 7.6%)
N155H	2 (0.6%; 4.8%)	9 (2.6%; 25.7%)	5 (1.4%; 5.8%)	16 (4.6%; 17.4%)

a Seventeen subjects in the EVG group and 19 subjects in the RAL group were also analyzed during Year 1.

b Primary integrase strand transfer inhibitor resistance (INSTI-R) mutations are T66[illegible]K, E92Q/G, T97A, Y143R/H/C, S147G, Q148H/K/R, and N155H/S in integrase.

Approximately 75% in the RAP had no primary HIV-1 integrase resistance mutations in their viruses. The baseline PR/RT resistance profiles of these viruses were significantly less likely to have baseline PR/RT resistance mutations compared to those that acquired INSTI-R or non-RAP subjects. The applicant concluded that these data suggest that those with virological failure without INSTI-R in their viruses may have been non-adherent. While those with INSTI-R were reported to have discontinued from study drug primarily due to lack of efficacy those without INSTI-R primarily discontinued due to study adherence related reasons (e.g. lost to follow-up, noncompliance, protocol violation).

In the phenotypic analysis of resistance paired viruses from the 180 RAP subjects and baseline samples from 156 subjects were analysed. Overall, the presence of genotypic resistance correlated well with the presence of phenotypic resistance. Low fold changes were associated with genotypic mutations that were present as mixtures with wild-type.

Table 47. GS-US-183-0145: Integrase Phenotypic Analyses by Week 96

Integrase Development Category[a]	Phenotypic Data	Baseline Fold Change from Control						Postbaseline Fold Change from Control[b]					
	Treatment	EVG		RAL		All		EVG		RAL		All	
	Drug	EVG	RAL	EVG	RAL	EVG	RAL	EVG	RAL	EVG	RAL	EVG	RAL
INSTI-R	N (N with data)	20 (17)	20 (17)	21 (21)	21 (21)	41 (38)	41 (38)	23 (20)	23 (20)	26 (23)	26 (23)	49 (43)	49 (43)
	Mean	1.3	1	1.2	0.9	1.2	0.9	23.7	4.8	75.1	50.5	51.2	29.2
	Range	0.79 - 2.69	0.59 - 1.36	0.85 - 1.62	0.37 - 1.5	0.79 - 2.69	0.37 - 1.5	1.63 - >158	0.6 - 53	1.21 - >207	1.08 - >170	1.21 - >207	0.6 - >170
	N above CO[c]	1				1		14	12[d]	20	21	34	33
Other	N (N with data)	36 (33)	36 (33)	43 (41)	43 (41)	79 (74)	79 (74)	44 (41)	44 (41)	49 (47)	49 (47)	93 (88)	93 (88)
	Mean	1.4	0.9	1.3	0.9	1.3	0.9	1.4	0.9	1.4	0.9	1.4	0.9
	Range	0.84 - 2.58	0.49 - 1.42	0.8 - 3.01	0.54 - 1.32	0.8 - 3.01	0.49 - 1.42	0.82 - 4.09	0.4 - 1.28	0.82 – 5.51	0.48 - 1.31	0.82 - 5.51	0.4 - 1.31
	N above CO[c]	1		1		2		1		1		2	
No Change from Baseline	N (N with data)	17 (16)	17 (16)	17 (17)	17 (17)	34 (33)	34 (33)	19 (19)	19 (19)	17 (17)	17 (17)	36 (36)	36 (36)
	Mean	1.3	1	1.4	1	1.3	1	1.4	1.1	1.5	1	1.4	1
	Range	0.88 - 1.85	0.85 - 1.14	0.97 - 2.06	0.75 - 1.37	0.88 - 2.06	0.75 - 1.37	1.03 - 2.21	0.81 - 1.34	0.76 – 2.17	0.73 - 1.29	0.76 - 2.21	0.73 - 1.34
	N above CO[c]												
All Subjects	N (N with data)	74 (67)	74 (67)	82 (80)	82 (80)	156 (147)	156 (147)	87 (80)	87 (80)	93 (87)	93 (87)	180 (167)	180 (167)
	Mean	1.3	0.9	1.3	0.9	1.3	0.9	7	1.9	7.9	14	14.2	8.2
	Range	0.79 - 2.69	0.49 - 1.42	0.8 - 3.01	0.37 - 1.5	0.79 - 3.01	0.37 - 1.5	0.82 - >158	0.4 - 53	0.76 - >207	0.48 - >170	0.76 - >207	0.4 - >170
	N above CO[c]	2		1		3		15	13	21	21	36	33

a Subjects in the assay failure category (1 subject in each treatment group: Subjects 1708-4105 and 4301-4222) are only represented in the "All Subjects" category.

b For subjects with multiple postbaseline phenotypic data, data from the last visit analyzed were used in the postbaseline calculations except for Subjects 2135-3298 and 0685-4010 because integrase resistance mutations were not present at the last visit analyzed for these 2 subjects.

c In the PhenoSense Integrase assay from Monogram Biosciences, the biological cutoffs (CO) for reduced susceptibility to EVG and RAL are 2.5 and 1.5, respectively.

d One EVG INSTI-R subject (Subject 0031-3253) had phenotypic fold change greater than the cutoff for RAL only.

In the RAL group 21/23 viruses that developed INSTI-R mutations had phenotypic resistance to RAL and 20/23 exhibited cross-resistance to EVG. In the EVG group 14/20 viruses that developed INSTI-R mutations had phenotypic resistance to EVG and 11/20 displayed cross-resistance to both drugs. Four subjects (2 per treatment group) had virus showing EVG fold-change above 2.5 (range 2.58 to 5.51) at baseline or post-baseline in the absence of INSTI resistance mutations. These increases were thought to reflect natural variability within the assay rather than actual phenotypic resistance. Development of NRTI-R, NNRTI-R, and PI-R occurred in 12.2%, 11.6% and 5.8%, respectively. Ten viruses acquired PI-R mutations (5 per group) of which 6/10 had PI-R at baseline.

Table 48. GS-US-183-0145: Development of Protease and RT Genotypic Resistance (Week 96 Dataset).

RT and Protease Resistance Mutations Developing	n (%) of Subjects		
	EVG (n = 87)	RAL (n = 93)	All (n = 180)
Subjects with data	82	90	172
Primary PI-Associated[a]	5 (6.1%)	5 (5.6%)	10 (5.8%)
V32I	0	2 (2.2%)	2 (1.2%)
L33F	0	2 (2.2%)	2 (1.2%)
I47V/A	1 (1.2%)	0	1 (0.6%)
G48V	0	1 (1.1%)	1 (0.6%)
Q58E	1 (1.2%)	0	1 (0.6%)
V82A/F/L/S/T	2 (2.4%)	2 (2.2%)	4 (2.3%)
I84V	1 (1.2%)	0	1 (0.6%)
L90M	0	1 (1.1%)	1 (0.6%)

Open label extension

In the ongoing open-label extension period all subjects wishing to continue on study drug at unblinding were offered an EVG-based regimen. There were 98 subjects (51 EVG and 47 RAL) in the Week 96 dataset for whom data were available up to 144 weeks. Proportions that maintained < 50 copies/mL at week 144 were similar in the EVG and RAL treatment groups. The mean (SD) increases from baseline in CD4 cell counts were also similar between treatment groups at Week 144 (EVG 243 [185.4] cells/mm^3 [n = 49], RAL 246 [156.1] cells/mm^3 [n = 46]).

Table 49. GS-US-183-0145: Subjects with < 50 copies/mL at Week 144 (M=E, ITT Analysis Set, Week 96 Dataset)

Subjects with < 50 copies/mL[b]	**EVG (N=351)**	**RAL (N=351)**	**EVG vs RAL Proportion Difference (95% CI)[a]**
HIV-1 RNA < 50 copies/mL	44/51 (86.3%)	40/47 (85.1%)	1.5% (–13.9% to 16.9%)
95% CI[c]	73.7% to 94.3%	71.7% to 93.8%	

a The difference in proportions and its 95% CIs between randomized treatment groups are based on stratum-adjusted (by baseline HIV-1 RNA level [≤ 100,000 or > 100,000 copies/mL] and the class of second agent [NRTI or other classes]) Mantel Haenszel (MH) proportions and normal approximation.
b Denominator for percentage is the number of ITT subjects (subjects with missing HIV-1 RNA data are excluded).
c The 95% CIs for the proportion estimate for a treatment group are based on the Exact method.

Summary of the main study

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

Table 5. Summary of Efficacy for trial GS-US-183-0145

Title: Safety and Efficacy of Ritonavir-Boosted Elvitegravir Versus Raltegravir Each Administered With a Background Regimen in HIV-1 Infected, Antiretroviral Treatment-Experienced Adults			
Study identifier	GS-US-183-0145 (EudraCT No. 2007-004225-26)		
Design	Phase 3, double-blind, double-dummy, multicentre, randomized, active-controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		96 weeks not applicable 144 weeks
Hypothesis	Non-inferiority		
Treatments groups	Elvitegravir (EVG) group		Treatment: EVG 150 mg once daily (85 mg once daily for subjects taking ATV/r or LPV/r as part of BR) + BR Duration: 96 weeks (double blind phase) Number randomized and treated: 354
	Raltegravir (RAL) group		Treatment: RAL 400 mg twice daily + BR Duration: 96 weeks (double blind phase) Number randomized and treated: 358
Endpoints and definitions	Primary endpoint	VR W48 TLOVR	Virologic response (percentage of subjects with HIV-1 RNA < 50 copies/mL) at Week 48, by TLOVR algorithm
	Secondary endpoint	VR W48 snapshot	Virologic response at Week 48, by snapshot algorithm

	Secondary endpoint	VR W96 snapshot	Virologic response at Week 96, by snapshot algorithm
	Secondary endpoint	CD4 W96	Mean change from baseline in CD4 cell count at week 96
Database lock	01 December 2011 (for week 96 data)		

Results and Analysis

Analysis description	**Primary and Secondary Analysis**			
Analysis population and time point description	Modified intent to treat (subjects randomised and treated, excluding subjects from one site (site 4390))			
Descriptive statistics and estimate variability	Treatment group		EVG group	RAL group
	Number of subject		351	351
	VR W48 TLOVR (%)		59.0	57.8
	variability statistic		Not reported	Not reported
	VR W48 snapshot (%)		59.8	57.5
	variability statistic		Not reported	Not reported
	VR W96 snapshot (%)		52.4	53.0
	variability statistic		Not reported	Not reported
	CD4 W96 (cells/mm3)		+205	+198
	standard deviation		191.5	162.2
Effect estimate per comparison	Comparison groups		EVG group vs. RAL group	
	Primary endpoint	Difference in VR W48 TLOVR		1.1 %
		95% CI		-6.0% to 8.2%
		P-value		0.76
	Secondary endpoint	Difference in VR W48 snapshot		2.2%
		95% CI		-5.0% to 9.3%
		P-value		0.55
	Secondary endpoint	Difference in VR W96 snapshot		-0.5%
		95% CI		-7.9% to 6.8%
		P-value		0.88
	Secondary endpoint	Difference in CD4 W96		7
		95% CI		-25 to 39
		P-value		Not reported

2.5.3. Supportive studies

Study GS-US-183-0130

This was an extension study that enrolled 192 HIV-infected subjects who had completed a prior EVG/r study (either GS-US-183-0105 or the adolescent study 0152) and wished to start (30) or continue to receive (162) RTV boosted EVG as part of their total regimen. The focus was on safety and on evaluating PK in a subset of 40 subjects that received 300 mg daily instead of 150 mg daily.

Subjects included had variable past treatment, baseline HIV-1 RNA < 50 copies/mL (n = 84) and ≥ 50 copies/mL (n = 107). There was a high attrition rate (79/192) for reasons other than lack of efficacy or death (50/79).

Among the 84 with < 50 copies/mL at study entry the suppression rates at Weeks 48, 96, 144 and 192 were 86.6%, 76.8%, 72.0% and 68.3%, respectively (M = F analysis). Rates were higher (89.9%, 86.3%, 88.1% and 90.3%) in the M = E analysis with corresponding rates for the 107 subjects with ≥ 50 copies/mL at entry that were 36.1%, 46.0%, 58.8% and 70.5%. CD4 cell counts increased over time in both subgroups.

The majority of resistance development was characterised as an evolution of RT, protease and integrase resistance that had existed prior to study entry in subjects who were not fully suppressed on their regimen. With regards to integrase resistance, mutation patterns were observed to evolve

resulting in a general increase in the level of phenotypic resistance. In subjects who entered the study with fully suppressed HIV-1 RNA, integrase resistance development was infrequent (3/84 subjects) and was observed along with evolution of RT and/or protease resistance that was present prior to EVG therapy.

2.5.4. Discussion on clinical efficacy

Design and conduct of clinical studies

Study GS-US-183-0105 was a randomised, partially blinded, multicentre study to assess non-inferiority of EVG/RTV vs. CPI/RTV when administered with an OBR. These data are not of great relevance to the indication claimed, and are difficult to interpret for efficacy due to the study design.

At the time that the protocol for the pivotal study GS-US-183-0145 was developed (with initiation in 2008) boosted PIs were and still are not very commonly used for first line treatment and a study in subjects failing their current ART regimen (HIV-1 RNA ≥ 1000 copies/mL) was planned. Due to the range of new agents that were already available it was not considered possible to use an add-on superiority vs. placebo design therefore as the objective it was chosen to demonstrate non-inferiority for EVG vs. RAL when each was co-administered with one RTV-boosted PI predicted to be fully active plus a third agent.

The pre-defined non-inferiority margin was derived by review of the Phase 3 RAL and etravirine (ETV) studies in treatment-experienced subjects. Taking into account differences in study populations and the content of treatment regimens the rationale for the pre-defined non-inferiority margin is questionable. Nevertheless, in a population that was failing treatment at study entry the actual lower bound of the 95% CI around the treatment differences at the < 50 copies/mL level (TLOVR analysis at week 48, using week 96 ITT dataset) was -6.0%. This result serves to differentiate an active treatment regimen from placebo and could be viewed as representing an acceptable difference between integrase inhibitors. These results were supported by the Week 96 data.

Efficacy data and additional analyses

While the performance of the comparator was not as expected from prior RAL studies in similar populations, GS-US-183-0145 was conducted under very different circumstances. It is pertinent that just over 40% of subjects had discontinued by week 96 (the rate was already ~30% by week 48) and non-adherence, withdrawal of consent and LTFU accounted for the majority of cases. These rates of discontinuation, however, are not surprising in light of the availability of licensed treatments, which likely made it less attractive to comply with the burden of study visits and procedures.

The subgroup analyses indicated some differences between EVG and RAL as well as unexpected results for both compounds in some subsets (e.g. baseline GSS 0 or 1 vs. > 1, whites vs. non-whites and US/Puerto Rico sites vs. other sites). While it seems difficult to ascribe all these findings to chance and/or to the relatively small sample sizes in some subgroups, the overall comparisons between EVG and RAL and the comparisons by PI subgroup are reassuring. The observed trend towards lower efficacy in women, however, is a potential concern – available data have been highlighted in the SmPC and this has been included in the RMP as a potential risk. Since no possible mechanism could be identified for lower efficacy in women, this is likely to be a chance finding and further action currently is not warranted.

This study allowed use of any of five RTV-boosted PIs and was not designed (and hence not powered) to assess non-inferiority by PI subset. In principle, this could be acceptable to support the indication claimed taking into account that (with the discussed exception of use of EVG with TPV/r):

- Comparable proportions in EVG and RAL groups received each of the PIs allowed and other features of the population, ART regimens and GSS/PSS scores were comparable between integrase inhibitor groups
- The use of EVG with each of the recommended PI/r is supported by adequate PK data
- There are supportive efficacy data (i.e. from short-term EVG monotherapy and STB studies)

The data on use of EVG in combination with TPV/r is very limited, and 3 of the 6 patients in this group failed the treatment. The use of this combination therefore cannot be recommended.

2.5.5. Conclusions on the clinical efficacy

EVG achieved a 2-log drop in HIV RNA over 10 days when administered as 50 mg EVG plus 100 mg RTV daily in the short-term monotherapy study. When used at an appropriate dose regimen to treat susceptible virus it could be expected to contribute to the overall effect of an ART regimen, including co-administration with RTV-boosted PIs as proposed by the applicant. Taking into account also the data from study GS-US-183-0145, EVG may be considered as an alternative to the only currently licensed integrase inhibitor (raltegravir).

The clinical efficacy programme for EVG was decided upon at a time of transition with regard to study feasibility and regulatory guidance. This led to conduct of a single pivotal study in which EVG was co-administered with one of five RTV-boosted PIs predicted to be active against the individual subject's virus plus at least one other agent. Overall, this study demonstrated comparable efficacy for EVG vs. RAL, with a lower bound of the 95% CI around the treatment difference (< 50 copies/mL at Week 48) of -6.0%. The sensitivity and secondary analyses support a conclusion of comparable efficacy for EVG vs. RAL. The study was not designed to provide PI-specific efficacy data although the numerical comparisons suggest no major differences between EVG and RAL for the PI/r subgroups. Nevertheless, much of the justification for use rests on the PK data indicating the need for either 150 mg or 85 mg EVG with individual PI/r combinations. At present there are doubts regarding co-administration of EVG 150 mg with TPV/RTV, however, TPV/RTV has been excluded from the recommended combinations. Lower efficacy was observed in women, however, numbers are too limited to draw firm conclusions.

At present the virological data, including the resistance analysis population data, suggest that EVG is not associated with a higher risk of selecting for INSTI-R mutations compared to RAL and there is incomplete cross-resistance between the two. The experience is currently too limited to discern whether in practise EVG has a similarly low genetic barrier to resistance as RAL.

2.6. Clinical safety

Patient exposure

With a focus on the safety data for EVG when co-administered with an RTV-boosted PI, the principal safety data come from the Week 96 dataset of GS-US-183-0145. By Week 96 ~ 40% of subjects had discontinued. Additional supportive safety data are provided by studies GS-US-183-0105 and GS-US-183-0130. Also, in the Phase 1 studies 1064 subjects were exposed to EVG (not including QUAD STR),

boosted or not. Supportive safety data were provided also from studies with QUAD STR, which are not discussed in details in this Assessment Report[2].

Table 50. GS-US-183-0145, 0105, and 0130: Summary of Treatment Groups and Exposure

Study	Duration	Treatment Group	Number of Subjects
GS-US-183-0145	96 weeks	Group 1: EVG 150 mg once daily plus background regimen (BR) containing a PI/r (EVG 85 mg for subjects taking ATV/r or LPV/r as part of their BR)	354
		Group 2: RAL 400 mg twice daily plus BR containing a PI/r	358
GS-US-183-0130	192 weeks[a]	EVG 85-mg, 150-mg, or 300-mg strength tablets once daily, with RTV and BR	192
GS-US-183-0105	48 weeks	EVG 20 mg once daily with 100 mg RTV and BR	71
		EVG 50 mg once daily with 100 mg RTV and BR	71
		EVG 125 mg once daily with 100 mg RTV and BR	73
		Comparator PI/r and BR	63

Adverse events

Treatment emergent adverse events in study GS-US-183-0145

At least one TEAE was reported by 90.1% EVG and 88.8% RAL subjects with comparable rates for TEAEs of any severity considered related to study drug as well as those of Grades 2, 3 or 4.

Table 51. GS-US-183-0145: Overall Summary of Treatment-Emergent Adverse Events (Safety Analysis Set, Week 96 Dataset).

Adverse Event Category, n (%)[a,b]	EVG (N=354)	RAL (N=358)
Subjects Experiencing any Treatment-Emergent Adverse Events	319 (90.1%)	318 (88.8%)
Grade 3 or 4 Treatment-Emergent Adverse Events	86 (24.3%)	85 (23.7%)
Grade 2, 3, or 4 Treatment-Emergent Adverse Events	241 (68.1%)	245 (68.4%)
Treatment-Emergent Study Drug Related Adverse Events	84 (23.7%)	73 (20.4%)
Grade 3 or 4 Treatment-Emergent Study Drug Related Adverse Events	8 (2.3%)	11 (3.1%)
Grade 2, 3, or 4 Treatment-Emergent Study Drug Related Adverse Events	50 (14.1%)	35 (9.8%)
Treatment-Emergent Serious Adverse Events	71 (20.1%)	84 (23.5%)
Treatment-Emergent Study Drug Related Serious Adverse Events	4 (1.1%)	7 (2.0%)
Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation	11 (3.1%)	15 (4.2%)
Treatment-Emergent Adverse Events Leading to Temporary Interruption of Study Drug	16 (4.5%)	32 (8.9%)
Treatment-Emergent Death[c]	2 (0.6%)	7 (2.0%)

a Denominator for percentages is the number of subjects in the safety analysis set within the treatment group.

b Adverse events with onset after the last dose date plus 30 days are excluded from analysis.

c Treatment-emergent death refers to the deaths occurring between the first dose date and the last dose date plus 30 days (inclusive). A total of 12 subjects died by Week 96 data cutoff date (Appendix 16.2, Listing 23). Three deaths (EVG Subject 0595-4154 and RAL Subjects 0744-3151 and 1543-3294) were not treatment-emergent.

[2] for more information, see CHMP Assessment Report / European Public Assessment Report for Stribild

The most frequently reported AEs in each group (see below) were as follows:

- EVG: diarrhoea (33.6%), URTI (18.9%) and headache (13.3%)
- RAL: diarrhoea (21.8%), URTI (15.6%) and cough (13.1%)

The majority of the diarrhoea reported in both groups was mild to moderate in severity. No subjects discontinued study drug due to diarrhoea. Two cases (both in the RAL group) were SAEs.

The most frequently reported Grade 2, 3, or 4 AEs in each group were as follows:

- EVG: diarrhoea (13.3%, 47) and back pain and depression (each reported for 5.9%, 21)
- RAL: diarrhoea (7.8%, 28), bronchitis (5.9%, 21) and depression (5.6%, 20)

Table 52. GS-US-183-0145: Treatment-Emergent Adverse Events Reported for ≥5% Subjects in Either Treatment Group (Safety Analysis Set, Week 96 Dataset).

Adverse Events by System Organ Class and Preferred Term[a, b, c, d]	EVG (N=354)	RAL (N=358)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Events	319 (90.1%)	318 (88.8%)
Gastrointestinal Disorders	202 (57.1%)	179 (50.0%)
Diarrhoea	119 (33.6%)	78 (21.8%)
Nausea	44 (12.4%)	41 (11.5%)
Vomiting	20 (5.6%)	29 (8.1%)
Abdominal Pain	23 (6.5%)	20 (5.6%)
General Disorders and Administration Site Conditions	92 (26.0%)	86 (24.0%)
Fatigue	37 (10.5%)	26 (7.3%)
Pyrexia	15 ([illegible])	20 (5.6%)
Oedema Peripheral	18 (5.1%)	11 (3.1%)
Infections and Infestations	240 (67.8%)	227 (63.4%)
Upper Respiratory Tract Infection	67 (18.9%)	56 (15.6%)
Bronchitis	36 (10.2%)	36 (10.1%)
Nasopharyngitis	33 (9.3%)	30 (8.4%)
Urinary Tract Infection	26 (7.3%)	35 (9.8%)
Sinusitis	29 (8.2%)	28 (7.8%)
Pneumonia	18 (5.1%)	9 (2.5%)
Folliculitis	18 (5.1%)	7 (2.0%)
Metabolism and Nutrition Disorders	79 (22.3%)	76 (21.2%)
Hypercholesterolaemia	12 (3.4%)	18 (5.0%)
Musculoskeletal and Connective Tissue Disorders	113 (31.9%)	104 (29.1%)
Back Pain	39 (11.0%)	35 (9.8%)
Arthralgia	28 (7.9%)	26 (7.3%)
Pain in Extremity	25 (7.1%)	25 (7.0%)
Nervous System Disorders	95 (26.8%)	88 (24.6%)
Headache	47 (13.3%)	37 (10.3%)
Psychiatric Disorders	73 (20.6%)	71 (19.8%)
Depression	29 (8.2%)	31 (8.7%)
Insomnia	23 (6.5%)	21 (5.9%)
Respiratory, Thoracic and Mediastinal Disorders	114 (32.2%)	105 (29.3%)
Cough	37 (10.5%)	47 (13.1%)
Skin and Subcutaneous Tissue Disorders	112 (31.6%)	98 (27.4%)
Rash	26 (7.3%)	27 (7.5%)
Vascular Disorders	25 (7.1%)	38 (10.6%)
Hypertension	14 (4.0%)	23 (6.4%)

a Denominator for percentages is the number of subjects in the safety analysis set within the treatment group.
b Adverse events are mapped according to the MedDRA dictionary, Version 14.0.
c System organ classes are sorted alphabetically. Within each SOC, PTs are sorted in decreasing order of frequency.
d Adverse events with onset after the last dose date plus 30 days are excluded from analysis.

Grade 3 or 4 AEs reported for > 1% of subjects in either treatment group were as follows:

- Pneumonia (EVG 1.7%, 6; RAL 1.4%, 5)
- Cellulitis (EVG 1.1%, 4; RAL 0.3%, 1)
- Blood bilirubin increased, diarrhoea and hypercholesterolaemia (1 each EVG; RAL 1.1%; 4)

- Liver function test abnormal (EVG 0 subjects; RAL 1.4%, 5 subjects).

In both treatment groups, the most frequently reported AEs considered related to study drug by the investigator were diarrhoea (EVG 7.1%, 25; RAL 5.3%, 19), nausea (EVG 4.0%, 14; RAL 2.5%, 9) and headache (EVG 2.8%, 10; RAL 2.5%, 9).

Table 53. GS-US-183-0145: Treatment-Emergent Adverse Related to Study Drug Reported in >1% of subject in Either Treatment Group (Safety Analysis Set, Week 96 Dataset).

Adverse Events by System Organ Class and Preferred Term[a, b, c, d]	EVG (N=354)	RAL (N=358)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug Related Adverse Events	84 (23.7%)	73 (20.4%)
Gastrointestinal Disorders	46 (13.0%)	40 (11.2%)
Diarrhoea	25 (7.1%)	19 (5.3%)
Nausea	14 (4.0%)	9 (2.5%)
Vomiting	4 (1.1%)	5 (1.4%)
Abdominal Distension	2 (0.6%)	4 (1.1%)
General Disorders and Administration Site Conditions	10 (2.8%)	9 (2.5%)
Fatigue	7 (2.0%)	4 (1.1%)
Nervous System Disorders	19 (5.4%)	21 (5.9%)
Headache	10 (2.8%)	9 (2.5%)
Dizziness	2 (0.6%)	5 (1.4%)
Dysgeusia	2 (0.6%)	4 (1.1%)
Skin and Subcutaneous Tissue Disorders	10 (2.8%)	11 ([illegible]%)
Rash	3 (0.8%)	5 ([illegible]%)

The table below summarises safety by EVG dose. However, since the EVG 85 mg group received ATV/r or LPV/r and the 150 mg group received DRV/r, FPV/r or TPV/r there are differences between regimens that are inherently aligned with the dose of EVG.

Table 54. GS-US-183-0145: TEAEs by EVG Dose (Week 96 Safety Analysis Set)

	EVG 85 mg QD with ATV/r or LPV/r N= 125	EVG 150 mg QD with DRV/r, FPV/r, or TPV/r N = 229	RAL Overall N = 358
Subjects Experiencing Any Treatment-Emergent			
AE	111 (88.8%)	208 (90.8%)	318 (88.8%)
Grade 3 or 4 AE	28 (22.4%)	58 (25.3%)	85 (23.7%)
Study-Drug-Related AE	27 (21.6%)	57 (24.9%)	73 (20.4%)
Grade 3 or 4 Study-Drug-Related AE	2 (1.6%)	6 (2.6%)	11 (3.1%)
Subjects Experiencing Any Treatment-Emergent SAE	19 (15.2%)	52 (22.7%)	84 (23.5%)
Study-Drug-Related SAE	1 (0.8%)	3 (1.3%)	7 (2.0%)
AE Leading to Premature Study Drug Discontinuation	1 (0.8%)	10 (4.4%)	15 (4.2%)
AE Leading to Study Drug Interruption	6 (4.8%)	10 (4.4%)	32 (8.9%)
Treatment-Emergent Death	1 (0.8%)	1 (0.4%)	7 (2.0%)

Rates for the most frequently reported AEs (≥ 10% in either EVG dose group) were generally similar between EVG dose groups and also generally similar to those for the overall RAL group except that the rate of diarrhoea was higher for both EVG groups vs. the RAL group.

Table 55. GS-US-183-0145: TEAEs Reported for ≥ 10.0% with EVG (Week 96 Safety Set)

	EVG		RAL
AE by PT	**85 mg with ATV/r or LPV/r N = 125**	**150 mg with DRV/r, FPV/r, or TPV/r N = 229**	**Overall N = 358**

Diarrhoea	40 (32.0%)	79 (34.5%)	78 (21.8%)
Upper Respiratory Tract Infection	28 (22.4%)	39 (17.0%)	56 (15.6%)
Cough	9 (7.2%)	28 (12.2%)	47 (13.1%)
Nausea	13 (10.4%)	31 (13.5%)	41 (11.5%)
Headache	14 (11.2%)	33 (14.4%)	37 (10.3%)
Bronchitis	14 (11.2%)	22 (9.6%)	36 (10.1%)
Back Pain	8 (6.4%)	31 (13.5%)	35 (9.8%)
Depression	14 (11.2%)	15 (6.6%)	31 (8.7%)
Nasopharyngitis	10 (8.0%)	23 (10.0%)	30 (8.4%)
Fatigue	11 (8.8%)	26 (11.4%)	26 (7.3%)

a Denominator for percentages is the number of subjects in the safety analysis set within the treatment group of the subgroup of interest.
b Preferred terms are sorted in decreasing order of frequency in the Overall RAL group.
c Adverse events are mapped according to MedDRA Version 14.0.

The overall safety profile for subjects treated with EVG was generally similar to that for the overall RAL treatment group. In the three largest PI sub-groups the most notable difference observed was a lower rate of SAEs with LPV/r (11.8%) compared with ATV/r (20.3%) and DRV/r (23.2%).

Table 56. GS-US-183-0145: TEAEs by Protease Inhibitor (Week 96 Safety Analysis Set)

	EVG					
	85 mg QD		**150 mg QD**			**RAL**
	ATV/r N = 64	**LPV/r N = 68**	**DRV/r N = 202**	**FPV/r N = 14**	**TPV/r N = 6**	**Overall N = 358**
Any TEAE	56 (87.5%)	62 (91.2%)	181 (89.6%)	14 (100.0%)	6 (100.0%)	318 (88.8%)
Grade 3 or 4 AE	15 (23.4%)	16 (23.5%)	49 (24.3%)	4 (28.6%)	2 (33.3%)	85 (23.7%)
Study-Drug-Related AE	16 (25.0%)	14 (20.6%)	50 (24.8%)	3 (21.4%)	1 (16.7%)	73 (20.4%)
Grade 3 or 4 Study-Drug-Related AE	2 (3.1%)	0	4 (2.0%)	2 (14.3%)	0	11 (3.1%)
SAE	13 (20.3%)	8 (11.8%)	47 (23.3%)	2 (14.3%)	1 (16.7%)	84 (23.5%)
Study-Drug-Related SAE	1 (1.6%)	0	2 (1.0%)	1 (7.1%)	0	7 (2.0%)
AE Leading to Premature Study Drug Discontinuation	2 (3.1%)	0	8 (4.0%)	1 (7.1%)	0	15 (4.2%)
AE Leading to Study Drug Interruption	3 (4.7%)	3 (4.4%)	8 (4.0%)	2 (14.3%)	0	32 (8.9%)
Treatment-Emergent Death	1 (1.6%)	0	1 (0.5%)	0	0	7 (2.0%)

In the three largest PI sub-groups diarrhoea occurred at a higher (≥ 5% treatment difference) rate with EVG + LPV/r (47.1%) compared with EVG given with DRV/r (30.2%) or with ATV/r (21.9%). Rates for nausea and headache were comparable across EVG + PI sub-groups. Compared to the overall RAL group, diarrhoea occurred more frequently with EVG + LPV/r or DRV/r. Rates of nausea and headache were similar across PI groups and RAL.

Table 57. GS-US-183-0145: Most Common TEAEs by PI/r (Week 96 Safety Analysis Set)

Adverse Event by Preferred Term	EVG 85 or 150 mg QD					RAL Overall N = 354
	ATV/r N = 64	LPV/r N = 68	DRV/r N = 202	FPV/r N = 14	TPV/r N = 6	
Diarrhoea	14 (21.9%)	32 (47.1%)	61 (30.2%)	10 (71.4%)	2 (33.3%)	78 (21.8%)
URTI	15 (23.4%)	15 (22.1%)	33 (16.3%)	3 (21.4%)	1 (16.7%)	56 (15.6%)
Nausea	8 (12.5%)	7 (10.3%)	23 (11.4%)	5 (35.7%)	1 (16.7%)	41 (11.5%)
Headache	8 (12.5%)	10 (14.7%)	27 (13.4%)	1 (7.1%)	1 (16.7%)	37 (10.3%)

Rates of AEs, SAEs and AEs leading to discontinuation were similar to or lower for EVG vs. RAL regardless of the dosing frequency of the PI/r but interpretation of these data is very limited by the small sample size of several groups. Overall, the incidence of diarrhoea was higher when EVG was given with twice-daily RTV (36.8%, 93/253) compared to once-daily RTV (25.7%, 26/101). No other clinically significant differences between RTV dosing frequencies were noted.

Treatment emergent adverse events in study GS-US-183-0130

At least one TEAE was reported by 92% (177/192) of subjects. The most frequently reported were URTI (25.5%), diarrhoea (22.4%), sinusitis (18.2%), bronchitis (17.7%), nasopharyngitis (13.0%), nausea (13.0%), fatigue (12.5%), arthralgia (10.9%), depression (10.9%) and back pain (10.4%). Grade 3 or 4 AEs were reported for 38% but those reported in > 1 subjects were very wide-ranging in nature. Drug-related TEAEs were experienced by 24 subjects (12.5%). Four subjects (2.1%) experienced a Grade 3 AE considered to be drug-related (acute pancreatitis, hepatitis B and peripheral neuropathy [2 subjects]). The case of Grade 3 HBV was HBsAg negative at baseline but had Grade 4 ALT with Grade 3 AST and GGT elevations, which resolved during temporary interruption of ARV and did not occur following resumption of therapy (EVG, DRV/RTV, TDF and ABC).

Treatment emergent adverse events in study GS-US-183-0105

At least one TEAE was reported by the majority of subjects with broadly comparable rates across treatments. The most frequently reported were diarrhoea, nausea, constipation, vomiting, fatigue, injection site reactions, pyrexia, URTI, sinusitis, headache, cough and pharyngolaryngeal pain.

Table 58. Number of subjects experiencing any TEAE in study GS-US-183-0105

Number (%) of Subjects with Adverse Events by System Organ Class, High Level Term, and Preferred Term	CPI/r (N = 63)	EVG/r 20/100 mg QD (N = 71)	EVG/r 50/100 mg QD (N = 71)	EVG/r 125/100 mg QD (N = 73)	CPI/r –> EVG/r (N = 30)[a]
Number of Subjects Experiencing Any Treatment Emergent Adverse Event[b]	59 (93.7%)	63 (88.7%)	67 (94.4%)	72 (98.6%)	26 (86.7%)

The commonest TEAEs considered drug-related were diarrhoea, nausea and vomiting but there was no consistent pattern for rates in relation to EVG dose.

Table 59. GS-US-183-0105: Treatment-Related Adverse Events Reported by at Least 5% of Subjects by Treatment through Week 48 (Randomised and Treated Analysis Set).

Number (%) of Subjects with Adverse Events by System Organ Class, High-Level Term, and Preferred Term	CPI/r (N = 63)	EVG/r 20/100 mg QD (N = 71)	EVG/r 50/100 mg QD (N = 71)	EVG/r 125/100 mg QD (N = 73)	CPI/r –> EVG/r (N = 30)[a]
Number of Subjects Experiencing Any Related Treatment Emergent Adverse Events[b]	25 (39.7%)	19 (26.8%)	21 (29.6%)	19 (26.0%)	3 (10.0%)
Gastrointestinal Disorders	14 (22.2%)	11 (15.5%)	13 (18.3%)	9 (12.3%)	0 (0.0%)
Diarrhea (excl infective)	10 (15.9%)	4 (5.6%)	4 (5.6%)	2 (2.7%)	0 (0.0%)
Diarrhea	10 (15.9%)	4 (5.6%)	4 (5.6%)	2 (2.7%)	0 (0.0%)
Nausea and Vomiting Symptoms	5 (7.9%)	6 (8.5%)	5 (7.0%)	6 (8.2%)	0 (0.0%)
Nausea	5 (7.9%)	5 (7.0%)	4 (5.6%)	5 (6.8%)	0 (0.0%)

Phase 1 studies in non HIV-infected subjects

The applicant did not summarise AEs from the Phase 1 studies but SAEs and discontinuations due to SAEs are described (see below). For the most part the TEAEs observed in the various studies in healthy subjects were as expected in these study populations. In several of the DDI studies the AEs observed on co-administration of EVG with other medicinal products reflected the known safety profiles of the other drugs (e.g. jaundice with ATV). In some studies rates for certain AEs were higher on co-administration.

Serious adverse event / deaths / other significant events

Deaths

Twelve male subjects died during GS-US-183-0145 up to the cut-off date for the CSR (EVG 3; RAL 9 subjects). Nine of these 12 deaths were considered treatment-emergent (EVG 2; RAL 7). The AEs associated with treatment-emergent death in the EVG group (acute myocardial infarction and rectal haemorrhage) were not considered related to study drug.

Three deaths occurred during GS-US-183-0105 but these were not considered related to study drugs by the investigators. One in the EVG/RTV 50/100 mg group died of cardiorespiratory failure on Day 221. The two deaths in the EVG/RTV 20/100 mg group were due to B-cell lymphoma on Day 159 and *Pneumocystis jirovecii* pneumonia on Day 143.

Eleven deaths occurred during GS-US-183-0130 but none was considered to be related to study drug. Causes of death included subdural hematoma, complications from *Pneumocystis* pneumonia, presumptive self-asphyxiation, perforated ulcer, colorectal carcinoma, sepsis, coronary arterial sclerosis and dilated cardiomyopathy, advanced HIV disease, strangulation, progressive multifocal leucoencephalopathy and Hodgkin lymphoma.

Serious adverse events

In Phase 1 studies:

- A 20-year-old healthy female subject experienced intrauterine foetal death on day 44 after the last dose of EVG 125 mg and RTV 50 mg.

- Spontaneous abortion occurred in a subject who received EVG/RTV who was discovered to be pregnant in the latter part of the study due to failure of contraception. She was immediately discontinued but had a spontaneous abortion 14 days later.
- One SAE of diabetic foot ulcer not considered to be related to EVG/COBI occurred in a 71 year-old subject with severe renal impairment and type 2 diabetes.

In GS-US-183-0145 SAEs were reported for 20.1% (71 subjects) in the EVG group and 23.5% (84 subjects) in the RAL group. The majority concerned infections (mostly pneumonia and cellulitis) and were not considered to be related to study drug by investigators. SAEs considered related to study drug were reported for 4 EVG and 7 RAL subjects. Those in the EVG group concerned type 1 diabetes, cerebral infarction plus subarachnoid haemorrhage, haemolytic anaemia and cholestatic hepatitis. Convulsion was the only SAE considered related to study drug by the investigator that was reported for > 1 subject in a treatment group (2 subjects in the RAL group).

Table 60. GS-US-183-0145: Treatment-Emergent Serious Adverse Events Reported in >1% of Subjects in Either Treatment Group (Safety Analysis Set, Week 96 Dataset).

Adverse Events by System Organ Class and Preferred Term[a, b, c, d]	EVG (N=354)	RAL (N=358)
Number of Subjects Experiencing Any Treatment-Emergent Serious Adverse Events	71 (20.1%)	84 (23.5%)
General Disorders and Administration Site Conditions	3 (0.8%)	5 (1.4%)
Chest Pain	1 (0.3%)	4 (1.1%)
Infections and Infestations	34 (9.6%)	24 (6.7%)
Pneumonia	12 (3.4%)	7 (2.0%)
Cellulitis	5 (1.4%)	4 (1.1%)
Bronchitis	2 (0.6%)	4 (1.1%)
Psychiatric Disorders	5 (1.4%)	10 (2.8%)
Suicidal Ideation	3 (0.8%)	4 (1.1%)

Of note, all subjects who experienced an AE related to suicidal ideation or suicide attempt when receiving EVG in different studies had a pre-existing history of depression or psychiatric illness.

There were 52 subjects who had at least one SAE in GS-US-183-0105 (including the 3 deaths) and 41 occurred in one of the EVG groups. Another 6 subjects who switched to open-label EVG had SAEs. The only SAEs reported in > 1 subject within a treatment group were pneumonia (2 in the 125/100 mg group) and B-cell lymphoma (2 in the 20/100 mg group). Three SAEs assessed as related or possibly related to study drugs included two in EVG-treated subjects (syncope and hypersensitivity reaction).

In GS-US-183-0130, 72 subjects (37.5%) who received EVG/RTV experienced at least one SAE. Those reported in >1% included pneumonia (3.1%), cellulitis (2.1%), myocardial infarction (1.6%), chest pain (1.6%), gastro-enteritis (1.6%), influenza (1.6%) and acute renal failure (1.6%). All of these SAEs were considered by the investigators to be not related to study drug. The two SAEs considered by the investigator to be related to study drug involved acute pancreatitis on Day 496 and acute necrotising retinitis on Day 1220.

Pregnancies

In Phase 1 studies five pregnancies were reported in subjects who received EVG and two more in subjects who received EVG during Phase 1 studies with COBI. See above section on SAEs. Two have resulted in healthy infants and one had a termination. One infant born to a subject with a positive pregnancy test on Day 7 of 125 mg EVG with DRV/RTV had bilateral extra fingers at the fifth digit.

There was a family history of extra fingers and the congenital abnormality was deemed to be unrelated to treatment.

In GS-US-183-0145 seven pregnancies were reported (4 EVG and 3 RAL). Two subjects were determined to have been pregnant before study drug administration was initiated, of which one had a spontaneous abortion and the other had an induced abortion. Of 5 exposed to study drug during pregnancy, 2 subjects in the EVG group delivered healthy babies while one in the RAL group had a spontaneous abortion. Two were ongoing at the time of the report. In GS-US-183-0130 one pregnancy occurred that ended in spontaneous abortion.

Laboratory findings

In GS-US-183-0145 the numbers with TE laboratory abnormalities of any Grade were comparable between treatment groups. Grade 3 or 4 laboratory abnormalities were reported for EVG 36.7% vs. RAL 41.8% and the difference primarily reflected lower rates in the EVG group for LFT abnormalities.

Grade 3 or 4 abnormalities were reported for a higher percentage of subjects in the EVG group for lipase (13.6% vs. 6.9%; although rates for amylase were 6.3% vs. 5.9%) and creatinine kinase (6.0% vs. 3.7%). The most frequently reported Grade 3 or 4 treatment-emergent laboratory abnormalities were:

- EVG: lipase (only performed if amylase > 1.5 ULN; 13.6%); amylase (6.3%); haematuria (6.0%); hyperbilirubinaemia and creatinine kinase (each 6.0%)
- RAL: hyperbilirubinaemia (8.5%); lipase (6.9%); GGT and haematuria (each 6.5%)

Marked laboratory abnormalities were reported for comparable percentages in each group (EVG 27.5%; RAL 30.2%).

Thirteen subjects (EVG 6, RAL 7) had ALT or AST values > 3 × ULN and total bilirubin > 2 × ULN occurring at the same study visit. The likely causes for these liver laboratory abnormalities are shown in the table below. No subject in the study met the definition of Hy's law. Two subjects (one per treatment group) had changes in liver laboratory values potentially associated with drug-induced chemical hepatitis. The enzyme elevations were transient, resolved after discontinuation and had no sequelae.

Table 61. Summary of Subjects with ALT or AST Values >3 x ULN and Total Bilirubin Values >2 x ULN at the Same Study Visit (Safety Analysis Set, Week 96 Dataset).

Subject	Treatment Group	Event	Likely Cause
0566-3310	EVG	No liver-related AE; Grade 3 laboratory results	On ATV; acute myocardial infarction with AST elevation but normal ALT
0595-4154	EVG	Chronic hepatic failure (SAE)	Chronic hepatitis C, with liver cirrhosis and liver failure
0991-3142	EVG	No liver-related AE; Grade 3 laboratory results	On ATV
1543-3404	EVG	No liver-related AE; Grade 2 laboratory results	On ATV
3959-3076	EVG	No liver-related AE; Grade 3 laboratory results	On ATV; HCV infection
4099-4121	EVG	Hepatitis cholestatic (SAE)	On DRV, RTV, etravirine; HCV infection
0566-3135	RAL	No liver-related AE; Grade 2 laboratory results	On ATV
0566-3443	RAL	Hepatitis B, hepatitis alcoholic; Grade 3 laboratory results	On ATV; HBV infection; alcoholism
0637-3382	RAL	Allergic drug reaction (SAE)	Blinded study drug (RAL) and DRV
1493-4088	RAL	Hepatitis (SAE)	Acute hepatitis B infection
1534-3303	RAL	No liver-related AE; Grade 3 laboratory results	HCV infection
4024-4043	RAL	Metastases to liver (SAE); Grade 2 laboratory results	On DRV/r; metastases to liver
5007-3451	RAL	Hepatitis (SAE)	On DRV/r, Truvada, blinded study drug (RAL)

Serum creatinine increased with median change from baseline at Week 96 of 0.10 mg/dL in both groups. Treatment-emergent serum creatinine abnormalities were reported for 32 EVG subjects and 36 RAL subjects while Grade 3 or 4 abnormalities were reported for 2 subjects in each group. Blood creatinine increased was reported as an AE for 2 EVG and 3 RAL subjects and considered related to study drug for one EVG subject. There was a decrease in median values for eGFRCG in both treatment groups (EVG median change at Week 96 of −10.8 mL/min; RAL −11.7 mL/min).

Hypophosphataemia was reported for EVG 41 vs. RAL 31 subjects. Grade 3 hypophosphataemia was reported for 2 EVG subjects. Hypophosphataemia was reported as an AE for 2 subjects in each group but no case was considered related to study drug and no action was taken. Glycosuria was reported for EVG 31 vs. RAL 26 subjects and Grade 3 glycosuria was reported for 13 (3.7%) vs. 11 (3.1%). Proteinuria was reported in EVG 170 and RAL 176 subjects (Grade 3 in one EVG subject). Similar numbers in each treatment group had treatment-emergent abnormalities reported for fasting total cholesterol or fasting triglycerides. AEs of blood triglycerides increased or hypertriglyceridaemia were reported for comparable percentages per group.

In study GS-US-183-0105 parameters for which > 1 subject per treatment had a TE Grade 3 or 4 abnormality included cholesterol, triglycerides, CK, GGT, lipase, amylase, total bilirubin, phosphorus, raised serum glucose, haemoglobin, neutrophils, platelets, WBC count, urine blood and urine glucose but no treatment-related trends were apparent.

In study GS-US-183-0130 the most frequent Grade 3 and 4 laboratory abnormalities involved CK, GGT, serum amylase, fasting triglycerides and urine glucose. Most were not considered to be clinically relevant (e.g. CK elevation or amylase elevation without associated TEAEs) or were due to underlying conditions (e.g. diabetes, HCV).

Discontinuation due to adverse events

Discontinuations due to TEAS in the Phase 1 studies did not show treatment-related trends.

Up to the Week 96 CSR cut-off date for GS-US-183-0145 the rates of premature study drug discontinuation due to TEAEs were EVG 3.1% (11) vs. RAL 4.2% (15). TEAEs leading to discontinuation reported in > 1 EVG subject were nausea (2) and vomiting (2). In six EVG and nine RAL subjects TEAEs leading to study drug discontinuation were considered related to study drug by the investigator, including cases of nausea and abdominal pain in the EVG group.

Table 62. GS-US-183-0145: Treatment-Emergent Adverse Events Leading to Premature Study Drug Discontinuation (Safety Analysis Set, Week 96 Dataset).

Adverse Events by System Organ Class and Preferred Term[a, b, c, d]	EVG (N=354)	RAL (N=358)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Events Leading to Premature Study Drug Discontinuation	11 (3.1%)	15 (4.2%)
Blood and Lymphatic System Disorders	1 (0.3%)	0
Haemolytic Anaemia	1 (0.3%)	0
Gastrointestinal Disorders	4 (1.1%)	1 (0.3%)
Abdominal Pain	1 (0.3%)	1 (0.3%)
Nausea	2 (0.6%)	0
Vomiting	2 (0.6%)	0
Rectal Haemorrhage	1 (0.3%)	0
General Disorders and Administration Site Conditions	1 (0.3%)	0
Fatigue	1 (0.3%)	0
Hepatobiliary Disorders	2 (0.6%)	3 (0.8%)
Hepatitis	0	2 (0.6%)
Chronic Hepatic Failure	1 (0.3%)	0
Hepatitis Acute	0	1 (0.3%)
Hepatitis Cholestatic	1 (0.3%)	0
Immune System Disorders	0	1 (0.3%)
Serum Sickness	0	1 (0.3%)
Infections and Infestations	0	1 (0.3%)
Hepatitis C	0	1 (0.3%)
Investigations	2 (0.6%)	4 (1.1%)
Blood Triglycerides Increased	0	1 (0.3%)
Gamma-Glutamyltransferase Increased	0	1 (0.3%)
Hepatic Enzyme Increased	0	1 (0.3%)
Lipids Increased	0	1 (0.3%)
Transaminases Increased	1 (0.3%)	0
Waist Circumference Increased	1 (0.3%)	0
Musculoskeletal and Connective Tissue Disorders	1 (0.3%)	0
Myalgia	1 (0.3%)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	3 (0.8%)	2 (0.6%)
Diffuse Large B-Cell Lymphoma	1 (0.3%)	0
Lung Cancer Metastatic	1 (0.3%)	0
Lung Neoplasm Malignant	0	1 (0.3%)
Lung Squamous Cell Carcinoma Stage Unspecified	1 (0.3%)	0
Renal Cell Carcinoma	0	1 (0.3%)
Nervous System Disorders	1 (0.3%)	0
Headache	1 (0.3%)	0
Psychiatric Disorders	0	1 (0.3%)
Substance Abuse	0	1 (0.3%)
Renal and Urinary Disorders	1 (0.3%)	1 (0.3%)
Nephritis	0	1 (0.3%)
Renal Failure Acute	1 (0.3%)	0
Skin and Subcutaneous Tissue Disorders	0	3 (0.8%)
Lipohypertrophy	0	1 (0.3%)
Rash Maculo-Papular	0	1 (0.3%)
Vasculitic Rash	0	1 (0.3%)

In GS-US-183-0105 discontinuation from study due to TEAEs occurred in 2 subjects (3.2%) in the CPI/r group compared to 3 (4.2%), 2 (2.8%) and 1 (1.4%) in each of the EVG/r 20/100, 50/100, and 125/100 mg groups, respectively. These included cases of hypersensitivity (EVG/r 20/100 mg) and convulsion (EVG/r 50/100 mg) that were considered by the investigators to be study drug related.

In GS-US-183-0130 10 subjects (5.2%) had TEAEs that led to premature discontinuation of study drug but none was reported in > 1 subject or considered by the investigator to be related to study drug. All except one were SAEs.

2.6.1. Discussion on clinical safety

The total exposure of HIV-infected subjects to EVG specifically when administered in conjunction with RTV-boosted PIs is limited to 354, of which ~60% had been exposed for > 96 weeks when the CSR was finalised. This is not an overly large database for a new agent but it is supported by considerable numbers exposed to EVG as part of QUAD STR and in the Phase 1 and 2 studies.

Results from study GS-US-183-0145 suggested comparable overall AE/SAE rates between EVG and RAL except for slightly higher rates for AEs considered drug-related, including those of Grades 2-4 (but not 3-4).

Taking into account the data for EVG + PI/r in this study and the STB data there seems to be a particular association between EVG and diarrhoea, including Grades 2-4. Rates were higher for EVG vs. RAL in study GS-US-183-0145 but no subject in the EVG group discontinued due to this AE. Although one third had Grade 2-4 diarrhoea, no case was serious. Diarrhoea also occurred more often with STB vs. Atripla (although not vs. ATV/r + TVD). Rates of nausea and vomiting were generally comparable for EVG vs. RAL in GS-US-183-0145.

EVG and STB have been associated with several cases of elevated ALT and AST. The available data do not suggest that EVG was more likely to trigger LFT abnormalities than RAL or that STB is associated with higher rates of abnormal liver parameters compared to Truvada or Atripla.

For other laboratory parameters there was no indication that EVG was associated with a higher rate of abnormal values vs. RAL except that hypophosphataemia was reported for 41 EVG and 31 RAL subjects. Urinary phosphate excretion was not measured. Very few subjects had co-existing hypophosphataemia and urinary abnormalities and in the EVG group subjects the most likely explanation was the co-administered TDF.

From the safety database all the adverse events reported in clinical trials that are deemed by the CHMP to be adverse reactions have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

There are no major safety concerns for use of EVG raised by the data. For the most part the safety profile of EVG was comparable with that of RAL when each was co-administered with RTV-boosted PIs and other agents in GS-US-183-0145. There seems to be a clear association between EVG and diarrhoea and this is one of the few AEs that occurred at a higher rate vs. RAL but it was not identified as the trigger for discontinuations due to AEs.

2.7. Pharmacovigilance system

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

2.8. Risk Management Plan

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

considered that the risk management system version 0.3 could be acceptable with revisions required as described in the attached PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The Applicant implemented the changes in the RMP as requested by PRAC. The CHMP endorsed the updated Risk Management Plan version 0.4 with the following content:

Safety concerns

Table 6. Summary of Safety Concerns

Important Identified Risks	Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness
	Drug resistance to EVG
Important Potential Risks	Concurrent use of drugs whose coadministration with EVG is contraindicated
	Medication errors that may result in reduced exposure to EVG
	Reduced efficacy in women
Missing Information	Safety in children
	Safety in elderly patients
	Safety in pregnancy
	Safety in lactation
	Safety in severe hepatic impairment (CPT score C)
	PK of EVG in subjects with UGT1A1 polymorphisms
	Long-term suppression of HIV-1 infection

Pharmacovigilance plans

Table 7. 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-183-0145 A Phase 3, multicenter, randomized, double-blind, double-dummy, study of the safety and efficacy of ritonavir-boosted elvitegravir (EVG/r) versus raltegravir (RAL) each administered with a background regimen in HIV-1 infected, antiretroviral treatment-experienced adults	To evaluate the long-term efficacy of EVG administered with a background regimen in adults	Missing information: Long-term suppression of HIV-1 infection	Ongoing	Q2 2015 (Final report)
GS-US-183-0160 A Phase 2/3, open-label, 2-part study evaluating the pharmacokinetics, safety, and antiviral activity of EVG administered with a background regimen containing a RTV-boosted PI in HIV-1 infected, antiretroviral treatment-experienced children aged < 18 years	To evaluate the PK, safety, and antiviral activity of EVG administered with a background regimen containing a PI/r in HIV-1 infected, ARV treatment-experienced children aged < 18 years	Missing information: Safety in children	Planned	April 2016 (48-week report [adolescents]) December 2016 (48-week report [0-12 years])

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
CO-US-183-0165 (PENTA 17) A Phase 2/3, multicenter, randomized, open-label, multicohort study comparing the safety and antiviral activity of current therapy versus EVG administered with RTV-boosted darunavir (DRV/r) or versus DRV/r in HIV-1 infected, antiretroviral treatment-experienced, virologically suppressed pediatric subjects aged 6 to < 18 years of age	To compare the safety and antiviral activity of current therapy versus EVG administered with DRV/r or versus DRV/r in HIV-1 infected, ARV treatment-experienced, virologically suppressed pediatric subjects aged 6 to < 18 years of age	Missing information: Safety in children	Planned	September 2017 (final report)
GS-US-183-0154 A Phase 2/3, open-label, 2-part study evaluating the pharmacokinetics, safety, and antiviral activity of EVG coadministered with COBI and 2-first-line NRTIs in HIV-1 infected, antiretroviral treatment-naive children aged < 18 years	To evaluate the PK, safety, and antiviral activity of EVG coadministered with COBI and 2-first-line NRTIs in HIV-1 infected, ARV treatment-naive children aged < 18 years	Missing information: Safety in children	Planned	October 2021 (final report)
Planned PK study of EVG following administration of STB in subjects with UGT1A1*28/*28 genotype	To evaluate the PK of EVG in subjects with UGT1A1*28/*28 genotype administered STB	Missing information: PK of EVG in subjects with UGT1A1 polymorphisms	Planned	Q2 2015 (final report)
Category 3 (Non-interventional studies)				
Drug utilization study	To determine the use of rifampicin, St. John's wort, carbamazepine, phenobarbital and phenytoin with EVG in the postmarketing setting.	Important potential risk: Concurrent use of drugs whose coadministration with EVG is contraindicated	Planned	25 February 2014 (Feasibility assessment report)

Study / Title	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
	To determine the incidence/prevalence and outcome of medication errors in the postmarketing setting that may result in reduced exposure to EVG.	Important potential risk: Medication errors that may result in reduced exposure to EVG		
Antiretroviral Pregnancy Registry	To determine the risk of birth defects in patients exposed to ARVs, including EVG, during pregnancy	Missing information: Safety in pregnancy	Ongoing	Interim reports available every 6 months (June and December each year)

Risk minimisation measures

Table 8. Summary Table of Risk Minimization Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Mini-mization Measures
Important identified risks		
Suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness	The SmPC (section 4.8) lists suicidal ideation and suicide attempt (in patients with a pre-existing history of depression or psychiatric illness) as an uncommon ADR.	None
Drug resistance to EVG	The SmPC (Section 4.4) states that EVG has a relatively low genetic barrier to resistance when used as part of a suboptimal regimen, and that, whenever possible, EVG should be administered with a fully active PI/r and a second fully active ARV agent to minimize the potential for virological failure and the development of resistance	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Important potential risks		
Concurrent use of drugs whose coadministration with EVG is contraindicated	The SmPC (Sections 4.3 and 4.5) includes information that coadministration with strong CYP3A inducers (rifampicin, St. John's wort, carbamazepine, phenobarbital and phenytoin) is contraindicated due to the potential for loss of virologic response and possible resistance. The Package Leaflet instructs patients that rifampicin, St. John's wort, carbamazepine, phenobarbital and phenytoin should never be taken with EVG	None
Medication errors that may result in reduced exposure to EVG	The SmPC (Section 4.2) states that EVG must be administered in combination with a PI/r, and includes information on the recommended dosing regimens for EVG and the coadministered PI/r and that no data are available to recommend the use of EVG with dosing frequencies or PIs other than those recommended in the Vitekta SmPC. The SmPC (Section 4.4) contains warnings that the dose of EVG should be decreased from 150 mg once daily to 85 mg once daily when used in combination with ritonavir-boosted atazanavir (ATV/r) and ritonavir-boosted lopinavir (LPV/r), that EVG should only be used in combination with a PI/r, that EVG should not be used with a PI boosted by another agent, that boosting EVG with an agent other than ritonavir may result in inadequate plasma levels of EVG and/or the PI, leading to loss of therapeutic effect and possible development of resistance, and that EVG should not be used in combination with products containing elvitegravir or pharmacokinetic boosting agents other than ritonavir. The Package Leaflet contains information on the appropriate EVG dose for each recommended PI and instructs patients to always take the dose recommended by the doctor and not to change the dose unless instructed to do so by the doctor.	None
Reduced efficacy in women	None	None
Missing information		
Safety in children	The SmPC (Section 4.2) states that the safety and efficacy of EVG in children aged 0 to less than 18 years have not yet been established and that no data are available. The SmPC (Section 4.8) states that no safety data are available for children below 18 years of age and that EVG is not recommended in this population	None
Safety in elderly patients	The SmPC (Section 4.2) states that no data are available on which to make a dose recommendation for patients over the age of 65 years.	None

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
Safety in pregnancy	The SmPC (Section 4.6) states that there are no or limited clinical data with EVG in pregnant women and that EVG should not be used during pregnancy unless the clinical condition of the woman requires treatment with EVG.	None
Safety in lactation	The SmPC (Section 4.6) states that it is unknown whether EVG is excreted in human milk, that a risk to the newborns/infants cannot be excluded and therefore EVG 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 severe hepatic impairment (CPT score C)	The SmPC (Sections 4.2 and 4.4) states that EVG has not been studied in patients with severe hepatic impairment (Child Pugh Class C). The SmPC (Section 4.4) includes a class warning for ARVs that patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice, and that if there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.	None
PK of EVG in subjects with UGT1A1 polymorphisms	None	None
Long-term viral suppression of HIV-1 infection	None	None

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

EVG is clearly active against HIV *in vitro* and achieved a 2-log drop in HIV RNA over 10 days when administered as 50 mg EVG plus 100 mg RTV daily in the short-term monotherapy study. When used at an appropriate dose regimen to treat susceptible virus it could be expected to contribute to the overall effect of an ART regimen, including co-administration with RTV-boosted PIs as proposed by the applicant. Taking into account also the data from study GS-US-183-0145, EVG may be considered as an alternative to the only currently licensed integrase inhibitor raltegravir. Overall, this study demonstrated comparable efficacy for EVG vs. RAL, with a lower bound of the 95% CI around the treatment difference (< 50 copies/mL at Week 48) of -6.0%. The sensitivity and secondary analyses support a conclusion of comparable efficacy for EVG vs. RAL.

Uncertainty in the knowledge about the beneficial effects

EVG is intended to be used only in co-administration with a PI/r. Due to the PK properties of EVG itself and the various possible PI/r regimens the total risk of possible interactions is difficult to assess and to predict.

EVG has only been evaluated in PK studies with twice daily DRV/RTV or LPV/RTV. In addition, the few data available from study 0145 strongly point against using EVG with once daily DRV/RTV. Off-label use of EVG with these regimens therefore constitutes a major concern and respective warning has been included in the SmPC.

The clinical efficacy programme for EVG was decided upon at a time of transition with regard to study feasibility and regulatory guidance. This led to conduct of a single pivotal study in which EVG was co-administered with one of five RTV-boosted PIs predicted to be active against the individual subject's virus plus at least one other agent. The study was not designed to provide PI-specific efficacy data although the numerical comparisons suggest no major differences between EVG and RAL for the PI/r subgroups. Nevertheless, much of the justification for use rests on the PK data indicating the need for either 150 mg or 85 mg EVG with individual PI/r combinations. At present there are doubts regarding only co-administration of EVG 150 mg with TPV/RTV, and this combination has therefore been excluded from the recommended combinations in the SmPC.

Although the numbers are too limited to draw firm conclusions, the observed lower efficacy in women warrants close attention and has been added to the RMP as a potential risk.

At present the virological data, including the resistance analysis population data, suggest that EVG is not associated with a higher risk of selecting for INSTI-R mutations compared to RAL and there is incomplete cross-resistance between the two. However, the experience is currently too limited to discern whether EVG has a similarly low genetic barrier to resistance as RAL in practice. Furthermore, there is sufficient evidence to support a warning regarding the need to ensure use in combination with other known active agents.

Risks

Unfavourable effects

The safety profile of EVG is mostly unremarkable among the HIV agents and is generally comparable with that of RAL. While EVG has a particular propensity to be associated with diarrhoea, thus far diarrhoea does not seem to have been a treatment-limiting issue. Although the final reasons for study discontinuation that are captured on CRFs sometimes mislead (e.g. subjects may be recorded as 'lost to follow-up' when in reality they had AEs in the clinical trial that prompted them to seek other treatment outside of the study and fail to attend further visits) there was not an overall excess of discontinuations from EVG vs. from RAL.

Uncertainties regarding the possible antibacterial effects of EVG and its impact have been identified from non-clinical data, but in absence of clinical findings those are regarded as minor.

Uncertainty in the knowledge about the unfavourable effects

Strictly with regard to use of EVG with boosted PIs in HIV-infected subjects the safety database is limited to 354 subjects, of which ~40 % discontinued before week 96. Despite of the overall safety profile of elvitegravir not being of any major concern, this limits the reliance that can be placed on the identification of adverse reactions and their rates.

Benefit-risk balance

Importance of favourable and unfavourable effects

The activity of EVG against HIV-1 has been clearly demonstrated, including in a confirmatory phase III study in comparison with another active treatment. Therefore, EVG has a potential to address the medical need that exists in the proposed HIV-1 infected target population.

No major unfavourable effects have been identified for EVG. However, the amount of safety data currently available limits the knowledge about the exact safety profile of EVG. Longer term data are expected to be available from additional pharmacovigilance activities agreed in the RMP.

Even though the possible PK interactions of EVG have been extensively studied, due to the many different possible combinations of co-administered medicines, the exact nature and extent of interactions is difficult to predict. The risks related to possible coadministration of EVG in non-recommended combinations or medication errors is to be addressed in a drug utilisation study agreed in the RMP.

The experience is currently too limited to discern whether in practise EVG has a similarly low genetic barrier to resistance as RAL, however the risk of resistance development does not prevent use of EVG in combination with other known active agents. Development of resistance has been included as an identified risk in the RMP.

Despite the limitations of the data available, taking into account the lack of serious safety concerns and the need for alternative treatments for the proposed target population there is sufficient evidence to support use of EVG with the four proposed PI/r combinations.

Benefit-risk balance

Current evidence suggests that the benefit-risk balance is in favour of use of EVG at the recommended dose with once daily ATV/r or with twice daily LPV/r, DRV/r or FPV/r and with other retroviral agents for treatment of HIV-1 infection in adults who are infected with HIV-1 without known mutations associated with resistance to EVG.

Discussion on the benefit-risk balance

The PK data and the evidence for efficacy, including the actual 95% CI observed in GS-US-183-0145 support use of EVG with RTV-boosted PIs as discussed above.

There are no safety concerns that would preclude use of EVG as recommended, however, there is a considerable potential for drug-drug interactions to occur, which has been reflected in the SmPC.

Efficacy results in women were numerically lower, but the number of subjects was too low to draw any firm conclusions. In addition, no potential mechanism has been identified that would explain such differences. Furthermore, even if numerically lower, efficacy was seen also in the subgroup of women.

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 Vitekta co-administered with ritonavir-boosted protease inhibitor and with other antiretroviral agent in the treatment of HIV-1 infection in adults who are infected with HIV-1 without known mutations associated with resistance to elvitegravir is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products 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 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 CHMP review of data on the quality properties of the active substance, the CHMP considers that elvitegravir is to be qualified as a new active substance at the time of submission of the Application for Marketing Authorisation.