Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Tenofovir disoproxil fumarate/Emtricitabine/Elvitegravir/ Cobicistat

Proprietary Product Name: Stribild

Sponsor: Gilead Sciences Pty Ltd

Date of first round CER:
30 May 2012

Date of second round CER:
19 September 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
³	At or greater than
£	At or lesser than
/co	boosted with cobicistat
/r	boosted with ritonavir
<	Less than
>	Greater than
AAG	α1-acid glycoprotein
AE	adverse event
aGFR	actual glomerular filtration rate
AIDS	Acquired Immunodeficiency Syndrome
ANOVA	analysis of variance
ARV	antiretroviral
ATR	efavirenz/emtricitabine/tenofovir disoproxil fumarate, coformulated (Atripla®)
ATV	atazanavir (Reyataz®)
ATV/co	cobicistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
CG	Cockroft-Gault
CI	Confidence interval
CLcr	creatinine clearance
COBI	cobicistat
CPI	comparative protease inhibitor
CSR	Clinical Study Report
CV	coefficient of variation
CYP	cytochrome P450 enzyme(s)

Abbreviation	Meaning
DAVG	difference between time-weighted average postbaseline and baseline
DMI	desipramine
DRV	darunavir (Prezista®)
e.g.	Exempli gratia; for example
ECG	electrocardiogram
ECHO	echocardiogram
EE	ethinyl estradiol
EFV	efavirenz (Sustiva®)
eGFR	estimated glomerular filtration rate
eGFRCG	estimated glomerular filtration rate calculated using the Cockroft-Gault equation
EU	European Union
EVG	elvitegravir
EVG/co	cobicistat-boosted elvitegravir
EVG/COBI/FTC /TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (QUAD),
EVG/r	ritonavir-boosted elvitegravir
FDA	Food and Drug Administration
FTC	emtricitabine (Emtriva®)
FTC/RPV/TDF	emtricitabine/rilpivirine/tenofovir disoproxil fumarate, coformulated (Complera™)
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GS-9200	metabolite of elvitegravir, produced by glucuronic acid conjugation; also named M4

Abbreviation	Meaning
GS-9202	metabolite of elvitegravir, produced by cytochrome P450-mediated oxidation; also
HIV	human immunodeficiency virus
HIV, HIV-1	human immunodeficiency virus, type 1
i.e.	Id est; that is
INSTI	integrase strand-transfer inhibitor
IQ	inhibitory quotient
ITT	intent-to-treat
KTZ	ketoconazole
L	Litre
LPV/r	lopinavir/ritonavir, coformulated (Kaletra®)
LSM	least-squares mean
MDZ	midazolam
mg	Milligram
mL	Millilitre
N(t)RTIs	nucleoside/tide analogue reverse transcriptase inhibitors named M1
NGM	norgestimate
NGMN	norelgestromin, the primary and pharmacologically active metabolite of norgestimate
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
Pgp or MDR1	P-glycoprotein
PI	protease inhibitor

Abbreviation	Meaning
PK	pharmacokinetic(s)
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QUAD	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, coformulated
RPV	rilpivirine (Edurant™)
RT	reverse transcriptase
RTV	ritonavir (Norvir®)
SD	standard deviation
STR	single-tablet regimen
TDF	tenofovir disoproxil fumarate, (Viread®)
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TGA	Therapeutic Goods Administration
TLOVR	Time to Loss Of Virologic Response algorithm
TSH	thyroid stimulating-hormone
TVD	emtricitabine/tenofovir disoproxil fumarate, coformulated (Truvada®)
UGT	uridine diphosphate glucuronosyltransferase
US	United States
vs.	versus

Note on product trade name: the sponsor changed the product name from QUAD to 'STRIBILD' during the evaluation of this application. 'QUAD', 'THEQUAD' and 'STRIBILD' should be considered interchangeable for the purpose of this evaluation report

1. Introduction

This is a submission to register a new chemical entity, a fixed-dose combination tablet comprising of 300mg of tenofovir disoproxil fumarate (TDF), 200 mg of emtricitabine (FTC), 150 mg of elvitegravir (EVG) and 150 mg of cobicistat (COBI).

TDF 300mg and FTC 200mg have been previously approved as single active ingredient medicines by TGA (under the brand names of Viread and Emtriva, respectively) for the treatment of HIV infection. A fixed-dose combination tablet combining 300 mg of TDF and 200 mg of FTC (Truvada) has also been previously approved by TGA. Elvitegravir and Cobicistat are new chemical entities.

QUAD is a fixed-dose combination anti-retroviral (ARV) drug, comprising of TDF, FTC, EVG and COBI. TDF is a nucleotide reverse transcriptase inhibitor (NtRTI). FTC is a nucleoside reverse transcriptase inhibitor (NRTI). EVG is a HIV-1 integrase strand-transfer inhibitor (INSTI) and works by preventing integration of the HIV-1 DNA into the host-cell genome. COBI is a selective mechanism-based inhibitor of cytochrome P450 of the CYP3A subfamily. Inhibition of CYP3A-mediated metabolism by COBI enhances the systemic exposure of CYP3A substrates, one of which is EVG.

The proposed indication is for the use of QUAD as a complete regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of QUAD[1].

2. Clinical rationale

In the clinical dossier for this submission, the sponsor has stated that current treatment guidelines recommend that initial treatment for ARV treatment-naive HIV-1 infected patients should involve 2 N(t)RTIs (e.g. FTC and TDF) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) (e.g. efavirenz [EFV]), a boosted protease inhibitor (PI), or an INSTI. Currently in Australia, raltegravir is the only INSTI approved for use in adults, and it requires twice-daily dosing regimen.

As adherence to ARV drug regimen is important in preventing viral rebound and to reduce risk of drug resistance development, fixed-dose combination single-tablet regimens (STRs) have been developed to improve compliance. Currently in Australia, there are 2 NNRTI/N(t)RTI based-STRs approved for once-daily administration in the treatment of HIV-1 infection: Atripla (FTC/TDF/EFV) (approved in July 2009) and Eviplera (FTC/TDF/ rilpivirine) (approved in January 2012). No STRs exist that combine an INSTI with an N(t)RTI backbone.

The sponsor has stated that the clinical rationale for formulating QUAD is that there remains a need for alternative STRs with potent and sustained efficacy and with a favourable tolerability and safety profile across subgroups of the HIV-1 infected patient population. The sponsor cited an example of EFV having been classified as pregnancy class D, which limits the use of Atripla in women of childbearing potential.

[1] Proposed Australian Product Information, Module 1.3.1.2 of current submission.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5:

- 2 pivotal Phase III efficacy/safety studies (GS-US-236-0102 and GS-US-236-0103)
- 1 Phase II efficacy/safety study (GS-US-236-0104)

Module 1:

- Application letter, application form, draft Australian PI and CMI

Module 2:

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

3.2. Paediatric data

This submission did not include paediatric data. In addition, as the sponsor is not proposing to include an indication for use in children (aged <18 years), information on a Paediatric Development Program was not included in this application.

3.3. Good clinical practice

The 3 clinical studies reviewed in this evaluation were in compliance with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

4. Pharmacokinetics

4.1.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic		Study ID	Primary Drug
PK in healthy adults	General PK	Single dose	GS-US-216-0101	COBI
			GS-US-216-0113	COBI
		Multi-dose	GS-US-216-0101	COBI
			GS-US-216-0113	COBI
	Bioequivalence†	Single dose	GS-US-236-0105 GS-US-183-0140	EVG* EVG*
		Multi-dose	GS-US-236-0105 GS-US-183-0140	EVG* EVG* QUAD*
	Food effect		GS-US-236-0105	EVG
	Mass Balance Study		GS-US-183-0126 GS-US-216-0111	EVG COBI

PK topic	Subtopic	Study ID	Primary Drug
PK in special populations	Target population § Single dose		
	Multi-dose	GS-US-183-0101 GS-US-183-0105	EVG EVG
	Hepatic impairment	GS-US-183-0133	EVG/COBI
	Renal impairment	GS-US-216-0124	EVG/COBI
PK interactions	ritonavir	GS-US-183-0102	EVG/COBI
	ritonavir	GS-US-183-0113	EVG/COBI
	atazanavir	GS-US-183-0106	EVG/COBI
	ritonavir	GS-US-183-0106	EVG/COBI
	atazanavir	GS-US-183-0108	EVG/COBI
	lopinavir	GS-US-183-0116	EVG/COBI
	omeprazole	GS-US-183-0119	EVG/COBI
	ketoconazole	GS-US-183-0146	EVG/COBI
	darunavir	GS-US-201-0104	EVG/COBI
	dmeprazole	GS-US-216-0120	EVG/COBI
	famotidine	GS-US-216-0120	EVG/COBI
	famotidine	GS-US-216-0122	EVG/COBI
	atazanavir	GS-US-216-0123	EVG/COBI
	rosuvastatin	GS-US-216-0123	EVG/COBI
	rifabutin	GS-US-216-0123	EVG/COBI
	Oral Contraceptive	GS-US-236-0106	EVG/COBI
Population PK analyses	Healthy subjects		EVG
	Target population		EVG§

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

Elvitegravir (EVG) is a potent HIV-1 integrase strand-transfer inhibitor. Emtricitabine (FTC) and Tenofovir (TFV) are potent and selective inhibitors of HIV-1 reverse transcriptase (RT). Cobicistat (COBI) is a pharmaco-enhancer that is a potent mechanism-based inhibitor of CYP3A enzymes that reduces systemic clearance and increases exposure of EVG. Both EVG and COBI undergo hepatic metabolism and are minimally excreted in the urine. EVG is primarily metabolized via CYP-mediated aromatic and aliphatic hydroxylation and/or primary or secondary glucuronidation. There are two main metabolites M1 (GS-9202) and M4 (GS-9200) both of which are present at lower concentrations than EVG in plasma. Both metabolites are much less potent than EVG and do not contribute to the clinical effects of the drug. Similarly COBI was the predominant species in plasma; observed metabolites were at undetectable to very low concentrations relative to systemic exposure of COBI. Metabolites M21, M26, and M31 are weaker inhibitors of CYP3A compared with COBI, and due to their low systemic concentrations, should not contribute to the primary PD effect of CYP3A inhibition

EVG is rapidly absorbed with peak plasma concentrations occurring 3-4hours after the dose. Taken with a high fat meal the absorption is increased. EVG is highly bound (>95%) to plasma proteins with a large volume of distribution (exceeding total body water) indicating extensive distribution to the tissues. EVG demonstrates non-linear pharmacokinetics with less than dose proportional increases in systemic exposure with increasing doses of EVG alone. In the presence

of a CYP3A inhibitor (as in the QUAD) systemic exposures were greater than dose proportional. Elimination half life was also prolonged (from ~3h to ~9h) in the presence of ritonavir (a CYP3A inhibitor).

No clinically relevant changes in EVG or COBI exposures are observed in the setting of renal or moderate hepatic impairment. The PK profiles of FTC, EVG, COBI, and TDF, and of QUAD have been established in HIV-1 infected subjects and some special populations. No clinically relevant differences in the PK of the QUAD STR were observed with respect to demographic variables.

COBI has been shown to decrease estimated CLcr, due to inhibition of tubular secretion of creatinine, without affecting renal glomerular function. Dose adjustment of EVG or COBI would not be warranted in subjects with renal impairment. However, dose-interval adjustment is required for FTC and TDF in patients with CLcr < 50 mL/min which cannot be achieved with the fixed-dose combination tablet. Consequently, QUAD would need to be discontinued in such patients (CLcr < 50 mL/min).

Dose adjustment of QUAD STR in mildly or moderately hepatically impaired patients would appear to be unnecessary as the PK of its components is unaffected in moderate hepatic impairment. No data are available regarding the use of EVG or COBI in subjects with severe hepatic impairment. QUAD STR is not recommended for use in these patients.

Based on the drug-drug interaction profile of EVG and COBI the QUAD STR may have clinically significant interactions with drugs metabolised by or which inhibit CYP3A. Thus potent CYP3A inducers could decrease COBI and EVG plasma concentrations potentially reducing therapeutic efficacy. Similarly QUAD STR may inhibit the metabolism of drugs dependent on CYP3A for clearance and potentiate adverse or life threatening events. Antacids co-administered with EVG reduced the absorption due to a chelating effect. Staggered dosing, by at least two hours, has been shown to avoid this issue.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

Following oral administration, peak EVG concentrations are observed ~ 3 to 4 hours after dosing, regardless of dose level in HIV-1 infected patients and healthy subjects, and its absorption is unaffected by local gastrointestinal pH; however, EVG is subject to chelating in the gastrointestinal tract by cations present in high-strength antacids. The PK of boosted EVG in the presence of acid-reducing agents was evaluated using simultaneous or staggered (± 2 hours or ± 4 hours) administration of antacid (20mL of magnesium hydroxide/aluminum hydroxide; 2000 mg each total dose), staggered (12 hours) or co-administration with a representative proton pump inhibitor, omeprazole (40 mg once daily), using different boosters for EVG (RTV or COBI), and staggered (12 hours) or co-administration with a representative H2-receptor antagonist, famotidine (40 mg once daily)). Elvitegravir absorption and systemic exposures were lower (40%−50%) upon simultaneous co-administration with antacids (GS-US-183-0119). Staggering EVG and antacid administration by ± 2 hours or ± 4 hours offsets the interaction. Elvitegravir absorption was unaffected upon staggered or co-administration of boosted EVG with omeprazole (GS-US-183-0119; GS-US-216-0122), with EVG exposure parameters being within bioequivalence limits (90% CI within 80%−125%). Similarly, EVG exposures were unaffected (within bioequivalence bounds) following staggered or co-administration of boosted EVG with famotidine, indicating that changes in gastric pH do not affect EVG PK (GS-US-216-0120; GS-US-216-0122).

Since cobicistat has 3 basic ionizable groups and the intrinsic aqueous solubility is significantly enhanced under acidic conditions at pH 2, clinical studies were conducted to examine the relative bioavailability and disposition of COBI (in combination with EVG) when co-administered with acid-reducing agents (Studies GS-US-216-0120; GS-US-216-0122,). Cobicistat absorption was unaffected upon staggered (12 hours) or co-administration with omeprazole, with exposure parameters within bioequivalence limits (GS-US-216-0120). Similarly, COBI

exposures were unaffected following staggered (12 hours) or co-administration with famotidine (GS-US-216-0122).

4.2.1.2. Bioavailability

4.2.1.2.1. Absolute bioavailability

No studies were conducted. The drug is formulated as an oral tablet; no intravenous formulations are available.

4.2.1.2.2. Bioequivalence of clinical trial and market formulations

Bioequivalence of EVG and COBI exposures when administered as components of the QUAD STR formulation (Phase 3 studies, proposed commercial formulation) relative to the original QUAD STR formulation (used in Phase 2 study GS-US-236-0104) was assessed in healthy volunteers after multiple doses (GS-US-236-0110). Bioequivalent EVG and COBI exposures between Formulation 2 and Formulation 1 were demonstrated. Emtricitabine exposure was bioequivalent when administered as a component of the new QUAD STR relative to administration of FTC + TDF alone. Tenofovir AUC_{tau}, C_{tau}, and C_{max} were 26%, 28%, and 50% higher, respectively, following Formulation 2 administration than following FTC + TDF administration.

4.2.1.2.3. Bioequivalence of different dosage forms and strengths

The relative bioavailability of the fixed-dose combination (FDC) tablet versus administration of individual components was evaluated in a multiple dose study in healthy volunteers (GS-US-236-0101). The components of an STR contained EVG 150 mg, FTC 200 mg, and TDF 300 mg plus the pharmaco-enhancer COBI at doses of 100 mg or 150 mg relative and were compared to EVG/r 150/100 mg, and also to FTC 200 mg plus TDF 300 mg co-administered as separate components. Administration of EVG as an STR with COBI at a dose of 100 mg resulted in bioequivalent EVG exposure as assessed by AUC_{tau} and C_{max}, but 37% lower as assessed by C_{tau} estimate relative to EVG/r . With the STR containing COBI 150 mg, EVG exposure was modestly higher with C_{max} but met the definition of bioequivalence, while the upper bound of the 90% confidence interval (CI) of AUC_{tau} exceeded the criteria by 1%. Higher EVG trough concentrations (C_{tau}) (9% higher than with EVG/r) were achieved at this COBI dose (150 mg). Tenofovir AUC_{tau} was bioequivalent with slightly higher C_{max} and C_{tau} with administration of the QUAD STR relative to administration of FTC and TDF together as individual components, but was comparable with TFV exposure when TDF was co-administered with RTV-boosted protease inhibitors. Higher TFV exposures with the QUAD STR are attributed to the effect of COBI on P-glycoprotein (Pgp or MDR1) transporter in the gut. Emtricitabine AUC_{tau}, C_{max}, and C_{tau} were modestly higher with the STR. Tenofovir and FTC exposures were considered clinically equivalent.

The relative bioavailability of the Phase 3 formulation (Formulation 2) of elvitegravir boosted with ritonavir was examined in a randomized, open label, multiple-dose, two-way crossover study in healthy subjects (GS-US-183-0140). Subjects were stratified (1:1) by both gender and ethnicity (Hispanic: Non-Hispanic). Both the 125/100mg and 150/100mg elvitegravir/r formulations were pharmacokinetically equivalent: AUC_{tau}, C_{max}, and C_{tau} ratios (%) of the geometric least-squares means and their corresponding 90% CIs fell within the predetermined bioequivalence bounds of 80% to 125% for elvitegravir and 70% to 143% for ritonavir.

The multiple-dose pharmacokinetics of cobicstat Formulation 2 and Formulation 1 were compared in a randomized, open-label, multiple-dose, crossoverstudy (GS-US-216-0116). In addition the pharmacodynamics (anti-CYP3A activity) of Formulation 2 of cobicstat, and the multiple-dose pharmacokinetics of EVG as a stand-alone tablet administered with Formulation 2 of cobicstat were also evaluated. Subjects were enrolled into 1 of 2 parallel cohorts (Cohort 1 or Cohort 2), and within their assigned cohort, were randomized to 1 of 2 treatment sequences. Each treatment sequence consisted of two 10-day treatment periods during which subjects

received both treatments in their assigned cohort. In Cohort 1, the GLSM ratios for cobicstat AUC_{tau}, C_{tau}, and C_{max}, and the associated 90% CIs, were contained within the 80% to 125% range, indicating bioequivalent cobicstat exposures from the 2 formulations. GLSM ratios for midazolam (CYP3A activity probe) AUC_{inf}, AUC_{last}, C_{max}, and C_{last}, and the associated 90% CIs, were contained within the 80% to 125% range for the comparison of cobicstat Formulation 2 versus Formulation 1. Thus bioequivalent MDZ exposures were achieved indicating similar inhibition of CYP3A by the two formulations. In Cohort 2, the GLSM ratios for EVG AUC_{tau}, C_{tau}, and C_{max}, and the associated 90% CIs, were contained within the 80% to 125% for the comparison of EVG boosted with cobicstat Formulation 2 versus RTV, indicating bioequivalent exposures to EVG from these treatments.

4.2.1.2.4. Influence of food

The effect of a light meal and a high-calorie, high-fat meal on the absorption/bioavailability of boosted EVG was evaluated using the QUAD STR (GS-US-236-0105). Elvitegravir mean (%CV) C_{max} and AUC_{inf} were 22% and 34% higher with a light meal and 56% and 87% higher with a high-calorie/high-fat meal, compared to fasted dosing. The increased EVG exposures between a light meal and a high-calorie/high-fat meal were not considered clinically relevant. Boosted EVG and QUAD STR have been administered with food throughout the clinical development program.

The effect of a light meal and a high-calorie, high-fat meal on the absorption/bioavailability of COBI and its pharmaco-enhancing abilities on EVG was evaluated using the QUAD STR (GS-US-236-0105). Cobicistat exposure parameters AUC_{inf}, AUC_{last}, and C_{max} were bioequivalent under light meal and fasted conditions. For the high-calorie/high-fat meal condition, respective decreases in AUC_{inf}, AUC_{last}, and C_{max} were 19%, 20%, and 27% relative to the light meal condition and were 17%, 18%, and 24% relative to the fasted condition. The effect of a high-calorie/high-fat meal on COBI exposure did not negatively affect EVG exposures.

Mean FTC AUC_{inf}, AUC_{0-last}, and C_{max} were bioequivalent between the 3 treatment conditions. Relative to the fasted condition, TFV AUC_{inf} and AUC_{0-last} increased by 24% and 25% with a light meal and by 23% and 25% with a high-calorie/high-fat meal, respectively. The AUC estimates were bioequivalent between the two fed conditions. Tenofovir C_{max} increased by 20% with a light meal relative to the fasted condition, but was similar between the high-calorie/high-fat meal condition versus the fasted condition. Tenofovir C_{max} decreased by 14% with a high-calorie/high-fat meal relative to a light meal.

4.2.1.2.5. Dose proportionality

Elvitegravir plasma exposures are non-linear and less than dose proportional, likely due to solubility-limited absorption. Dose proportionality of EVG PK at steady state can be concluded from a study examining therapeutic and supra-therapeutic doses of EVG on QT interval in healthy volunteers (GS-US-183-0128). The dose-normalized AUC_{tau} of EVG following multiple 250/100 mg EVG/r doses was 75.2% of the 125/100 mg dose. The corresponding values for C_{max} and C_{tau} were 81.1% and 71.8% of the 125/100 mg dose, respectively, indicating that EVG exposures were less than dose proportional.

This finding was confirmed from a single- and multiple-dose PK study of unboosted EVG at doses of 200, 400, and 800 mg twice daily, 800 mg once daily(GS-US-183-0101). Elvitegravir 200, 400, and 800mg twice-daily doses resulted in 31%, 23%, and 52% lower exposure, respectively, at steady state compared to a single dose, consistent with auto-induction of CYP3A. Non proportionality was also shown in a multiple-dose PK study of EVG/r at doses of 20/100 mg, 50/100 mg, and 125/100 mg in HIV positive patients (GS-US-183-0105). Elvitegravir exposures increased in an approximately dose-proportional manner between EVG doses of 20 and 50 mg, but were less than dose proportional between 50 and 125 mg. Cobicstat exhibited nonlinear pharmacokinetics (GS-US-216-0101). Single-dose escalation from 50 mg to 100 mg and from 100 mg to 200 mg resulted in decreases in the apparent clearance (CL/F means ratios of 23.55% for 100 vs.50 mg and 38.43% for 200 vs.100 mg). Similar results were seen following

multiple doses: mean ratios of 33.49% for 100 vs.50 mg and 42.48% for 200 vs.100 mg. Lower apparent clearances were also observed following multiple dosing relative to single dosing at each dose level.

4.2.1.2.6. Bioavailability during multiple-dosing

Pharmacokinetic data following administration of the QUAD STR in healthy subjects were obtained from a multiple-dose bioavailability study (GS-US-236-0110) and from a single-dose food-effect study (GS-US-236-0105). Both studies used the Phase 3 intended commercial formulation. Elvitegravir AUC and C_{max} were comparable between single (AUC_{inf}) and multiple (AUC_{tau}) doses of the QUAD STR, indicating substantial inhibition of EVG metabolism by COBI even after a single dose, consistent with potent competitive CYP3A inhibition. Elvitegravir T_{max} was similar following single- or multiple-dose administration. In comparison, EVG mean C_{24} was ~ 43% higher (508 vs 355 ng/mL) following multiple-dose administration relative to single-dose administration. These results are consistent with those obtained using RTV and mechanism-based inhibition of CYP3A by COBI resulting in reduction in EVG systemic clearance and attaining steady-state.

The multiple-dose PK of COBI Formulation 2 and Formulation 1 were compared after multiple-doses in healthy volunteers using a two cohort, crossover design (GS-US-216-0116). The GLSM ratios for COBI AUC_{tau}, C_{tau}, and C_{max}, and the associated 90% CIs, were contained within the protocol-defined bounds of 80% to 125%, indicating bioequivalence of COBI exposures from the two formulations.

4.2.1.3. Distribution

4.2.1.3.1. Volume of distribution

The apparent volume of distribution for elvitegravir was available from a single and repeated dose study in which the drug was administered alone or with ritonavir in healthy subjects (GS-US-183-0102). The apparent volume of distribution for the drug taken alone as a single dose was 536L (CV 23%) and after repeated doses was 668L (CV 41%). When taken with repeated doses of ritonavir the apparent distribution volume was reduced to 161L (CV 123%). Mean clearance declined from 148.4L/h, (CV 27.8%) taken alone to 7.44L/h (30.1%) when taken with ritonavir.

A similar study was conducted for cobicstat (GS-US-216-0113). No distribution volumes were reported in this study but using standard equations and mean values for clearance and half life an apparent volume was calculated as 116L after a 300mg single dose and 72L after a 400mg single dose.

4.2.1.3.2. Plasma protein binding

Based on equilibrium dialysis studies (*in vitro* and plasma samples from HIV-1 infected patients and healthy subjects from clinical studies, including subjects with renal or hepatic impairment), EVG was, on average, 98% to 99% bound to human plasma proteins regardless of concentration, with preferential binding to albumin over α1-acid –glycoprotein.

The plasma protein binding of COBI was 97.3% in samples from clinical studies with healthy human subjects, which occurred in a concentration-independent manner.

4.2.1.3.3. Erythrocyte distribution

After a single oral 50-mg dose of [14C] EVG in healthy subjects, 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 (GS-US-183-0126).

After an oral 150-mg dose of [^{14}C] COBI in healthy subjects, the blood-to-plasma ratio of ^{14}C-radioactivity was time-independent and ~ 0.5, indicating that COBI and its metabolites are excluded from the cellular components of the blood (GS-US-216-0111).

4.2.1.3.4. Tissue distribution

The distribution of EVG into compartments other than plasma has not been clinically evaluated. The distribution of COBI into compartments other than plasma has not been clinically evaluated.

4.2.1.4. Metabolism and Excretion

4.2.1.4.1. EVG

The mass-balance, PK, and metabolite profile of EVG following administration of an oral dose of boosted [14C] EVG in healthy subjects were evaluated in Study (GS-US-183-0126). Serial blood (whole blood and plasma), urine, and stool samples were obtained for analysis. Quantifiable levels of [14C]-radioactivity in whole blood and plasma were observed for up to 36 and 48 hours, respectively. Recovery of the radioactive dose was primarily from the feces (94.8%) relative to urine (6.7%), suggesting primarily hepatobiliary excretion of EVG. The combined fecal and urinary recovery (101.4% ± 4.2%) accounted for the entire administered radioactive dose.

In **plasma**, the predominant circulating species was EVG (approximately 94%), with the remaining radioactivity made up of low levels of metabolites from hydroxylation and/or glucuronidation pathways, including GS-9200 and GS-9202 (the M4 and M1 metabolites of EVG, respectively). Quantifiable levels of GS-9200 were observed only up to 8 hours postdose, and represented < 5% of the parent exposure. Plasma exposures of the CYP3A-mediated metabolite, GS-9202, were generally below the limit of quantitation, consistent with its inhibition by pharmaco-enhancers such as RTV or COBI. Low levels of minor metabolites M7 (phenyl-hydroxylated-EVG-glucuronide) and M19 (isopropylhydroxylated-EVG-glucuronide-3) were observed at a few postdose time points (< 3% of parent exposure). Trace levels of glucuronides and hydroxylated metabolites were also observed.

Radioactivity in **urine** (approximately 6.7% of the administered dose) consisted primarily of 4 minor metabolites each representing > 1% of the administered dose. Several trace metabolites (< 1% of the dose) were observed. No parent drug was detected in urine. The 4 minor metabolites, M19, M7, M20 (quinolone-hydroxylated-EVG-glucuronide), and GS-9200 accounted for means of 1.48%, 1.44%, 1.41%, and 1.26% of the administered dose, respectively**.**

The radioactivity in **feces** (pooled samples) was accounted for mainly by EVG and hydroxylation products. The presence of EVG in feces (30.8%) is likely a combination of unabsorbed drug from the gastrointestinal tract, biliary secretion of EVG, and biliary secretion of GS-9200 converted back to EVG by the β-glucuronidases in the intestinal microflora. Metabolites in the feces included GS-9202 (33.8%) and low levels of M9 (dihydroxylated-dihydro-EVG-1; 1.49%–3.26%), M13 (quinolone-hydroxylated-EVG; 1.44%–2.83%), and M15 (isopropylhydroxylated-EVG; 3.48%–7.37%) in some samples. Elvitegravir is primarily metabolized via aromatic and aliphatic hydroxylation and/or primary or secondary glucuronidation.

Elvitegravir was predominantly metabolized by CYP3A4, and the resulting pattern of metabolites most closely resembled that generated by human hepatic microsomal fractions. UGT1A1 and UGT1A3 generated appreciable amounts of GS-9200, suggesting that these would be the major catalysts for the glucuronidation of EVG in humans.

From the population PK study the apparent systemic clearance of EVG (CL/F) was estimated to be 6.55 L/h (relative standard error=2.0%) with an inter-individual variability of 31.6%. The mean elimination half life of elvitegravir administered as the QUAD was ~5hours and was not affected by a meal (GS-US-236-0105)**.** The elimination half life of elvitegravir was increased in the presence of the CYP3A inhibitor ritonavir to 7-14h after a single oral dose (GS-US-183-

0140). At steady state in this study the elimination half life was 6-14h. In a comparative bioavailability study of the QUAD the elimination half life of elvitegravir was 9-14h for both formulations with a mean of ~12 hours (GS-US-236-0110).

4.2.1.4.2. COBI

The mass-balance, PK, and metabolite profile of COBI following administration of an oral dose of boosted [^{14}C] COBI were evaluated in healthy subjects (GS-US-216-0111)**.** COBI is primarily metabolized via CYP3A- and/or CYP2D6-mediated oxidation, with no evidence of Phase 2 metabolism. The total combined mean (SD) recovery of 14C-radioactivity in feces and urine was 94.4% (3.75%), with most of the radioactive dose recovered from the feces (86.2% [3.95%]), consistent with the hepatobiliary excretion of COBI and primarily as parent drug or metabolites M21 (GS-9454, or E1) or M31 (GS-9612, or E3); 8.2% of the administered dose was recovered in urine, primarily as unchanged parent drug and with low levels of metabolites M21 and M31. The predominant species circulating in plasma was COBI, which accounted for 98.6% of the total ^{14}C-radioactivity over 24 hours. In some instances at individual time points (≤ 2 time points), low levels of radioactive metabolite(s) were detected in pooled plasma samples; however, composite concentration-time profiles could not be drawn, precluding quantification of these metabolites.

Analysis by HPLC radiometry and LC/MS/MS showed that COBI was the major species in the feces (27%), followed by known oxidative metabolites, E3 (14%), which results from hydroxylation of isopropyl thiazole; and E1 (5.5%), which results from carbamate cleavage. All other metabolites detected in the feces were in trace amounts, with no values exceeding 3% of the administered radioactive dose.

In a comparative bioavailability study of the QUAD the elimination half life of cobicstat was ~3.5h with a range of 3-4hours (GS-US-236-0110). Similarly the mean elimination half-life of cobicstat administered as the QUAD was ~3hours and was not affected by a meal (GS-US-236-0105).

4.2.1.4.3. Activity of Metabolites

EVG administration without a CYP3A inhibitor produces two primary metabolites: (1) M1 (GS-9202) whose formation is almost completely inhibited when administered with RTV or COBI (typically M1 concentrations are below the lower limit of quantification [20 ng/mL] in clinical studies), and (2) M4 (GS-9200), produced by uridine glucuronosyltransferase (UGT) 1A1/3 and which becomes the predominant route of metabolism in the boosted state.

Plasma exposure (AUC_{tau}) of GS-9200 (M4) is typically < 10% of that observed for EVG and is unaffected by boosting. The M1 and M4 metabolites are markedly less potent (M1: 5- to 18-fold and M4: 10- to 38-fold in antiviral activity assays) than parent drug; thus **metabolites are not considered to contribute to the antiviral activity of EVG**.

A summary table for the PK parameters of elvitegravir after single and repeated doses is shown in Table 2. A summary table for the PK parameters of cobicstat after single doses is shown in Table 3.

Table 2. Summary of elvitegravir pharmacokinetic parameters after single or multiple doses taken alone

GS-9137 PK Parameter	Single Dose (Day 1) (N = 12)	Multiple Doses (Day 10) (N = 12)
C_{max} (ng/mL), Mean (%CV)	200.1 (30.4)	164.1 (28.8)
T_{max} (h), Median (Min, Max)	3.00 (2.00, 4.00)	2.50 (1.00, 4.00)
C_{tau} (ng/mL), Mean (%CV)	19.2 (52.5)	12.4 (63.7)
T_{last} (h), Median (Min, Max)	11.5 (11.5, 11.6)	20.0 (16.0, 24.0)[a]
AUC_{tau} (ng•h/mL), Mean (%CV)	817.3 (25.1)	719.3 (26.2)
AUC_{inf} (ng•h/mL), Mean (%CV)	908.1 (28.3)	Not applicable
$\%AUC_{exp}$, Mean (%CV)	10.1 (55.0)	Not applicable
$T_{½}$ (h), Median (Min, Max)	3.1 (2.2, 4.8)[b]	3.5 (2.2, 4.1)[a]
V_z/F (L), Mean, (%CV)	536.1 (23.8)	668.3 (41.1)
CL/F (L/h), Mean (%CV)	119.0 (30.1)	148.4 (27.8)

C_{tau} represents the concentration at the end of the dosing interval on Days 1, 10, 11, and 20.

On Day 1, $C_{tau} = C_{last}$ and $AUC_{tau} = AUC_{0-last}$.

a The Day 10 evening dose was withheld, and the 16-hour and 24-hour (i.e., predose on Day 11) time points were used.

b Sampling for half-life was limited to 12 hours postdose.

Table 3. Summary of cobicistat single-dose pharmacokinetic parameters

GS-9350 PK Parameter	Cohort 1 (300 mg) n = 12	Cohort 2 (400 mg) n = 12
AUC_{inf} (ng•h/mL), mean (% CV)	20772.5 (27.7)	39898.6 (26.2)
C_{max} (ng/mL), mean (% CV)	2338.5 (16.9)	4113.0 (17.2)
T_{max} (h), median (Q1, Q3)	3.75 (3.50, 4.50)	4.25 (3.75, 4.50)
C_{last} (ng/mL), mean (% CV)	152.4 (55.5)	14.2 (58.3)
T_{last} (h), median (Q1, Q3)	23.95 (23.95, 23.95)	42.00 (36.00, 48.00)
$T_{½}$ (h), median (Q1, Q3)	5.20 (4.25, 5.83)	4.75 (4.13, 4.93)
CL/F (ml/hr), mean (% CV)	15525.9 (28.8)	10591.5 (23.2)

CV = coefficient of variation, h = hour(s), Q1 = first quartile, Q3 = third quartile

4.2.1.4.4. Interconversion between enantiomers

Although elvitegravir is designated as an 'S' enantiomer inter-conversion *in vivo* does not appear to have been studied.

4.2.1.4.5. Intra- and inter-individual variability of pharmacokinetics

As AUC provides the best measure of total systemic exposure to a medication, inter-individual variation in PK for QUAD STR components has been assessed from the reported coefficient of variation for the appropriate AUC measure used in single and multiple dose studies.

After single doses in healthy volunteers receiving QUAD STR the reported variance in elvitegravir AUC_{last} was 22.6% after a high fat, high calorie meal (GS-US-236-0105). In the same study the variance was 28% after a light meal and 40.2% in the fasted state. For cobicstat the variance was 44.4 to 49.5% for AUC_{last} irrespective of the fasted/fed state. Smaller variance was reported for the other components of QUAD: 17-24% for tenofovir and 19-21% for emtricitabine across the fasted/fed conditions.

A comparative repeated dose bioavailability of two formulations QUAD STR, administered after an overnight fast, reported variance of 20-30% in AUC_{tau} for all four components and both formulations of the tablet (GS-US-236-0110).

A similar inter-individual variability was observed in a repeated dose study comparing the bioavailability of two formulations of elvitegravir boosted with ritonavir in healthy controls (GS-US-183-0140). In this study the variance in AUC_{tau} was about 30% after both formulations administered within 5 minutes of a standardised meal.

Somewhat higher variability in AUC_{tau} was reported in subjects with moderate hepatic impairment (40.6%) compared to controls (27.8%) for elvitegravir kinetics (US-GS-183-0133). For cobicstat there was no difference between the two groups. In severe renal impairment the variance for elvitegravir was the same as for normal controls (US-GS-216-0124). On the other hand the variance cobicstat AUC_{tau} was higher in the severe renal impairment (36.8%) than in normal renal function (24.4%).

In other reported studies the variance in elvitegravir AUC values tended to be around 30 to 40% with an occasional report of up to 50%. Variability appeared to be reduced by taking the medication with meals. For cobicstat the variance was also between 20-40% for various AUC values. However the variance appears to be dose dependent. In a single and multiple dose study the variance in AUC_{tau} after 50mg repeated doses was 81.6% (GS-US-216-0101). At higher doses the variance declined to ~34% at 100 and 200mg.

There were no specific studies examining the intra-individual variability in PK parameters.

4.2.2. Pharmacokinetics in the target population

Single- and multiple-dose PK of unboosted EVG at doses of 200, 400, and 800 mg twice daily, 800 mg once daily, and of once-daily EVG/r 50/100 mg demonstrated that unboosted EVG $T_{1/2}$ was ~ 3 hours versus ~ 9 hours upon multiple-dose co-administration with RTV (GS-US-183-0101). Elvitegravir 200, 400, and 800 mg twice-daily doses resulted in 31%, 23%, and 52% lower exposure, respectively, at steady state compared to a single dose, consistent with auto-induction of CYP3A by unboosted EVG. In contrast, exposure of boosted EVG was ~ 35% higher at steady state compared to a single dose, indicating the ability of a booster to overcome CYP3A auto-inductive effects of EVG.

The multiple-dose PK of EVG/r was evaluated at doses of 20/100 mg, 50/100 mg, and 125/100 mg in HIV positive patients (GS-US-183-0105). Elvitegravir exposures increased in an approximately dose-proportional manner between EVG doses of 20 and 50 mg, but were less than dose proportional between 50 and 125 mg (~ 2-fold higher AUC_{tau} over a 2.5-fold dose increase). The variability at 20 mg was higher relative to that at 50 or 125 mg with AUC, C_{max}, and C_{tau} (% coefficient of variation: ~ 176% vs 52%–78% at higher doses).

Intensive PK studies were conducted in a limited number of HIV-1 positive patients from the efficacy trials (GS-US-236-0102; GS-US-0103; GS-US-0104). PK sampling was performed once between the Week 2 and Week 8 visits (GS-US-236-0102; GS-US-0103) or at the week 2 visit

(GS-US-0104). Blood samples were collected to 24 hours after the dose of study drug. The drug was administered within 5 minutes of a meal. All subjects, including subjects in the PK sub-study, had a single blood sample collected at all study visits from Weeks 2 to 48 for determination of trough concentrations. Concentrations of EVG, COBI, FTC, and TFV in plasma samples were determined using LC/MS/MS. Steady state PK data are summarised in Table 4.

Table 4. Pharmacokinetic parameters of EVG, COBI, FTC, and TFV at steady-state following administration of QUAD TO HIV-1 positive patients (Efficacy Trials)

Analyte	AUCtau (ng.h/mL)	Cmax (ng/mL)	Ctau (ng/mL)	Tmax (h)	t½ (h)
GS-US-216-0102					
EVG	17,446.4 (42.7)	1658.1 (34.7)	262.4 (75.0)	4.00 (3.00, 4.50)	7.29 (5.94, 9.81)
COBI	8033.9 (51.6)	1114.5 (45.4)	31.4 (128.1)	3.00 (3.00, 4.50)	3.27 (2.62, 4.19)
FTC*	11,545.5 (9837.5, 13,294.1)	1708.4 (1446.8, 2491.8)	96.2 (76.7, 144.0)	3.00 (2.00, 3.00)	7.44 (6.82, 8.78)
TFV*	4062.7 (2923.6, 4821.4)	400.5 (325.5, 507.6)	78.5 (63.1, 109.4)	2.00 (2.00, 2.00)	12.27 (11.10, 16.16)
GS-US-216-0103					
EVG	21073.6 (44.6)	2024.1 (40.1)	257.4 (70.2)	4.00 (3.50, 5.00)	6.50 (5.06, 7.95)
COBI	8486.8 (46.0)	1171.6 (29.4)	31.5 (156.2)	3.00 (2.00, 4.00)	3.26 (2.90, 3.99)
FTC	12567.2 (23.5)	1923.2 (22.4)	102.2 (38.2)	2.00 (2.00, 3.00)	7.35 (6.16, 8.37)
TFV	4160.1 (29.6)	455.0 (27.8)	83.9 (36.1)	2.00 (1.00, 3.50)	12.79 (11.34, 15.35)
GS-US-236-0104					
EVG	21479.9 (29.7)	1772.5 (32.0)	321.4 (103.8)	4.00 (3.00, 4.94)	6.72 (5.17, 8.68)
COBI	8427.1 (39.1)	1126.5 (30.7)	88.4 (296.4)	2.03 (2.00, 3.50)	3.06 (2.64, 3.28)
FTC	12539.1 (32.8)	1844.9 (22.8)	243.2 (221.0)	2.00 (1.52, 2.52)	6.30 (5.90, 7.02)
TFV	3954.9 (29.2)	447.6 (30.2)	101.6 (97.2)	1.06 (1.00, 2.50)	12.52 (11.56, 13.37)

Data are Mean and CV % (coefficient of variation) for AUCtau, Cmax, Ctau;
Tmax and t ½ presented as mean and first and third interquartiles (Q1, Q3);
* FTC and TFV AUCtau, Cmax, Ctau are presented as Median (Q1, Q3) due to unusually high TFV (3- to 4.5-fol d) and FTC (2- to 3-fold) exposures for subject 2003-6267.

The plasma exposures of EVG, COBI, FTC, and TFV at steady-state following administration of QUAD were consistent with historical data. The mean EVG C_{tau} observed in the PK sub-studies were 6- to 13-fold above the protein-binding IC95 (44.5 ng/mL) for wild-type HIV-1 virus. Throughout the 48-week dosing period, mean EVG trough concentrations were up to 13-fold higher than the IC95. Thus it can be concluded that are no differences in EVG exposures between healthy and HIV-1 infected subjects.

This conclusion is also supported by the population PK modeling.

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

The PK of EVG and COBI were evaluated in non-HIV-1 infected subjects with normal and moderate hepatic impairment (Child-Pugh-Turcotte Classification B). The two groups were matched for age, gender, and body mass index (Study GS-US-183-0133).

The steady-state plasma exposure of EVG was modestly higher (AUC_{tau}, C_{tau}, and C_{max} were 35%, 80%, and 41% higher, respectively) in the subjects with moderate hepatic impairment relative to matched control subjects with normal hepatic function. A clinically significant increase of EVG AUC_{tau} or C_{max} as 50% was defined *a priori* for subjects with moderate hepatic impairment compared to normal matched control subjects. By this cut-off steady-state systemic exposure of EVG was not considered clinically relevant.

The AUC_{tau} and C_{max} of COBI were comparable between subjects with moderate hepatic impairment matched controls (90%CI of ratio between 0.8 and 1.25). On the other hand C_{tau} was significantly higher (geometric least-squares mean ratio 208%). This was not considered clinically relevant. The mean (SD) percentage free fraction for EVG in the normal matched control subjects and moderate hepatic impairment subjects was 1.15 (0.14) and 1.22 (0.23), respectively, suggesting no effect of hepatic impairment on protein binding.

Emtricitabine and TDF are primarily renally eliminated and do not require dose adjustment in patients with hepatic impairment.

No data are available regarding the use of EVG or COBI in patients with severe hepatic impairment. Thus QUAD STR is not recommended for use in this population.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

The steady state PK of EVG and of COBI in non-HIV-1 infected subjects with severe renal impairment ($eGFR_{CG}$ < 30 mL/min) and compared to age, gender and BMI matched data from subjects with normal renal function (eGFR ≥ 90 mL/min) (Study GS-US-216-0124).

For EVG, AUC_{tau}, C_{max}, and C_{tau} following once-daily administration of EVG/co for 7 days were approximately 25%, 33%, and 31% lower in subjects with severe renal impairment than in matched controls. For COBI, AUC_{tau}, C_{max}, and C_{tau} were approximately 25%, 22%, and 13% higher in subjects with severe renal impairment than in matched control subjects. The differences in exposures between subjects with severe renal impairment and those with normal renal function were not considered clinically relevant. There were no differences in EVG or COBI plasma protein binding between the 2 groups.

In a population PK analysis of EVG, baseline eGFR was not a significant covariate, indicating no effect of eGFR on EVG PK.

The study suggests that dose adjustment of EVG or COBI would not be warranted in subjects with renal impairment. However, dose-interval adjustment may be required for the other components of QUAD-STR (FTC and TDF) in renally impaired patients. This cannot be achieved with the fixed-dose combination therefore QUAD should be discontinued in patients with significant renal impairment. Furthermore, QUAD should be avoided during concurrent use with drugs likely to alter renal function (e.g., lithium).

4.2.3.3. Pharmacokinetics according to age

Age did not have an effect on EVG exposures in HIV-1 infected subjects and was not a clinically relevant covariate based on population PK analyses.

4.2.3.4. Pharmacokinetics according to gender

Gender did not have an effect on EVG exposures in HIV-1 infected subjects and was not a clinically relevant covariate based on population PK analyses.

4.2.3.5. Hepatitis B and / or hepatitis C virus co-infection

Pharmacokinetics of tenofovir DF and emtricitabine have not been fully evaluated in hepatitis B and/or C co-infected patients. Limited data from population pharmacokinetic analysis (N=24) indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the exposure of boosted elvitegravir.

4.2.3.6. Pharmacokinetics according to race

Race did not have an effect on EVG exposures in HIV-1 infected subjects and was not a clinically relevant covariate based on population PK analyses.

4.2.3.7. Pharmacokinetics in other special populations

There is no information on the use of the drug in pregnancy, lactation or in children and adolescents.

4.2.4. Population Pharmacokinetics

A population kinetic study was undertaken to develop a model to describe EVG PK based on data from healthy volunteers and patients and to assess the effects of such covariates as age, gender, race, health status (patient versus healthy volunteer), formulation (administered as QUAD or EVG/COBI), body weight, body mass index, body surface area, creatinine clearance (estimated GFR), COBI AUC and COBI C_{min}, and HBV and/or HCV co-infection. The model was developed based on six Phase I studies (236-0101, 236-0105, 236-0106, 236-0110, 216-0116, 216-0123) in healthy subjects, one Phase II study (236-0104) in HIV-1 infected subjects, and a two Phase III studies (236-0102 and 236-0103) in HIV-1 infected subjects. A mixed effect modeling approach using NONMEM software was applied in analyzing pooled data from COBI-boosted EVG data from the nine studies comprising data from 161 healthy subjects and 458 HIV infected subjects. Nine studies included intensive PK sampling (6 in healthy volunteers; n = 161; 3 in HIV-1 subjects; n = 62), while sparse PK sampling was used in two of the three studies in HIV-1 infected subjects (n = 396). Various structural PK models as well as inclusion of inter-individual variability (IIV) terms on structural model parameters were tested. The best model was chosen based on graphical examinations, the accuracy and meaningfulness of parameter estimates, and a drop of more than 10.8 (equal to a significance level of 0.001) in the objective function value (OFV) as provided by NONMEM. Once the base model was established, relationships between model parameters and covariates were examined graphically. Those subject characteristics deemed to be significantly correlated with a model parameter were then formally tested as a covariate in the model. Clinical data from studies using EVG/COBI or EVG/COBI/FTC/TDF (QUAD) were used as a dataset for the final model and entailed boosted-EVG pharmacokinetics with COBI 150 mg, consistent with its use in Phase 2 and Phase 3 studies.

A two-compartment PK model with first-order absorption rate constant and absorption lag-time provided a good description of the PK of EVG in both healthy volunteers and HIV infected patients. Apparent systemic clearance of EVG (CL/F) was estimated to be 6.55 L/h (RSE=2.0%) with an IIV of 31.6% (8.0%). Apparent volume (Vc/F) of the central compartment was estimated to be 12.9 L (6.4%) with an IIV of 49.1% (22.7%). The absorption rate of EVG was estimated at 0.134 h^{-1} (3.5%) with an IIV of 22.1% (25.4%) with a lag-time of 1.55 (4.3%) hours with an IIV=64.8% (11.1%). A modest, statistically significant effect of BSA on EVG apparent clearance was observed but was not considered clinically relevant. No dose adjustments based individual BSA was deemed necessary. No other relevant effects of demographic covariates, formulation characteristics (i.e., EVG plus COBI or QUAD), or COBI 150 mg exposures were observed on EVG PK.

4.2.5. Pharmacokinetic interactions

The pharmacophore of HIV IN inhibitors such as EVG forms a complex with divalent cations (Mg2+) at the active site of the IN enzyme. Such binding with cations predisposes EVG and IN inhibitors, in general, to local gastrointestinal drug-antacid interactions upon coadministration

due to high concentrations of divalent and trivalent cations in antacids. Due to the prevalent use of acid-reducing agents in the HIV population, clinical studies were performed to assess the effect of antacid-based interactions and to delineate them from the general influence of gastric pH on EVG absorption.

4.2.5.1. Pharmacokinetic interactions demonstrated in human studies

Based on the clinical pharmacology of the individual agents in the QUAD STR, a set of *in vitro* and clinical PK drug-drug interaction studies was conducted to evaluate the potential for clinically significant drug interactions with medications frequently used by the HIV-1 infected population.

4.2.5.2. Clinical implications of in vitro findings

4.2.5.2.1. Key Cytochrome P450 Interaction Potential for EVG

The potential for EVG to inhibit major human drug metabolizing CYPs was evaluated using pooled human hepatic microsomal fractions and enzyme-specific activities. Elvitegravir was reported to show no detectable inhibition of human hepatic microsomal CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 activity (IC50 > 30 μg/mL), and weak inhibition of CYP3A at concentrations > 10-fold above the C_{max} observed in HIV-1 infected patients (IC50 28.3 μg/mL). Elvitegravir is thus unlikely to cause drug interactions through inhibition of the metabolism of other drugs.

Elvitegravir was reported to show weak inhibition of human MDR1 (Pgp) and OATP1B1, but more potent inhibition of human OATP1B3 (IC50 0.44 μM). EVG is predicted to have very low liability to cause drug interactions through inhibition of human CYPs or MDR1. A clinical study (GS-US-216-0123) examining the effect of COBI-boosted EVG on the PK of the OATP1B1/3 substrate, rosuvastatin, indicated modest (~ 38%) increases in rosuvastatin AUC driven primarily by higher C_{max}, indicating a transient effect of these agents on this transporter.

The potential for EVG to cause drug interactions through induction was assessed in primary cultures of human hepatocytes. EVG at concentrations up to 10μg/mL was reported to result in a ≤ 1.6-fold increase of CYP1A2 activity compared to ~ 48-fold increase for the positive control. EVG is unlikely to induce CYP1A2 at clinically relevant doses. Treatment with EVG was reported to result in concentration-dependent increases of CYP3A activity, with calculated mean increases of 18.9% of the positive control at EVG 1 μg/mL, which increased to a mean of 46.8% of the positive control at EVG 10 μg/mL. EVG is a weak inducer of CYP3A activity, which is countered by co-administration with potent CYP3A-inhibitors, such as RTV or COBI.

The effects of enzyme-selective inhibitors on the oxidative metabolism of [14C]-EVG by human hepatic microsomal fraction were determined. While the CYP2C9-selective inhibitor, sulfaphenazole, and the CYP2D6-selective inhibitor, quinidine, were reported to display relatively little effect on EVG metabolism, the CYP3A-selective inhibitor, KTZ, showed potent, concentration-dependent inhibition of EVG and the formation of oxidative metabolites.

The effects of KTZ and the UGT1A1-selective inhibitor, atazanavir (ATV), on the formation of GS-9200 (M4) were determined using human hepatic microsomal fractions. Atazanavir was reported to be a potent inhibitor of EVG glucuronidation with an IC50 value of 0.4 μM, as was ketoconazole (IC50 of 9.6 μM. The rates of formation of GS-9200 (M4) from EVG were reported to be extensively inhibited by ATV, a selective and potent UGT1A1 inhibitor. Thus, other potent clinical UGT1A1 inhibitors may affect the glucuronidation of EVG in vivo.

4.2.5.3. Interactions with medications interfering with gastric pH

A randomized drug interaction study was designed to evaluate the PK of ritonavir-boosted EVG (EVG/r) with concomitant administration of antacid or omeprazole (GS-US-183-0119). Co-administration of staggered antacid with EVG/r resulted in EVG exposures that were within the protocol-defined lack of pharmacokinetic alteration bounds. Similarly, co-administration of

omeprazole with EVG/r did not affect the pharmacokinetics of EVG. Plasma exposures of M4, the glucuronide metabolite of EVG, were 5% to 8% of corresponding EVG exposures. Plasma levels of M1, the ritonavir-inhibited hydroxylation metabolite of EVG, were below quantifiable limits (< 20 ng/mL) at all sampled time points. The plasma pharmacokinetics of ritonavir was also unaffected by antacid or omeprazole co-administration.

A randomized, open-label, multiple-dose, 2-way crossover study in healthy volunteers was designed to investigate if cobicistat–boosted elvitegravir (COBI-boosted EVG) and H2-Receptor Antagonists (H2RAs) could be co-administered simultaneously, in addition to 12 hours apart (GS-US-216-0122). Subjects were randomized to 1 of 2 treatment sequences. The predefined lack of PK interaction criteria for EVG and COBI for the primary PK parameters (AUC_{tau} and C_{max}) and the secondary PK parameter (C_{tau}) were all met. The lower bounds of the 2-sided 90% CIs of all geometric LSM ratios were greater than 70% for EVG and COBI co-administered with an H2RA (famotidine) These data indicate that simultaneous administration of COBI-boosted EVG with famotidine, a representative H2RA, has no effect on the exposure of COBI itself or of a to-be-boosted drug (EVG).

A randomized, open-label, single-center, multiple-dose, crossover study that compared the relative bioavailability and PK of COBI-boosted EVG when co-administered once daily for 7 days either: alone (reference Treatment A), with famotidine staggered 12 hours after GS-9350-boosted EVG dose (test Treatment B), with omeprazole 2 hours prior to GS-9350-boosted EVG dose (test Treatment C), or with omeprazole staggered 12 hours after GS-9350-boosted EVG dose (test Treatment D) (GS-US-216-0120). Eligible subjects were randomized to 1 of 3 treatment sequences. All treatments consisted of 8 days of COBI-boosted EVG to reach steady-state conditions, with a 24-hour PK collection starting on Day 7. This was followed by dosing with COBI-boosted EVG and the addition of an H2RA (famotidine) or PPI (omeprazole). The data indicated that administration of COBI-boosted EVG with omeprazole, a representative PPI, had no effect on the exposure of COBI itself or of EVG when the PPI was staggered from COBI-boosted EVG by 12 hours. Similarly co-administration of an H2RA had no effect on COBI or EVG exposures when the H2RA was staggered from COBI-boosted EVG by 12 hours. Accordingly, PPIs may be co-administered with COBI-boosted EVG without dosing restrictions. It is recommended that administration of H2RA be separated from COBI-containing regimens by 12 hours.

4.2.5.4. Interactions with anti-retroviral medications

An open-label, crossover study to determine the effect of ritonavir (RTV) 100 mg twice daily co-administration on the steady-state PK of elvitegravir was conducted in healthy subjects (GS-US-183-0102). Comparison of the systemic exposure of EVG (AUC_{inf}) after a single dose (Day 1) with that at steady state (AUC_{tau} (Day 10) was approximately 20% lower indicating auto-induction of EVG metabolism**.** Co-administration with ritonavir resulted in a net inhibition of EVG metabolism, as evidenced by both greater-than-predicted steady-state exposures and a relatively long median elimination half-life (9.5 vs. 3.5 hours, at steady state). The increase in EVG exposure after co-administration of ritonavir is likely due to a combination of improved oral bioavailability due to decreased first-pass metabolism, with a component of reduced systemic clearance, as indicated by the change in T½. Overall, these data support the study of low-dose ritonavir as a pharmacokinetic booster of EVG to enable achievement of higher trough concentrations and less frequent dosing intervals.

The effect of a range of ritonavir doses (20, 50, 100, and 200 mg once daily) on the PK of elvitegravir and on hepatic cytochrome P450 3A (CYP3A) activity using a CYP3A substrate (midazolam) was examined in a randomized, open-label, multiple-dose, two-group study in healthy subjects (GS-US-183-0113)**.** Increasing doses of ritonavir resulted in an increase in C_{max}**,** AUC_{tau}**,** and C_{tau} of EVG; however, the increase was less than dose proportional. EVG CL/F decreased with increasing doses of ritonavir, reaching a plateau around 100-mg ritonavir indicating near maximal inhibition of CYP3A was attained between 50- and 100-mg ritonavir.

M4 exposure, specifically AUC_{tau}, following multiple doses of EVG plus ritonavir (20, 50, 100, and 200 mg), comprised < 10% of the corresponding EVG exposures, with the metabolite-to-parent ratio remaining unchanged in the presence of increasing doses of ritonavir. Non-linear pharmacokinetics of ritonavir was observed and increasing ritonavir doses resulted in greater than dose proportional increases in ritonavir C_{max}, AUC_{tau}, and $C_{tau.}$ Low doses of ritonavir, 20 to 50 mg, provide substantial inhibition of both gut-associated and hepatic CYP3A. The dose-response curve ED50 for hepatic CYP3A4, (using midazolam) was 12.2 mg indicating that ritonavir substantially reduces hepatic CYP3A4 activity at doses as low as 20 mg and that ritonavir doses of 50 to 100 mg are sufficient for boosting of EVG.

A randomized, open-label, single-center, multiple-dose study to evaluate the PK interaction of elvitegravir and atazanavir/r was conducted in healthy volunteers (GS-US-183-0106). Plasma C_{max} and AUC_{tau} of EVG met the protocol-defined lack of alteration criteria after co-administration of 85 mg of EVG plus atazanavir/r compared with administration of 150/100 mg EVG/r. Similarly, atazanavir exposures (C_{max}, AUC_{tau}, and C_{tau}) were unaltered after atazanavir/r coadministration with 85 mg of EVG. M4 exposures were lower after administration of 85 mg of EVG plus atazanavir/r than administration of 150/100 mg of EVG. Plasma ritonavir exposures were within the exploratory lack of alteration bounds upon addition of 85 mg of EVG relative to atazanavir/r.

A similar randomized, open-label, multiple-dose study was performed in healthy subjects to evaluate the PK interaction of elvitegravir, atazanavir, and ritonavir after co-administration of EVG with ritonavir-boosted atazanavir sulfate (ATV/r) compared with administration of EVG/r or ATV/r individually (GS-US-183-0108). PK changes for all analytes were observed when EVG was co-administered with atazanavir/r. EVG AUC_{tau}, C_{max}, and C_{tau} were significantly increased in the presence of atazanavir/r. M4 exposure also increased in the presence of atazanavir/r, but the increase was less proportional than the increase observed in EVG exposure. Atazanavir AUC_{tau} and C_{max} were unaltered by co-administration with EVG, but trough concentrations were reduced by about 35%. Ritonavir AUC_{tau}, C_{max} and C_{tau} were differentially altered when co-administered with EVG or atazanavir. Due to the magnitude of increase in EVG exposure when co-administered with atazanavir/r, a decrease in the dose of EVG is recommended when the drugs are co-administered.

The PK of elvitegravir, lopinavir, and ritonavir after multiple-dose administration were evaluated in an open-label drug interaction study after one of three treatments: ritonavir-boosted EVG (EVG/r), lopinavir plus ritonavir (lopinavir/r), and EVG plus lopinavir/r (EVG + lopinavir/r) (GS-US-183-0116). The pharmacokinetics of EVG and its M4 metabolite were altered when EVG was co-administered with lopinavir/r as observed from the significant increase in AUC_{tau}, C_{max}, and C_{tau}. Lopinavir pharmacokinetics (assessed by AUC_{tau} and C_{max}) was unaltered in the presence of EVG and met the predefined criterion for lack of interaction. A marginal decrease in its trough concentrations (i.e., lower bound of C_{tau} fell outside of the established 80% to 125% range) was noted. Ritonavir C_{max} was altered when EVG was co-administered with lopinavir/r; the associated 90% CI fell outside the predefined criterion of 70% to 143%.

An open-label, randomized, 2-way crossover study to evaluate the single-dose PK of GS-8374 and DRV, and the multiple-dose pharmacokinetics and safety of GS-8374, DRV, and EVG following the administration of GS-8374 or DRV, each in combination with EVG and the pharmaco-enhancer COBI was conducted in healthy subjects (GS-US-201-0104). GS-8374 is a protease inhibitor. GS-8374 exposures were higher following multiple-dose administration with EVG and COBI relative to its single-dose administration alone, but GS-8374 C_{tau} was ~74% lower compared to administration of GS-8374 + COBI. Following multiple-dose administration of DRV + EVG + COBI, plasma exposures of all 3 agents were lower relative to multiple-dose administration with GS-8374 + EVG + COBI (for EVG and COBI).

An open-label, crossover, partially randomized, multi-cohort, single and multiple-dose, single-center study designed to evaluate the drug-interaction potential between EVG/co administered once daily and atazanavir (ATV), rosuvastatin (ROS), or rifabutin (RIF)in healthy subjects (GS-US-216-0123). Co-administration of EVG/co 85/150 mg with ATV 300 mg did not result in clinically relevant interaction or changes in EVG, ATV, or COBI exposures. Co-administration of EVG/co 150/150 mg with ROS 10 mg did not cause changes in EVG or COBI exposures. Transient increases (primarily C_{max}) in ROS exposures were observed, which do not necessitate dose modification. Coadministration of EVG/co 150/150 mg with RIF 150 mg every other day resulted in marked decreases in EVG and COBI Ctau, but no clinically relevant changes in RIF exposures or its antimycobacterial activity.

4.2.5.5. Interactions with CYP inhibitors

An open label, multiple-dose study was performed in healthy subjects to examine the effect of ketoconazole (KTZ) on the pharmacokinetics of EVG/r and the effect of KTZ on CYP3A enzyme activity using midazolam (MDZ) as the CYP3A probe substrate when administered concomitantly with EVG/r (GS-US-183-0146). Co-administration of MDZ and EVG/r resulted in increased MDZ AUC_{inf}, C_{max}, and C_{last} relative to MDZ administration alone. Slight additional increases in MDZ AUC_{inf} and C_{last} were observed following administration of EVG/r plus KTZ. Co-administration of MDZ with EVG/r resulted in significant decreases in 1'-OH-MDZ exposure parameters, whereas increases in mean 1'-OH-MDZ exposure parameters were noted following the addition of KTZ. Concurrent administration of EVG/r and KTZ resulted in modest increases in exposure of EVG (< 50%), M4, and RTV relative to EVG/r administration alone. A decrease in M4-to-EVG AUC_{tau} ratio was noted following concurrent administration of KTZ and EVG/r relative to EVG/r administration alone. Increases in EVG AUC in the presence of KTZ are likely due to inhibition of UGT1A1.

4.2.5.6. Interactions with oral contraceptives

The effect of the QUAD STR on the PK of a hormonal contraceptive containing Norgestimate/Ethinyl Estradiol was evaluated in healthy women over two menstrual cycles (GS-US-236-0106). Co-administration of NGM/EE + EVG/COBI/FTC/TDF resulted in NGMN AUC_{tau}, C_{max}, and C_{tau} increases, and EE AUC_{tau} and C_{tau} decreases, relative to NGM/EE administration alone. EE C_{max} values were similar with or without co-administration of EVG/COBI/FTC/TDF. Comparison of changes in hormone concnetrations from Day 0 to Day 21 after administration of NGM/EE + EVG/COBI/FTC/TDF vs. after NGM/EE revealed unchanged serum progesterone concentrations after both treatments, a similar decrease in serum FSH concentrations following both treatments, and a greater decrease in serum LH concentrations after NGM/EE + EVG/COBI/FTC/TDF than after NGM/EE alone. These results suggest that negative feedback inhibition for the secretion of LH and FSH was maintained in spite of an observed reduction in EE plasma concentrations. It is recommended that an oral contraceptive contain 30 µg of ethinyl estradiol if administered with EVG/COBI/FTC/TDF.

4.3. Evaluator's overall conclusions on pharmacokinetics

The main drug in the STR, for which the sponsor seeks approval, is EVG boosted with the CYP3A inhibitor COBI. The other two components of the QAUD are compounds which already have approval for use namely, FTC and TDF. The PK (and PD) studies have therefore mostly focused on EVG and COBI either alone or in combination with some studies conducted with the QUAD formulation. The sponsor has provided an extensive range of PK studies evaluating single and multiple doses of EVG, COBI or the combination usage in special populations as well as in patients with HIV. In general these studies have been performed to a high standard and for each of the studies *a priori* power analysis has been undertaken to justify sample sizes. The studies where power may have been an issue is in those of renal and hepatic impairment, where the numbers in each group were probably less than that needed to examine strict bioequivalence

(n=10-12 per group). A *post-hoc* calculation of power based on the observed differences may be more convincing for these two studies. The drug-drug interaction studies have primarily focused on the other antiretroviral viral agents and their potential for interaction with EVG. Based on the metabolism of EVG by CYP3A4, and the known propensity of antiretroviral agents to inhibit this cytochrome, this would seem to be appropriate. Similarly the ability of other known CYP3A4 inhibitors (e.g., ketoconazole) to affect EVG/COBI PK has also been investigated. Given the occurrence of psychiatric disorders in patients with HIV (mania/hypomania and depression) it was surprising that no formal *in vivo* studies were performed to examine potential PK interactions. While the *in vitro* profile of EVG/COBI suggests some interaction with psychotropic medications, there is no mention of a potential interaction with lithium, which is known to affect renal function. The proposed PI reflects adequately the PK studies that have been performed and provides suitable warnings about the potential for drug-drug interactions based on the studies that have been performed as well as theoretical possibilities given the known metabolic pathways for EVG and COBI.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 5. Studies relating to each pharmacodynamic topic.

PD Topic	Subtopic	Study ID	Primary drug
Primary Pharmacology	Antiviral activity	GS-US-183-0101	EVG
	Antiviral activity	GS-US-183-0105	EVG
Secondary Pharmacology	ECG (QTc F) ECG (QTcF)	GS-US-183-0128 GS-US-216-0107	EVG COBI
	Renal function (CrCL)	GS-US-216-0121	COBI
PD Interactions	P-glycoprotein, CYP2B6, CYP 2D6	GS-US-216-0112	COBI
	midazolam	GS-US-216-0116	COBI

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.
‡ And adolescents if applicable.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

Studies *in vitro* showed that the components of QUAD have antiviral synergy. The 3-drug combination anti-HIV activity of EVG + FTC + TFV showed synergy. The 4-drug combination of EVG + TFV + FTC + COBI (COBI at 25 µM) showed synergy that was identical to that of the 3-

drug combination of EVG + TFV + FTC. No evidence for antiviral antagonism was observed for these combinations.

Administration of EVG at doses up to 800mg twice daily; 800 mg once daily, or EVG 50 mg + RTV 100 mg once daily to integrase strand-transfer inhibitor-naive HIV-1 infected subjects as monotherapy for 10 consecutive days significantly reduced HIV-1 RNA compared with placebo at all dose levels examined. In a non-inferiority study of EVG/r relative to a comparator protease inhibitor/r (CPI/r), EVG/r 50/100-mg and 125/100-mg groups met criteria for non-inferiority for reduction of HIV-1 RNA from baseline.

A study in 126 healthy subjects receiving EVG at therapeutic or doses approximately twice the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

The electrocardiographic effects of COBI were determined in a study of 40 healthy adult subjects. Cobicistat did not prolong QTcF interval at exposures 2- and 4-fold above the recommended therapeutic dose. A modest increase in PR interval (+9.6 msec) occurred around C_{max}, 3 to 5 hours after dosing. This finding was not considered to be clinically significant. The effect of COBI on left ventricular function assessed with ECHO cardiograms showed no clinically significant change from baseline.

A study in subjects with normal and mildly impaired renal function indicated that COBI did not affect actual GFR (aGFR) but affected estimated GFR (eGFR) calculated using serum creatinine.

Two different formulations of COBI inhibited CYP3A4 activity to a similar extent based on the PK of the test substrate midazolam. Co-administration of COBI and desipramine (DMI) resulted in CYP2D6 inhibition, as assessed by increases in the PK data for DMI. COBI was regarded as a weak CYP2D6 inhibitor based on the less than 2-fold increase in DMI exposure. There was minimal effect on efavirenz PK a substrate for CYP2B6. Similarly co-administration of COBI with digoxin may result in transient inhibition of gut P-gp.

5.3. Mechanism of action

5.3.1. EVG

Elvitegravir is a low molecular weight, HIV-1 integrase strand-transfer inhibitor that prevents integration of the HIV-1 genetic material into the host-cell genome. Elvitegravir has been shown to specifically inhibit HIV-1 integrase strand-transfer activity (JTK303-PH-002) and the integration of viral deoxyribonucleic acid (DNA) into host chromosomal DNA in cell culture (JTK303-PH-005; PC-186-2006).

5.3.2. COBI

Cobicistat is devoid of HIV protease inhibition, unlike its structural analog, RTV (PC-216-2001). It is a potent, inhibitor of CYP3A, similar to RTV (AD-216-2028). Cobicistat also increases the systemic levels of co-administered CYP3A substrates such as EVG, and the protease inhibitors ATV and darunavir. Cobicistat has been shown *in vitro* to be a more specific CYP3A inhibitor than RTV (AD-216-2029, AD-216-2070), with no anti-retroviral activity (PC-216-2002; PC-216-2011).

5.3.3. QUAD STR

Emtricitabine is a nucleoside analog of cytidine, and TDF is a prodrug of TFV, a nucleotide analog of adenosine monophosphate. Both have established antiviral activity in combination *in vitro* and in clinical studies. Neither EVG nor COBI antagonize the anti-HIV effect of FTC or TFV *in vitro*. Cobicistat is a weak inhibitor of human Pgp, but concentrations of COBI in the intestinal lumen during absorption can increase systemic TFV exposure due to inhibition of Pgp-dependent efflux of TDF. The only significant PK drug interaction within the 4-drug combination

is likely to be the intended increase in the bioavailability of EVG, and reduction in its elimination due to inhibition of the CYP3A-dependent generation of the major EVG metabolite, M1.

5.4. Pharmacodynamic effects

5.4.1. Primary pharmacodynamic effects

Administration of EVG at doses of 200, 400, or 800 mg twice daily; 800 mg once daily, or EVG 50 mg + RTV 100 mg once daily to integrase strand-transfer inhibitor-naive HIV-1 infected subjects as monotherapy for 10 consecutive days significantly reduced HIV-1 RNA compared with placebo at all dose levels (Study GS-US-183-0101). Elvitegravir doses of 400 mg twice daily, 800 mg twice daily, and 50 mg + RTV 100 mg once daily resulted in mean declines from baseline in HIV-1 RNA of 1.94, 1.91, and 1.99 $\log_{10}$ copies/mL, respectively. An EVG exposure-response relationship was identified with EVG C_{tau} values that fitted to a simple E_{max} model with an EC_{50} of 14.4 ng/mL and an E_{max} of 2.32 log10 copies/mL reduction from baseline. The estimated inhibitory quotient of EVG, calculated as the observed mean C_{tau} divided by the protein-binding adjusted *in vitro* IC_{50} of 7.17 ng/mL, was 5.9, 6.7, and 18.8 at the 400mg twice-daily, 800mg twice-daily, and 50 mg + ritonavir once daily dose levels, respectively. EVG trough concentrations also exceeded the protein binding-adjusted in vitro IC_{95} of 44.9ng/mL (100nM) for the entire dosing interval.

In a Phase 2 dose-finding study designed to assess the non-inferiority of EVG/r relative to a CPI/r (Study GS-US-183-0105). The primary efficacy endpoint was the time-weighted average change from baseline through Week 24 in HIV-1 RNA (DAVG24). Changes in study drug treatment regimens recommended by the monitoring group confounded the interpretation of results in evaluating the non-inferiority of EVG/r versus CPI/r after Week 16. In the study report, efficacy data were analyzed as pre-specified in the protocol. EVG/r 50/100-mg and 125/100-mg groups met criteria for non-inferiority relative to CPI/r for the pre-specified primary efficacy endpoint. The EVG/r 125/100-mg group was statistically superior to CPI/r in the analysis of $DAVG_{16}$, $DAVG_{24}$, and in categorical reductions in viral load. Elvitegravir mean C_{trough} at the EVG/r doses of 20/100 mg, 50/100 mg, and 125/100 mg were ~ 1.5-, 4.7-, and 6-fold above the IC_{95} (45 ng/mL).

An Emax dose-response model for EVG using cumulative data from the mono-therapy study (GS-US-183-0101) and the Phase 2 dose-ranging study (GS-US-183-0105) in HIV-1 infected subjects evaluating antiviral activity as a function of steady-state trough EVG concentrations (C_{tau}: 16-fold dose range and 20-fold mean C_{tau}/C_{trough} range) is shown. Mean C_{trough} values from EVG 150 mg represent the plateau range of this relationship providing near-maximal antiviral activity.

5.4.2. Secondary pharmacodynamic effects

5.4.2.1. Cardiovascular effects of EVG and/or COBI

Short-term administration of therapeutic and supratherapeutic (2-fold higher) doses/exposures of boosted EVG, demonstrated no significant electrocardiogram (ECG) or wave morphology changes associated with either boosted EVG dose level (GS-US-183-0128). No relationships between EVG concentrations and QTc intervals were observed. Additionally, no serious adverse events or study discontinuations due to adverse events, clinical laboratory abnormality, or changes in vital signs or physical examination findings were observed.

The effect of COBI on QT/QTc study was conducted with COBI doses/exposures (AUC_{tau}) ~ 2- or 4-fold above therapeutic dose/exposures (GS-US-216-0107). Baseline–adjusted mean differences between COBI and placebo demonstrated a lack of GS-9350 prolongation effect on the QTcF interval (upper bounds of the 2-sided 90% CIs were below 10msec at all time points after dosing). A statistically significant, small, negative association between COBI plasma concentration and QTc interval was observed that is not considered to be clinically significant.

There was a small dose-related increase in PR interval between 3 and 5 hours after dosing was observed and is not considered to be clinically significant. Assay sensitivity established by showing that the mean difference between the positive control (moxifloxacin) and placebo was greater than 5msec at more than one time point after dosing.

The effect of COBI on left ventricular function in human subjects was evaluated healthy volunteers because of negative inotropic effect of COBI observed in isolated rabbit hearts. ECHO cardiogram evaluations showed no clinically significant change from baseline in left ventricular function when subjects were taking COBI (GS-US-216-0116). There were no notable changes in vital signs, physical findings, or ECGs in either cohort, except for 1 subject in Cohort 1, who had pulse rates > 100 bpm on 5 occasions during the study.

5.4.2.2. Effects on renal function

The effect of COBI on renal function was assessed using markers of glomerular filtration rate (GFR) in subjects with normal and mild/moderate renal impairment (GS-US-216-0121). Following 7 days of dosing with COBI, mean (SD) eGFR values decreased by 9.9 (13.14) mL/min and 11.9 (6.97) mL/min relative to baseline in subjects with baseline eGFR ≥ 80 mL/min and 50 to 79 mL/min, respectively. These changes were reversible and returned to baseline values following a 7-day washout period. The time to onset, magnitude, and time to resolution of the observed changes in eGFR are consistent with the inhibition of tubular secretion of creatinine by COBI. In contrast, GFR assessed via iohexol clearance or cystatin C-based were unchanged by COBI. These data indicated that COBI does not affect actual GFR (aGFR) but affects eGFR, which is calculated using serum creatinine.

5.5. Pharmacodynamic interactions

The effects of COBI as an enzyme inhibitor *in vivo* were evaluated in a Phase 1 study using MDZ as a specific probe CYP3A substrate (GS-US-216-0101). Midazolam, the probe, was administered as a single low dose alone or in combination with multiple doses of COBI over a COBI dose range of 50 to 200 mg, and with RTV, a known CYP3A inhibitor, at 100 mg. MDZ showed increased concentrations when administered with the CYP3A inhibitors, COBI and RTV. Near-maximal inhibition of CYP3A was observed with a low dose of COBI of 100 mg, as evidenced by modest increases in MDZ concentrations with higher COBI doses. The increase in MDZ concentrations following administration of COBI 100 or 200 mg appeared similar to the values observed with 100 mg of RTV.

When MDZ was co-administered with 50 mg of COBI, MDZ CL/F was reduced relative to MDZ administration alone (GLSM ratio 11.6%, or a 88.4% reduction). More modest incremental reductions were observed as the COBI dose was increased to 100 mg and 200 mg (GLSM ratio 7.3% and 5.20% relative to MDZ alone, reflecting 92.7% and 94.8% reductions, respectively), which were comparable to results observed upon co-administration with RTV(GLSM ratio 4.5%, or a 95.6% reduction).

Overall, comparable near-maximal CYPA3 inhibition (as assessed by the probe substrate MDZ) was achieved at steady state following administration of COBI at dose levels ≥ 100 mg, as evidenced by modest increases in MDZ concentrations with increased COBI doses. Concentrations of the 1'-OH metabolite of MDZ decreased with increasing doses of COBI, consistent with inhibition of CYP3A and the inhibitory trends exhibited by increasing doses of COBI on its probe.

Further evaluation of COBI 100-mg and 150-mg doses and the PD/CYP3A inhibition of EVG was evaluated in a relative bioavailability assessment of the components of the QUAD STR containing EVG 150 mg, FTC 200 mg, and TDF 300 mg plus the pharmacoenhancer COBI at doses of 100 mg and 150 mg relative to EVG/r 150/100 mg, FTC 200 mg, and TDF 300 mg administered as separate components (GS-US-236-0101). Administration of EVG as QUAD with

COBI at a dose of 100 mg resulted in bioequivalent exposures as assessed by AUC_{tau} and C_{max} but a 40% lower C_{tau} estimate relative to EVG/r. With the STR containing COBI 150 mg, EVG exposures were modestly higher with C_{max}, meeting the definition of bioequivalence, and the upper bound of the 90% CI of AUC_{tau} exceeding the criteria by 1%.

The effects of COBI on the CYP isoforms 2B6 and 2D6 and on the drug efflux transporter Pgp was evaluated in healthy subjects in a multiple dose study (GS-US-216-0112). Subjects in three separate cohorts received COBI 150 mg once daily for 10 days with a single dose of the test probes (desipramine 50 mg; digoxin 0.5 mg; efavirenz 600 mg) administered before starting COBI and co-administered on the 10th day of the COBI regimen. Co-administration of COBI and desipramine resulted in CYP2D6 inhibition, as assessed by 58% and 65% increases in AUC_{last} and AUC_{inf}, respectively, and a 24% increase in the C_{max} of desipramine. COBI may be classified as a weak CYP2D6 inhibitor. A small reduction in the Cmax of efavirenz was observed upon coadministration with COBI. Coadministration of COBI and digoxin may have resulted in transient inhibition of gut P-gp, as evidenced by an increase in digoxin C_{max}. These changes do not require preemptive dose modifications.

5.6. Evaluator's overall conclusions on pharmacodynamics

A small number of PD studies, which were generally well conducted and adequately powered, were presented by the sponsor. The primary endpoint of antiviral activity in HIV infected patients was assessed in a PK-PD analysis of data obtained from a short term (10day) study and a comparative 48 week trial. Taken alone EVG was able to reduce viral load. When combined with ritonavir, EVG demonstrated non-inferiority to a comparative protease inhibitor combined with ritonavir (CPI/r). In both studies the PK-PD data fitted simple Emax models. EVG trough concentrations with the dosing regimens used exceeded the IC_{95} for the entire dosing interval.

The cardiovascular safety of both EVG and COBI were assessed in healthy volunteers. Assay sensitivity was established in both studies by using moxafloxacin as a control condition. At doses which would exceed that recommended in clinical practise there was no significant effect on QTcF. The effect of COBI on left ventricular function assessed with ECHO cardiograms showed no clinically significant change from baseline. Taken together the data would suggest that EVG or COBI do not produce significant effects on cardiovascular function, at least at the doses investigated.

COBI tended to decrease the estimated GFR (Cockcroft-Gault). However measurement of actual GFR via assessment with iohexol clearance showed no effect on renal clearance.

Some studies appear to be out of place in the PD section: the studies on interactions were reported as PD studies by the sponsor but were clearly PK studies as there were no PD endpoints. Nevertheless, these studies addressed some issues of potential drug-drug interactions of COBI and supported the notion that it was a CYP3A4 inhibitor, which might be successfully used to increase systemic exposure to EVG, if administered together.

6. Dosage selection for the pivotal studies

The QUAD STR formulation used in the pivotal Phase III studies was a fixed-dose combination tablet comprising of 300mg of tenofovir disoproxil fumarate (TDF), 200 mg of emtricitabine (FTC), 150 mg of elvitegravir (EVG) and 150 mg of cobicistat (COBI). The doses of FTC and TDF in the proposed QUAD STR were the respective therapeutic doses approved for use in Australia.

EVG and COBI are both new chemical entities. In describing the justification for choice of dose of EVG, the sponsor has stated that in study GS-US-183-0105, which was a dose-finding study that assessed the noninferiority of RTV-boosted EVG relative to an RTV-boosted comparative Protease Inhibitor, the highest EVG dose tested was 125mg. Study GS-US-183-0140, which

evaluated the multiple-dose relative bioavailability of RTV-boosted EVG 125mg and RTV-boosted EVG 150mg, showed that the 125 mg dose and the 150 mg dose of EVG provided bioequivalent EVG exposures. No rationale was given by the sponsor for the eventual choice of 150mg instead of 125mg of EVG in the proposed QUAD STR.

In describing the justification of choice of dose of COBI, the sponsor has stated that study GS-US-236-0101 showed that although administration of EVG as an STR with COBI at a dose of 100 mg resulted in bioequivalent EVG exposure relative to RTV-boosted EVG as assessed by AUC_{tau} and Cmax, it was 37% lower relative to RTV-boosted EVG as assessed by Ctau estimate. With the STR containing COBI 150 mg, EVG exposure was modestly higher with Cmax and met the definition of bioequivalence, and the upper limit of the 90% confidence interval of AUC_{tau} exceeded the criteria by 1%. The sponsor has stated that it was also taken into consideration that there could be a potential difference in exposure of COBI and EVG in HIV-1 infected patients compared with healthy subjects, as boosted agents frequently have lower exposures in the HIV-1 infected patient population compared to in healthy subjects, and this led to the selection of 150 mg dose of COBI to be used in the proposed STR formulation.

7. Clinical efficacy

The principal clinical efficacy and safety data in support of this application submission were derived from 2 Phase III registration studies, Study GS-US-236-0102 and Study GS-US-236-0103. This was supplemented by data from a Phase II study, Study GS-US-236-0104, which had been conducted for the purpose of providing an estimation of the response rate of QUAD, to allow for the planning of the Phase III studies. The 2 Phase III studies contained data up to Week 48 of the respective studies. The sample size of the Phase II study was small (n=71), but provided data beyond Week 48 though Week 96, and hence provided some preliminary efficacy and safety data on the long-term use of QUAD beyond 48 weeks.

7.1. For proposed indication of QUAD as a complete regimen for the treatment of HIV infection in adults

7.1.1. Pivotal efficacy studies

7.1.1.1. Study GS-US-236-0102

7.1.1.1.1. Study design, objectives, locations and dates

Study GS-US-236-0102 was a Phase III, double-blind, double-dummy, multi-centre, randomised, active-control study to assess the safety and efficacy of the QUAD STR versus Atripla (ATR) STR in HIV-1 infected, ARV treatment-naive adult subjects. Subjects were randomised in a 1:1 ratio to QUAD or ATR once daily.

The primary objective of this study was to evaluate the efficacy of QUAD STR (containing 200mgFTC/300mgTDF/150mgEVG/150mgCOBI) versus ATR STR (containing 200mgFTC/300mgTDF/600mgEFV) in HIV-1 infected, ARV treatment-naïve adult subjects, as determined by the achievement of HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 48. The secondary study objective was to evaluate the efficacy, safety, and tolerability of the 2 STRs through 96 weeks of treatment.

This was a multi-centre study where subjects were enrolled in a total of 102 study sites (97 in the United States and 5 in Puerto Rico). The study start date (first subject screened) was 16th March 2010. This study was ongoing at the time of this submission, but the 48-week primary endpoint had been analysed, and was presented in the clinical study report (CSR) in this submission dossier. The date of last subject observation for this CSR was 10th August 2011.

7.1.1.1.2. Inclusion and exclusion criteria

Subjects enrolled in this study were HIV-1 infected, ARV treatment-naive adults aged ≥ 18 years, with plasma HIV-1 RNA levels ≥ 5000 copies/mL, estimated glomerular filtration rate (eGFR) > 70 mL/min at screening, expected life expectancy of ≥ 1 year, no prior use of any approved or experimental ARV drug, and with sensitivity to EFV, FTC, and TDF as demonstrated by the subject's HIV-1 genotype at screening. Female subjects of childbearing potential had to agree to utilise highly effective contraception methods[2] from screening, throughout the duration of study treatment and for 12 weeks following the last dose of study drug. Male subjects had to agree to utilise a highly effective method of contraception[3] throughout the study period and for 12 weeks following the last dose of study drug.

Main exclusion criteria were a new acquired immune deficiency syndrome (AIDS)-defining condition diagnosed within the 30 days prior to screening, breastfeeding or pregnant females, a history of malignancy within the past 5 years (prior to screening) or ongoing malignancy (other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma), and the presence of active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to baseline visit. In addition, patients receiving drug treatment for hepatitis C virus (HCV), or were anticipated to receive treatment for HCV during the course of the study, and patients experiencing decompensated cirrhosis were excluded. Subjects receiving ongoing therapy with medications that may interact with FTC, TDF, EVG, COBI, EFV, or ATR were also excluded.

A full list of inclusion and exclusion criteria is presented in the study report.

Comments: The inclusion and exclusion criteria were in line with recommendations on the study population in the TGA-adopted EMA guideline on the clinical development of medicinal products for the treatment of HIV infection[4].

7.1.1.1.3. Study treatments

The study treatments were QUAD STR tablet (200mgFTC/300mgTDF/150mgEVG/150mgCOBI) plus placebo for ATR STR tablet, or ATR STR tablet (200mgFTC/300mgTDF/600mgEFV) plus placebo for QUAD STR tablet. QUAD or its matching placebo tablet was administered orally, 1 tablet once daily with food, at approximately the same time each day. ATR or its matching placebo tablet was administered orally, 1 tablet once daily, on an empty stomach prior to bedtime, and at approximately the same time each day. Subjects were to be treated for 96 weeks in the randomised, double-blinded phase. However, the CSR submitted for this evaluation is that of the 48-week interim report, where the duration of study treatment had been 48 weeks.

With regards to the dose selection of the components of QUAD, the sponsor has stated that the two components of FTC 200 mg and TDF 300 mg are doses of ARV agents that are currently approved for the treatment of HIV-1 infection in the US and the EU, and that they are listed as preferred agents in the US and international treatment guidelines. The boosted 150 mg dose of EVG was selected based on results from a proof-of-concept monotherapy study (Study GS-US-183-0101) and a Phase II study (Study GS-US-183-0105) in heavily treatment-experienced, HIV-1 infected subjects where Ritonavir(RTV)-boosted EVG (125 mg dose) produced drug exposures that were considered safe, well tolerated, and resulted in statistically better antiviral activity versus RTV-boosted Protease Inhibitor-based comparator regimens. The sponsor has also stated that a multiple-dose biopharmaceutics study GS-US-183-0140 showed that the 125 mg dose and the 150 mg dose provided bioequivalent EVG exposures. The dose of COBI was

[2] defined as 2 separate forms of contraception (1 of which was an effective barrier method), or subjects were non-heterosexually active, practiced sexual abstinence, or had a vasectomized partner

[3] defined as 2 separate forms of contraception (1 of which was an effective barrier method), or male subject was non-heterosexually active, practiced sexual abstinence, or was vasectomised

[4] European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of HIV infection. 20 Nov 2008.

selected based on the results from 2 studies (GS-US-216-0101 and GS-US-236-0101) in healthy volunteers. Results from Study GS-US-216-0101 showed that 100mg and 200mg of COBI increased the systemic exposure of the CYP3A probe substrate midazolam, while results from Study GS-US-236-0101 showed that 100mg and 150mg of COBI increased EVG exposures in the COBI-containing STR.

Comments: The study design involving a positive control instead of a placebo is appropriate in HIV trials as placebo-controlled trials are not considered ethical in the HIV-1 infected patient population. The choice of positive control drug of ATR is in agreement with current treatment guidelines for HIV infection where the use of ARV regimen containing TDF/FTC/EFV was one of the recommended first-line treatment regimens for ARV treatment-naive HIV-1 infected patients[5]. The ATR dose used (200mgFTC/ 300mgTDF/ 600mgEFV) was the dose approved for use in Australia. The doses of FTC and TDF in QUAD were also the approved respective doses. EVG and COBI are both new chemical entities. In describing the justification for choice of dose of EVG, the sponsor has stated that in study GS-US-183-0105, RTV-boosted EVG of 125mg dose formulation was used, and that study GS-US-183-0140 showed that the 125 mg dose and the 150 mg dose of EVG provided bioequivalent EVG exposures. However, no rationale was given for the choice of 150mg instead of 125mg of EVG. In describing the justification of choice of dose of COBI, the sponsor has stated that study GS-US-236-0101 showed that although administration of EVG as an STR with COBI at a dose of 100 mg resulted in bioequivalent EVG exposure relative to RTV-boosted EVG as assessed by AUC_{tau} and Cmax, it was 37% lower relative to RTV-boosted EVG as assessed by Ctau estimate. With the STR containing COBI 150 mg, EVG exposure was modestly higher with Cmax and met the definition of bioequivalence, and the upper limit of the 90% confidence interval of AUC_{tau} exceeded the criteria by 1%. The sponsor has stated that it was also taken into consideration that there could be a potential difference in exposure of COBI and EVG in HIV-1 infected patients compared with healthy subjects, as boosted agents frequently have lower exposures in the HIV-1 infected patient population compared to in healthy subjects, and this led to the selection of 150 mg dose of COBI to be used in the proposed STR formulation.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48, as defined by the US Food and Drug Administration (FDA)-defined snapshot analysis algorithm.

The secondary efficacy endpoints were the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 96, as defined by the snapshot analysis algorithm, and the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48 and 96, as defined by the time to loss of virologic response (TLOVR) algorithm. As the CSR submitted for this evaluation is that of the 48-week interim report, the secondary efficacy endpoint evaluated for this Week 48 analysis was the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through 48 weeks based on the FDA-defined TLOVR algorithm.

Other efficacy endpoints (labelled as "tertiary efficacy endpoints" in the CSR) evaluated for the Week 48 analysis were pure virologic failure with HIV-1 RNA cut-off at 50 copies/mL, the percentage of subjects with HIV-1 RNA < 50 copies/mL using missing = failure (M = F) and missing = excluded (M = E) imputation methods, the change from baseline in HIV-1 RNA (log10 copies/mL), and the change from baseline in CD4 cell count and in CD4%.

[5] National Institutes of Health. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Jan 10th 2011.

Comments: The primary and secondary endpoints, and the endpoint of change from baseline in CD4 cell count are consistent with current HIV treatment and research guidelines[6,7]. The other tertiary endpoints allowed the robustness of the primary endpoint to be tested, by using a different definition of a virologic responder (pure virologic failure analysis) or by using different imputation methods (M=F and M=E analyses), and also allowed evaluation of the study drug effect in terms of change from baseline of HIV-1 RNA levels, and immunological response (change from baseline in CD4 cell count and CD4%).

7.1.1.1.5. Randomisation and blinding methods

Subjects were assigned a screening number at the time of consent. Once eligibility was confirmed, each subject was assigned a unique subject number. Prior to or during the baseline/Day 1 visit, the investigator randomised the subject using interactive voice response system/interactive web response system (IVRS/IWRS). Subjects were randomised in a 1:1 ratio to 1 of 2 treatment groups: QUAD STR and placebo for ATR each once daily, or ATR STR and placebo for QUAD each once daily. Randomisation was stratified based on HIV-1 RNA level (≤ 100 000 copies/mL or >100 000 copies/mL) at screening. The IVRS/IWRS assigned blinded study drug bottle numbers at each study visit (except Week 2 visit, when no study drug was dispensed). Investigators and subjects were both blinded to study treatments. The assignment of subjects to analysis sets was done before the study blind was broken.

7.1.1.1.6. Analysis populations

Study efficacy data was analysed in the intent-to-treat (ITT) analysis set and Per Protocol (PP) analysis set. The ITT dataset was the primary analysis set for efficacy analyses. The ITT analysis set included all subjects who were randomised and had received at least 1 dose of blinded study drug. All efficacy data were used for ITT analysis, including data collected after the last dose of study drug.

The PP analysis set included all subjects who were randomised, had received at least 1 dose of blinded study drug, and had not committed any major protocol violation. In addition, subjects were excluded from the PP dataset if they were subjects:

- who discontinued study drug prior to or on the upper bound of the Week 48 analysis window due to reasons other than lack of efficacy, and the assessments of HIV-1 RNA on randomised treatment were not available in the Week 48 analysis window;
- who did not discontinue study drug prior to or on the upper bound of the Week 48 analysis window, but for whom assessments of HIV-1 RNA on randomised treatment were not available in the Week 48 analysis window;
- who did not meet the key inclusion criterion of documented sensitivity to FTC, TDF, and EFV in a screening genotype report;
- who met the key exclusion criterion for receiving ongoing therapy with any of the medications listed in the excluded drug table in the protocol;
- who had an adherence rate for active study drug below the 2.5th percentile;
- who had missing HIV-1 RNA assessments in 3 consecutive scheduled visits prior to the Week 48 HIV-1 RNA assessment while on randomised treatment;
- who interrupted study drug for ≥ 4 consecutive weeks prior to the Week 48 HIV-1 RNA assessment while on randomized treatment; or

[6] European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of HIV infection. 20 Nov 2008.
[7] Centre for Drug Evaluation and Research. FDA Guidance for industry: antiretroviral drugs using plasma HIV RNA Measurements -Clinical considerations for accelerated and traditional approval. October 2002.

- who took ARV medication other than their randomised study drug regimen consecutively for ≥ 4 weeks prior to the Week 48 HIV-1 RNA assessment while on randomised treatment

In the PP analysis set, efficacy data were summarised up to the last dose date of blinded study drug.

Study safety data were analysed in the safety analysis set, which included all subjects who were randomised and who had received at least 1 dose of study drug. All data collected up to 30 days after permanent discontinuation of study drugs were included in the safety analyses.

7.1.1.1.7. Sample size

Sample size calculations assumed that both treatment groups had a response rate of 0.795 (based on a previous study, Study GS-01-934), a non-inferiority margin of 0.12, and a 1-sided, 0.025 significance level. It was estimated that a total sample size of 700 subjects randomised in a 1:1 ratio to the 2 treatment groups (i.e. 350 subjects per group) would have at least 95% power to establish non-inferiority between the 2 treatment groups, with respect to the response rate of HIV-1 RNA < 50 copies/mL at Week 48, as defined by the FDA snapshot analysis.

7.1.1.1.8. Statistical methods

- Primary efficacy outcome

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48, as defined by the FDA snapshot analysis algorithm. The analysis window for the snapshot analysis was defined as from Study Days 309 to 378 (inclusive). Values for missing data were not imputed. The analysis of the primary efficacy outcome was based on the ITT analysis set. The primary efficacy endpoint was analysed to determine if treatment with QUAD was non-inferior to treatment with ATR at Week 48. Non-inferiority was assessed using a 95% confidence interval (CI) approach[8], with a non-inferiority margin of 12%. It was to be concluded that QUAD was non-inferior to ATR if the lower limit of the 2-sided 95% CI of the difference in the response rate (QUAD group minus ATR group) was greater than −12%. If non-inferiority of QUAD versus ATR was established, the same 95% CI used to evaluate non-inferiority was to be used to evaluate superiority. The superiority of QUAD over ATR would be established if the lower limit of the 95% CI was found to be greater than 0. In addition, the number and percentage of subjects having virologic success, virologic failure, and reasons for no virologic data[9] at Week 48 were to be summarised and listed.

- Additional analyses on the primary efficacy endpoint

An additional analysis of the primary efficacy endpoint based on the PP analysis set, and a series of sensitivity analyses based on the ITT analysis set were done to evaluate the robustness of the primary efficacy outcome.

[8] As 2 interim independent data monitoring committee (IDMC) analyses were performed at Weeks 12 and 24, the alpha level for the Week 48 analysis was adjusted to 0.048 to account for multiplicity. Therefore, for the primary endpoint analysis at Week 48, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. The sponsor has stated that in view of the overall alpha level being maintained at 0.05, the primary endpoint analysis CI in the CSR was described as a "95% CI".

[9] For the primary efficacy outcome analysis, virologic outcome was defined as the following categories: (1) Virologic Success: subjects who had their last available HIV-1 RNA value < 50 copies/mL in the Week 48 analysis window while on randomised treatment (2) Virologic Failure: subjects who had their last available HIV-1 RNA value ≥ 50 copies/mL in the Week 48 analysis window while on randomised treatment, or who did not have on-treatment HIV-1 RNA data in the Week 48 analysis window due to discontinuation of study drug for lack of efficacy, or had discontinuation of study drug for reasons other than an AE, death, or lack of efficacy and their last available HIV-1 RNA value on treatment was ≥ 50 copies/mL (3) No Virologic Data in the Week 48 analysis window: subjects who did not have on-treatment HIV-1 RNA data in the Week 48 analysis window because: (a) study drug was discontinued due to AE or death (regardless of last available HIV-1 RNA result); (b) study drug was discontinued due to reasons other than AE/death and lack of efficacy (eg, withdrew consent, lost to follow-up) and the last available HIV-1 RNA value on treatment was < 50 copies/mL; or (c) subjects had missing data during the 48 Week analysis window, but remained on study drug.

The first sensitivity analysis of the primary endpoint excluded study drug discontinuations not related to virologic response (i.e. subjects who had no HIV-1 RNA data in the Week 48 analysis window due to study drug discontinuation for reasons other than lack of efficacy, AEs, or death and whose last available on-treatment HIV-1 RNA value was < 50 copies/mL were excluded from the numerator and denominator in the response rate computation) and included all HIV-1 RNA data for late discontinuation (i.e. for subjects with discontinuation of study drug due to reasons other than death in the Week 48 analysis window, all the HIV-1 RNA data in the Week 48 analysis window including data collected after the last dose of study drug were included in the evaluation of virologic response).

The second sensitivity analysis of the primary endpoint considered study drug discontinuations not related to virologic response as virologic successes and included all HIV-1 RNA data for late discontinuation. The third sensitivity analysis of the primary endpoint evaluated the impact of stratification factors (HIV-1 RNA level and region[10]) on the treatment effect at Week 48. Analyses were performed for the primary endpoint with stratification by region, and without any stratification factors. The results from these 2 analyses were compared with the primary analysis (i.e. stratified by baseline HIV-1 RNA level).

· Secondary and Tertiary efficacy endpoints

The secondary efficacy endpoint for this 48-Week analysis was the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48 as defined by TLOVR algorithm. Analysis for the secondary endpoint was performed using the ITT analysis set.

In this analysis, subjects were classified as responders if they had achieved a confirmed suppression (defined as HIV-1 RNA < 50 copies/mL on 2 consecutive visits) prior to or on the upper limit of the Week 48 analysis window, did not die or prematurely discontinue study drug prior to or on the upper limit of the Week 48 analysis window, and did not have a confirmed rebound (defined as having HIV-1 RNA ≥ 50 copies/mL at 2 consecutive visits or last available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study drug) by the upper limit of the Week 48 analysis window after achieving confirmed suppression.

TLOVR was estimated based on all HIV-1 RNA data. For subjects who had achieved a confirmed suppression, but had experienced confirmed rebound or discontinued study drug by the time of data cut, TLOVR was defined as the earliest time to death, discontinuation of study drug (last dose date), first occurrence of confirmed HIV-1 RNA ≥ 50 copies/mL, or the collection time of last HIV-1 RNA ≥ 50 copies/mL during study followed by premature discontinuation of study drug. For subjects who never achieved a confirmed suppression, TLOVR was defined as Study Day 1. Subjects who had achieved confirmed suppression, but had not experienced a confirmed rebound or discontinued study drug were censored at the last HIV-1 RNA collection date.

Tertiary efficacy endpoints were pure virologic failure with HIV-1 RNA cut-off at 50 copies/mL by Week 48, the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by 2 different missing data imputation methods (missing = failure [M=F] and missing = excluded [M=E] methods), the change from baseline in HIV-1 RNA (log10 copies/mL) at Week 48, and the change from baseline in CD4 cell count and CD4% at Week 48. Analyses for all tertiary efficacy endpoints were performed using the ITT analysis set. In addition, virologic responses using the M = F and M = E methods and the change from baseline in CD4 cell counts were also analysed using the PP analysis set.

In the pure virologic failure analysis, pure virologic responders at Week 48 were defined as subjects who achieved a confirmed suppression (i.e. HIV-1 RNA < 50 copies/mL on 2 consecutive visits) prior to or on the upper limit of the Week 48 analysis window, and did not have a confirmed rebound (i.e. HIV-1 RNA ≥ 50 copies/mL on 2 consecutive visits or the last

[10] Sites were combined according to geographic location into 8 regions. Each region needed to have > 40 subjects enrolled. In this analysis, Puerto Rico and Florida were combined into 1 region.

available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study) by the upper limit of the Week 48 analysis window after achieving confirmed suppression. Subjects who did not meet the above criteria were classified as pure virologic failures at Week 48.

· Subgroup Analysis

The primary analysis of virologic response (HIV-1 RNA < 50 copies/mL, snapshot analysis algorithm) was repeated within each of the following subgroups using the ITT analysis set: baseline HIV-1 RNA level (copies/mL; ≤ 100 000 and > 100 000), age (< 40 and ≥ 40 years), sex (male and female), race (white and non-white), baseline CD4 group (≤ 350 and > 350 cells/μL), and study drug adherence (< 95 and ≥ 95 %).

For each subgroup factor, the percentage difference between treatment groups and the respective 95% CIs were computed. The odds ratio and the associated 95% CI were estimated within each subgroup. The homogeneity of the treatment effects between subgroups was also evaluated using a Wald test based on the interaction between treatment and subgroup factor.

· Analysis of Resistance Data

Subjects who were on study drugs and experienced either suboptimal virologic response or virologic rebound were considered to have virologic failure and were included in the resistance analysis population (RAP). Suboptimal virologic response was assessed at Week 8 and was defined as having HIV-1 RNA ≥ 50 copies/mL and < 1 $\log_{10}$ reduction from baseline at the Week 8 visit, which was confirmed at the subsequent visit. Virologic rebound was defined as having 2 subsequent visits with HIV-1 RNA ≥ 400 copies/mL after achieving HIV-1 RNA < 50 copies/mL, or as having 2 subsequent visits with > 1 $\log_{10}$ increase in HIV-1 RNA from their nadir. In addition, subjects who were on study drugs, who had HIV-1 RNA ≥ 400 copies/mL at Week 48 or their last visit (at or after Week 8) and who had not been analysed previously, and were also analysed for resistance at their last visit. Subsequent to the first resistance testing, subjects experiencing repeated confirmed virologic failure were assessed for resistance retesting on a case-by-case basis, at the investigator's discretion.

In the RAP, protease/reverse transcriptase (PR/RT) and integrase (IN) genotyping and phenotyping assays were performed, using the PhenoSense GT, PhenoSense IN, and GeneSeq IN assays (Monogram Biosciences, South San Francisco, CA).

Comments: Analysis of the primary efficacy endpoint on the ITT dataset is appropriate and congruent with the ICH E9 guidelines[11]. The respective definitions of the ITT and PP datasets are appropriate. The primary endpoint and the use of the snapshot approach in the primary efficacy outcome are consistent with current HIV treatment and research guidelines[12,13]. The choice of a non-inferiority design over a superiority design as a primary objective is also in line with current HIV drug development trends, where trials are designed to demonstrate that a new treatment is not worse in efficacy than the current standard ARV drugs[14]. The benefit of the new treatment being investigated may be a better safety profile or ease of administration rather than better efficacy than the current standard ARV drugs. The use of the non-inferiority margin of 12% is consistent with that used in most HIV non-inferiority drug trials. The statistical management of multiplicity due to interim data analyses, to address its potential effect on type I error, is consistent with ICH E9 guidelines.

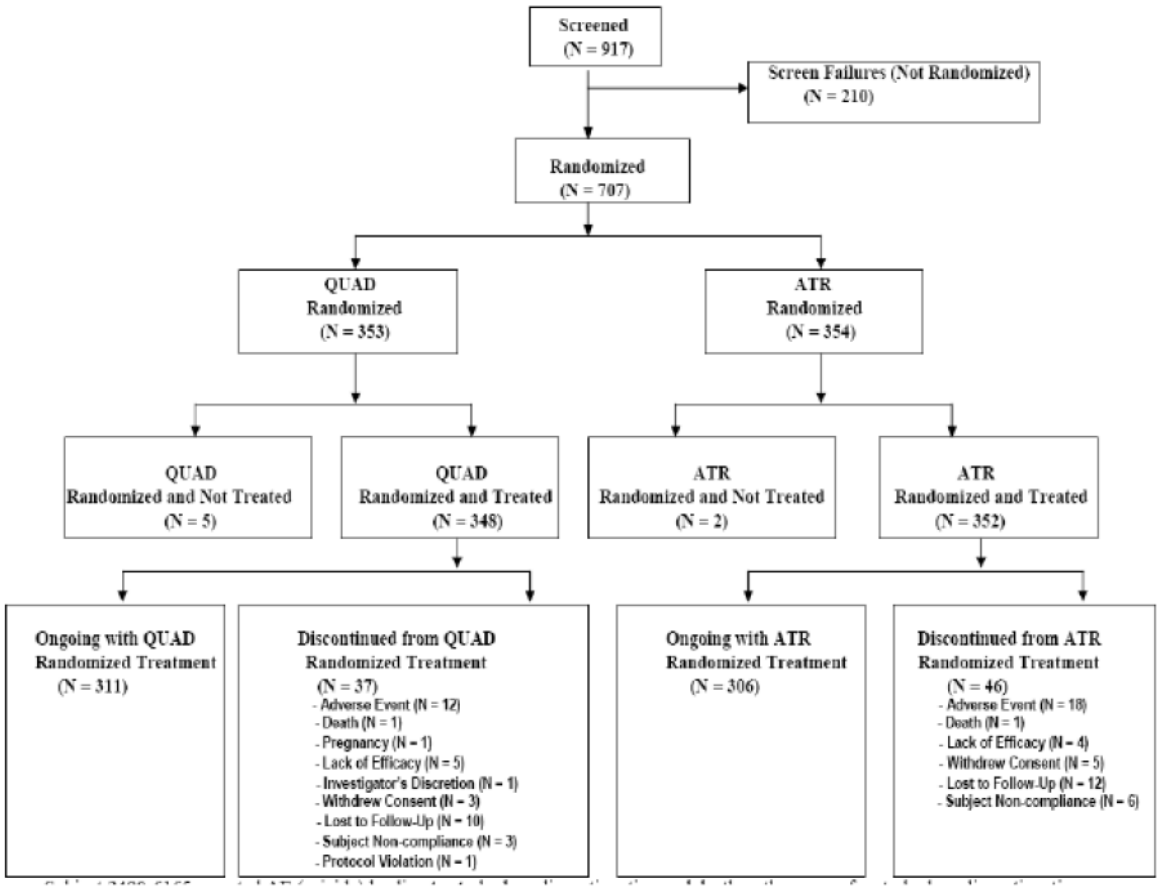
[11] ICH Efficacy Guidelines. E9: Statistical Principles for Clinical Trials. September 1998.
[12] Centre for Drug Evaluation and Research. FDA Guidance for industry: antiretroviral drugs using plasma HIV RNA Measurements -Clinical considerations for accelerated and traditional approval. October 2002.
[13] European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of HIV infection. 20 Nov 2008.
[14] Hill A, Sabin C. Designing and interpreting HIV noninferiority trials in naïve and experienced patients. *AIDS* 2008; 22:913-921

The additional analyses on the primary efficacy endpoint of analysing the primary efficacy endpoint in the PP dataset and additional sensitivity analyses are appropriate to assess the robustness of the primary efficacy outcome results. The secondary efficacy outcome measure of using the TLVOR is consistent with current HIV treatment and research guidelines[11,12]. To be a virologic responder in this algorithm, 2 consecutive viral load values < 50 copies/mL were required, and the subject should also not have discontinued study drug prematurely and not have virological rebound. This differed from the primary efficacy endpoint analysis which used the snapshot approach, where the single last available viral load value in the Week 48 time-point window was used in determination of whether there was virologic response.

The parameters used for the subgroup analyses were appropriate to assess effect of demographic characteristics (age, gender and race) and surrogate markers of HIV disease severity (baseline HIV-1 RNA level and baseline CD4 cell counts) on the primary efficacy endpoint. The 100 000 copies/mL cut-off for baseline HIV-1 RNA and the 350 cells/µL cut-off for baseline CD4 count are appropriate as they are clinically relevant values used for evaluations of severity of HIV infections, and for determining if ARV treatment should be initiated in treatment-naive patients[15].

7.1.1.1.9. Participant flow

Figure 1. Study GS-US-236-0102: Participant flow



[15] Thompson, MA et al. Antiretroviral Treatment of Adult HIV Infection: 2010 Recommendations of the International AIDS Society–USA Panel. *JAMA* July 21 2010; Vol 304 No. 3

Analysis sets for the Week 48 analysis are presented. Of the 707 subjects who were randomised, 700 (99.0%) were included in the safety and ITT analysis sets and 612 (86.6%) were included in the PP analysis set. The majority (n=68) of the 88 subjects excluded from the PP analysis set were due to discontinuation of study drug prior to the Week 48 analysis window for reasons other than lack of efficacy.

7.1.1.1.10. Major protocol violations/deviations

A total of 184 important protocol deviations occurred in 146 subjects during the study. The number and types of important protocol deviations was similar between the 2 treatment groups, except that there were more deviations involving incorrect dispensing of study drug in the ATR group (15 such deviations) than in the QUAD group (7 such deviations). The majority of these important protocol deviations (86 [49 in QUAD group and 37 in ATR group] out of 184 deviations) were for non-adherence[16], defined as a subject with < 70% adherence at any visit based on pill counts.

7.1.1.1.11. Baseline data

Overall, demographic and baseline disease characteristics were similar between the 2 treatment groups. The majority of subjects were male (89.0%) and white (63.0%). The mean (range) age was 38 years (18 to 67 years). The mean (Standard Deviation [SD]) baseline HIV-1 RNA value was 4.76 (0.583) $\log_{10}$ copies/mL, CD4 count was 386 (179.5) cells/μL, and CD4% was 22.9% (8.27). The median CD4 count was 380 cells/μL. Overall, 66.6% of subjects had baseline HIV-1 RNA ≤ 100,000 copies/mL and 78.7% of subjects had CD4 counts ≤ 500 cells/μL .

Comments: No information was found in the clinical dossier regarding the distribution of randomised subjects between the study sites in the US and those in Puerto Rico. It is noted that Puerto Rico is not an independent country but an unincorporated territory of the US, but it is considered to be important to distinguish between study sites in the US and those in Puerto Rico, as Puerto Rico is not located in North America but the Caribbean, and has different demographic and ethnic profile from North America. The listing of investigators provided in the clinical dossier for Study GS-US-236-0102 showed that 681 and 26 patients were enrolled in sites in the US and Puerto Rico, respectively. It is thus to be anticipated that only a small number of subjects from the Puerto Rico sites were eventually randomised into the study. In addition, it is noted that ethnic distribution was similar between the QUAD and ATR treatment groups.

7.1.1.1.12. Results for the primary efficacy outcome

Analysis of the primary efficacy outcome in the ITT analysis set showed that 87.6% (305 of 348) of subjects in the QUAD group and 84.1% (296 of 352) of subjects in the ATR group had virologic success (Table 6).

[16] Adherence to study drug was calculated based on pill count. Non-adherence was defined as <70% adherence, and was considered as important protocol deviations.

Table 6. Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis, ITT Analysis Set)

HIV-1 RNA Category	QUAD (N=348)	ATR (N=352)	QUAD vs. ATR p-value[a]	Difference in Percentages (95.2% CI)[b, c]
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	305 (87.6%)	296 (84.1%)	0.17	3.6% (-1.6% to 8.8%)
Virologic Failure at Week 48	25 (7.2%)	25 (7.1%)		
HIV-1 RNA >= 50 copies/mL	13 (3.7%)	11 (3.1%)		
Discontinued Study Drug Due to Lack of Efficacy	4 (1.1%)	2 (0.6%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[d]	8 (2.3%)	12 (3.4%)		
No Virologic Data in Week 48 Window[e]	18 (5.2%)	31 (8.8%)		
Discontinued Study Drug Due to AE/Death	10 (2.9%)	19 (5.4%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	8 (2.3%)	11 (3.1%)		
Missing Data During Window but on Study Drug	0	1 (0.3%)		

a P-value for the superiority test comparing the percentages of virologic success was from the Cochran-Mantel-Haenszel (CMH) test stratified by baseline HIV-1 RNA stratum.
b Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted Mantel-Haenszel (MH) proportion.
c At each of the 2 IDMC meetings, an analysis of efficacy was performed at the alpha level of 0.001; therefore, for theprimary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve theoverall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.
d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion,withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.
e Week 48 window is between Day 309 and 378 (inclusive).

The baseline HIV-1 RNA stratum-weighted difference in the percentage of subjects with virologic success was 3.6% (95% CI: −1.6% to 8.8%). As the lower limit of the 2-sided 95% CI of the difference in response rate was greater than the prespecified −12% non-inferiority margin, the primary efficacy outcome analysis was deemed to have demonstrated that the QUAD was non-inferior to ATR. As the lower limit of the 95% CI was not greater than 0, and the difference between treatment groups was not statistically significant (p=0.17), superiority of QUAD over ATR was not demonstrated.

Percentages of subjects with virologic failure at Week 48 were similar between the 2 treatment groups (Table 6 above). At Week 48, 7.2% (25/348) of subjects in the QUAD group compared with 7.1% (25/352) of subjects in the ATR group had virologic failure.

7.1.1.1.13. Results for other efficacy outcomes

· Additional analyses on the primary efficacy endpoint

A secondary analysis of the primary efficacy endpoint based on the PP analysis set and a series of sensitivity analyses based on the ITT analysis set were done to evaluate the robustness of the primary analysis of the primary endpoint.

Results of the analysis of the primary efficacy endpoint on the PP analysis set showed non-inferiority of QUAD compared to ATR. At Week 48, 94.9% (296/312) of subjects in the QUAD group and 96.0% (288/300) of subjects in the ATR group had virologic success. The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success was -1.0% (95% CI: −4.4% to 2.4%), indicating that QUAD was non-inferior to ATR for the PP analysis set.

Sensitivity analyses results were consistent with the primary efficacy outcome results. The first sensitivity analysis of the primary endpoint excluded study drug discontinuations not related to virologic response and included all HIV-1 RNA data for late discontinuation. At Week 48, 89.7% (305/348) of subjects in the QUAD group and 86.8% (296/352) of subjects in the ATR group had virologic success. The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success was 3.0% (95% CI: −1.9% to 7.8%), indicating that QUAD was non-inferior to ATR using the first sensitivity analysis.

The second sensitivity analysis of the primary endpoint considered study drug discontinuations not related to virologic response as virologic successes and included all HIV-1 RNA data for late discontinuation. At Week 48, 89.9% (313/348) of subjects in the QUAD group and 87.2% (307/352) of subjects in the ATR group had virologic success. The HIV-1 RNA stratum-weighted difference in the percentage of subjects with virologic success was 2.8% (95% CI: −2.0% to 7.5%), indicating that QUAD was non-inferior to ATR using the second sensitivity analysis.

The third sensitivity analysis of the primary endpoint evaluated the impact of stratification factors (HIV-1 RNA level and region) on the treatment effect at Week 48. Response rates in the 2 treatment groups when not accounting for any factors or when accounting for region, were the same as those observed for the primary endpoint analysis (when stratification was done for baseline HIV-1 RNA levels) i.e. 87.6% and 84.1% in the QUAD and ATR groups, respectively. Calculated odds ratios (QUAD to ATR) were similar: 1.35 (95% CI: 0.88 to 2.07) when accounting for baseline HIV-1 RNA level, 1.36 (95% CI: 0.89 to 2.09) when accounting for region, and 1.34 (95% CI: 0.87 to 2.06) when not accounting for any factors, indicating that the treatment effect in the primary endpoint analysis was not confounded by baseline HIV-1 RNA level or region.

- Secondary efficacy endpoint

The secondary efficacy endpoint for this 48-Week analysis was the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48 as defined by the TLOVR algorithm.

The TLOVR analysis results were consistent with the results of the snapshot analysis (primary efficacy outcome), showing that 85.9% (299/348) of subjects in the QUAD group and 83.2% (293/352) of subjects in the ATR group had confirmed HIV-1 RNA < 50 copies/mL through Week 48. The HIV-1 RNA stratum-weighted difference in the percentages of responders at Week 48 was 2.7% (95% CI: −2.6% to 8.1%), indicating that QUAD was non-inferior to ATR using the TLOVR analysis.

In the Kaplan-Meier (KM) analysis of TLOVR, separation in the KM curves was seen at baseline, with a higher percentage of subjects in the ATR group (8%) who were never suppressed compared to the QUAD group (4%). Convergence of the KM curves began to occur from Week 12, and by Week 48, there were similar percentages of subjects with loss of virologic response in each treatment group (14% and 17% in the QUAD and ATR groups, respectively, p-value = 0.65).

- Tertiary efficacy endpoints

Tertiary efficacy endpoints were pure virologic failure with HIV-1 RNA cut-off at 50 copies/mL by Week 48 (ITT analysis set), the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by 2 different missing data imputation methods (M=F and M=E methods) (ITT and PP analysis sets), the change from baseline in HIV-1 RNA (log10 copies/mL) at Week 48 (ITT analysis set), and the change from baseline in CD4 cell count and CD4% at Week 48 (ITT and PP analysis sets).

In the pure virologic failure analysis, the percentages of subjects who had pure virologic response (which definition was previously described above) through Week 48 were similar in

both treatment groups: 89.1% (310/348) and 86.6% (305/352) of subjects in the QUAD and ATR groups, respectively.

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using M = F and M = E imputation methods were similar between treatment groups, in both the ITT and PP datasets. In the M = F analysis (ITT dataset), at Week 48, the percentage of subjects with plasma HIV-1 RNA levels < 50 copies/mL was 88.8% (309/348) in the QUAD group and 85.5% (301/352) in the ATR group. The stratum weighted difference in response rates between treatment groups was 3.3% (95% CI: −1.6% to 8.3%; p=0.19), indicating that QUAD was non-inferior to ATR using the M = F method. In the M = E analysis (ITT dataset), at Week 48, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL was 95.1% (309/325) in the QUAD group and 95.3% (301/316) in the ATR group. The stratum-weighted difference in response rates between treatment groups was −0.1% (95% CI: −3.5% to 3.3%; p=0.94), indicating that QUAD was non-inferior to ATR using the M = E method. Similar results were obtained in the analyses on the PP dataset[17].

The percentage of subjects with HIV-1 RNA < 50 copies/mL through Week 48 (M = F) is shown. Mean (SD) baseline HIV-1 RNA levels were 4.73 (0.602) $\log_{10}$ copies/mL and 4.78 (0.564) $\log_{10}$ copies/mL in the QUAD and ATR groups, respectively. At Week 48, the mean (SD) changes from baseline in HIV-1 RNA were similar in the 2 treatment groups: −2.99 (0.660) $\log_{10}$ copies/mL in the QUAD group and −3.00 (0.690) $\log_{10}$ copies/mL in the ATR group. The difference in least-squares means was 0.03 (95% CI: −0.05 to 0.11). No test of statistical significance was reported in the CSR. The change from baseline in plasma HIV-1 RNA levels for the ITT analysis set is presented graphically in the study report.

Mean (SD) baseline CD4 cell counts were 391 (188.6) cells/μL and 382 (170.2) cells/μL in the QUAD and ATR groups, respectively. At Week 48, the mean (SD) increases from baseline in CD4 cell count were 239 (167.2) cells/μL in the QUAD group and 206 (153.4) cells/μL in the ATR group. The difference in least-squares means from an analysis of variance (ANOVA) model was 33 (95% CI: 8 to 58). This difference was statistically significant (p = 0.009) in favour of QUAD. Results were similar for the PP analysis set. The change from baseline in CD4 cell count for the ITT analysis set is presented graphically.

In the ITT analysis set, mean (SD) baseline CD4% was 23.1% (8.34) in the QUAD group and 22.8% (8.20) in the ATR group. At Week 48, the mean (SD) increases from baseline in CD4% were 9.1% (4.99) in the QUAD group and 9.9% (5.35) in the ATR group. The difference in LSM was −0.8 (95% CI: −1.6 to 0.0). No test of statistical significance was reported in the CSR.

· Subgroup analysis of primary efficacy endpoint

The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (snapshot analysis) by subgroup are presented. Subgroup analyses showed generally comparable pattern of virologic success to those observed for the primary endpoint, with the point estimate of treatment difference in virologic success >0 (i.e. in favour of QUAD) in all the subgroups, except for the subgroup of patients with age <40 years (where it was -0.1%), and the subgroup of patients with baseline CD4 cell counts ≤ 350 cells/μL (where it was -0.6%). The lower limits of the 95% CI of the difference in response rate in the subgroup analyses were greater than the prespecified −12% non-inferiority margin in all the subgroups, except for the subgroup of patients who were females (where it was -15.5%). In the subgroup with age ≥ 40 years and the subgroup with baseline CD4 cell count > 350 cells/μL, the lower-limits of the 95% CI of the point estimate of treatment difference in virologic success were > 0 (0.4% and 0.3% in the subgroups of age ≥ 40 years and baseline CD4 cell count > 350 cells/μL, respectively), suggesting superiority of QUAD

[17] In the PP dataset, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48 (M = F) was 94.9% (296 of 312 subjects) in the QUAD group and 96.0% (288 of 300 subjects) in the ATR group. The percentage of subjects with plasma HIV-1 RNA levels < 50 copies/mL at Week 48 (M = E) was 96.1% (296 of 308 subjects) in the QUAD group and 96.6% (288 of 298 subjects) in the ATR group.

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

7.1.1.1.14. Resistance analyses

A total of 31 subjects (4.4%; 31/700) met the virologic failure criteria previously described above, and were included in the RAP. The distribution of the RAP was similar between the 2 treatment groups, with 4.0% of subjects (14/348) analysed in the QUAD group and 4.8% of subjects (17/352) analysed in the ATR group**.**

In the QUAD group, 8 subjects (8 of 348, 2.3%) had emergent resistance to a study drug. All eight subjects developed reverse transcriptase resistance (RT-R) mutations. Seven of these subjects also developed integrase strand transfer inhibitor resistance (INSTI-R) mutations. In the ATR group, 8 subjects (8 of 352, 2.3%) had emergent resistance to a study drug. All eight subjects developed RT–R mutations. None of these subjects in the ATR group developed INSTI-R mutations. There was no development of primary Protease Inhibitors resistance (PI-R) mutations within both the QUAD and ATR groups.

Comments: Overall, demographic and baseline disease characteristics were similar between the 2 treatment groups. The overall mean and median CD4 counts of 386 and 380 cells/µL, respectively, and the overall percentage of subjects with CD4 counts ≤ 500 cells/µL of 78.7%, suggested that the study population was clinically relevant, as current treatment guidelines for treatment of HIV infection recommend initiation of ARV treatment when CD4 cell counts are <500 cells/µL[18].

The virologic response rates in the primary, secondary and tertiary endpoint analyses are summarised in Table 7 below.

Table 7. Study GS-US-236-0102 virologic response rates in the primary, secondary and tertiary endpoint analyses

	Percentage with virologic response (n/N)		Baseline HIV-1 RNA stratum-weighted difference^ (95%CI)
	QUAD group	ATR group	
Primary efficacy outcome (i.e. primary efficacy endpoint in ITT dataset)	87.6% (305/348)	84.1% (296/352)	3.6% (−1.6% to 8.8%)
Primary efficacy endpoint in PP dataset	94.9% (296/312)	96.0% (288/300)	-1.0% (−4.4% to 2.4%)
Sensitivity analyses of primary efficacy endpoint			
Exclude study drug discontinuations not related to virologic response and include all HIV-1 RNA data for late discontinuation	89.7% (305/348)	86.8% (296/352)	3.0% (−1.9% to 7.8%)

[18] National Institutes of Health, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, Jan 10th 2011.

	Percentage with virologic response (n/N)		Baseline HIV-1 RNA stratum-weighted difference^ (95%CI)
	QUAD group	ATR group	
Consider study drug discontinuations not related to virologic response as virologic successes and include all HIV-1 RNA data for late discontinuation	89.9% (313/348)	87.2% (307/352)	2.8% (−2.0% to 7.5%)
Sensitivity analysis on effect of stratification factors			
- Stratification factor of baseline HIV-1 RNA level	87.6% (305/348)	84.1% (296/352	1.35 (0.88 to 2.07)*
- Stratification factor of region	87.6% (305/348)	84.1% (296/352	1.36 (0.89 to 2.09)*
- No stratification factor	87.6% (305/348)	84.1% (296/352	1.34 (0.87 to 2.06)*
TLOVR analysis	85.9% (299/348)	83.2% (293/352)	2.7% (−2.6% to 8.1%)
Pure virologic failure analysis	89.1% (310/348)	86.6% (305/352)	NA
M = F analysis	88.8% (309/348)	85.5% (301/352)	3.3% (−1.6% to 8.3%)
M = E analysis	95.1% (309/325)	95.3% (301/316)	−0.1% (−3.5% to 3.3%)

^ QUAD minus ATR
**values are calculated odds ratio (95%CI)*
NA= not available

Comments

The efficacy results showed that the analysis outcome of non-inferiority of QUAD versus ATR obtained in the primary efficacy outcome was supported by other analyses, including analysis in the PP dataset, analysis using the TLVOR algorithm, and analysis using different imputation methods.

Virologic response measured in terms of decrease in HIV-1 RNA levels from baseline at Week 48 was also similar between treatment groups (mean change from baseline of −2.99 and -3.00 $\log_{10}$ copies/mL in the QUAD and ATR groups, respectively). Drug effect measured in terms of immunological response was statistically significant in favour of QUAD (mean increases from baseline in CD4 cell count of 239 and 206 cells/µL in the QUAD and ATR groups, respectively; p=0.009).

Subgroup analyses generally supported the primary efficacy results. The point estimates of treatment difference in virologic success were >0 (i.e. in favour of QUAD) in all the subgroups, except for the subgroup of patients with age <40 years and the subgroup of patients with baseline CD4 cell counts ≤ 350 cells/µL. However, in these 2 subgroups, the point estimates of treatment difference in virologic success were close to 0 (-0.1% and -0.6%, respectively). In addition, homogeneity tests performed for the primary endpoint did not show a

significant difference in treatment effects between subgroups. The lower limits of the 95% CI of the difference in response rate in the subgroup analyses were all greater than the prespecified non-inferiority margin of −12% in all the subgroups, except for the subgroup of patients who were females (where it was -15.5%). However, the 95% CI of the difference in response rate in this subgroup was very wide (-15.5% to 20.1%), reflecting the small sample size in this subgroup (n=41, versus n=307 for the subgroup of male patients).

With regards to emergent study drug resistance, the proportions of patients who developed emergent RT-R mutations were similar between treatment groups. However, seven out of the 8 subjects in the QUAD group who were tested for study drug resistance developed INSTI-R mutations, compared with none in the ATR group, which is consistent with the fact that ATR does not contain any INSTI. Within the QUAD group, the percentage of patients with emergent RT-R mutations was 2.3% (8 out of 348), and that for emergent INSTI-R mutations was 2.0% (7 out of 348).

7.1.1.2. Study GS-US-236-0103

7.1.1.2.1. Study design, objectives, locations and dates

Study GS-US-236-0103 is a Phase 3, double-blind, double dummy, multi-centre, randomised, active-control study to assess the safety and efficacy of the QUAD STR versus ritonavir (RTV)-boosted atazanavir (ATV/r) plus Truvada (TVD; comprising of 200mg FTC and 300mg TDF) in HIV-1 infected, ARV treatment-naive adult subjects. Subjects were randomised in a 1:1 ratio to 1 of 2 treatment groups: QUAD STR and placebo for RTV, ATV, and TVD each once daily, or ATV 300 mg, RTV 100 mg, and TVD (FTC 200 mg/TDF 300 mg) and placebo for QUAD STR each once daily.

The primary objective of this study was to evaluate the efficacy of QUAD STR versus a regimen containing ATV/r and TVD (ATVr+TVD) in HIV-1 infected, ARV treatment-naïve adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48. The secondary study objective was to evaluate the efficacy, safety, and tolerability of the 2 treatment regimens through 96 weeks of treatment.

This is a multicentre study where subjects were enrolled in a total of 146 study sites[19], the majority of which (87 centres) were in the US. The study start date (first subject screened) was 6th April 2010. This study was ongoing at the time of this submission, but the 48-week primary endpoint had been analysed, and was presented in the clinical study report (CSR) in this submission dossier. The date of last subject observation for this CSR was 13th September 2011.

As the study design was identical to that of Study GS-US-236-0102, except for the active control treatment regimen, reference will be made to Study GS-US-236-0102 in the description of the study design of Study GS-US-236-0103, and only differences will be elaborated.

7.1.1.2.2. Inclusion and exclusion criteria

The study inclusion and exclusion criteria were the same as for Study GS-US-236-0102 except for the parts relating to study treatments

7.1.1.2.3. Study treatments

The study treatments were QUAD STR tablets (200mgFTC/300mgTDF/150mgEVG/150mg COBI) plus placebos for ATV, RTV, and TVD, or ATV 300mg capsules, RTV 100mg tablets, and TVD tablets (FTC 200 mg/TDF 300 mg) plus placebos for QUAD STR tablets. All subjects

[19] 87 sites in the United States (US), 1 in Puerto Rico, 11 in France, 8 in Germany, 8 in Australia, 7 in Canada, 6 in United Kingdom, 3 in Belgium, 3 in Italy, 3 in Austria, 2 in Thailand, 2 in Netherlands, 1 in Portugal, 1 in Mexico, 1 in Denmark, 1 in Switzerland, and 1 in Sweden.

received 4 tablets of study drug in total (active drug and placebo) administered orally, once daily with food at approximately the same time each day. Subjects were to be treated for 96 weeks in the randomised, double-blinded phase. However, the CSR submitted for this evaluation is that of the 48-week interim report, where the duration of study treatment had been 48 weeks.

The rationale for dose selection of the components of QUAD STR was the same as that for Study GS-US-236-0102, and has been previously described above.

Comments: The choice of positive control drug regimen of ATV/r and TVD is in agreement with current treatment guidelines for HIV infection where the use of ARV regimen containing ATV/r and TDF/FTC was one of the recommended first-line treatment regimens for ARV treatment naive HIV-1 infected patients[20], where TVD provides the N(t)RTI backbone, and ATV is a Protease Inhibitor. The doses of ATV, RTV and TVD used were the approved doses in Australia.

7.1.1.2.4. Efficacy variables and outcomes

The primary, secondary and tertiary endpoints were identical to those of Study GS-US-236-0102.

7.1.1.2.5. Randomisation and blinding methods

The randomisation and blinding methods were identical to those of Study GS-US-236-0102.

7.1.1.2.6. Analysis populations

The analysis populations and their definitions were identical to those of Study GS-US-236-0102, except for the parts pertaining to study treatments, where mention of ATR or its components in Study GS-US-236-0102 was replaced with ATVr +TVD in Study GS-US-236-0103.

7.1.1.2.7. Sample size

The sample size calculation and estimated sample size were identical to those of Study GS-US-236-0102.

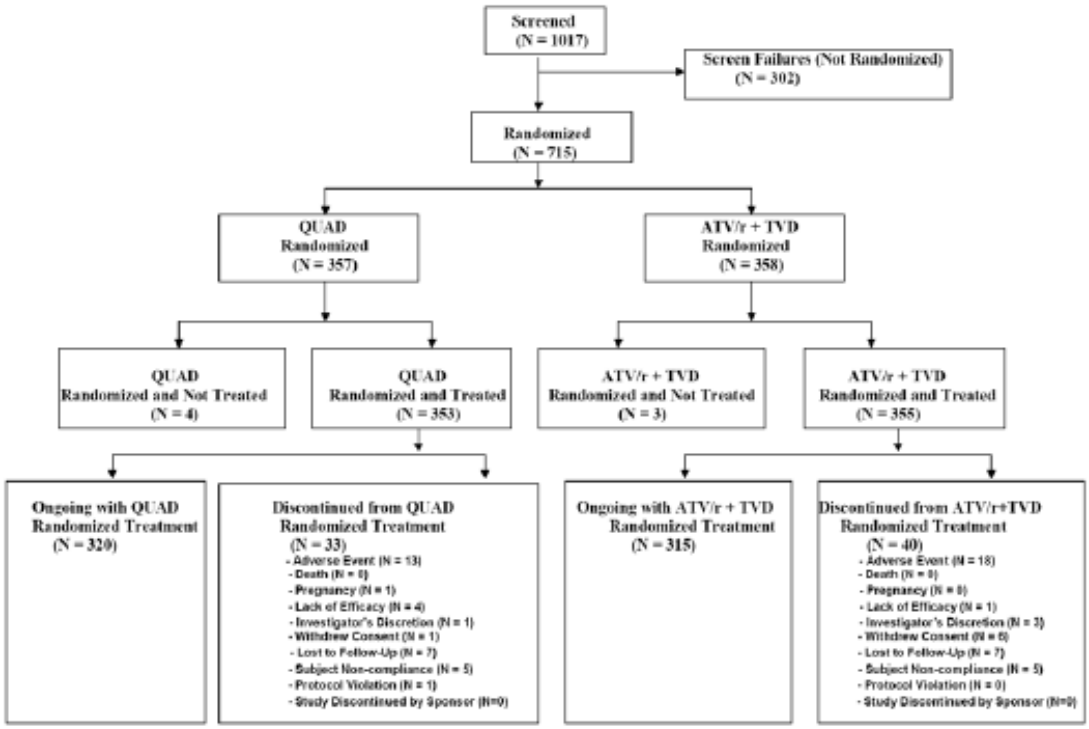
7.1.1.2.8. Statistical methods

The statistical methods were identical to those of Study GS-US-236-0102, except "ATR" was replaced with "ATVr+TVD".

[20] National Institutes of Health, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, Jan 10th 2011.

7.1.1.2.9. Participant flow

Figure 2. Study GS-US-236-0103: Participant flow



Analysis sets for the Week 48 analysis are presented**.** Of the 715 subjects who were randomised, 708 (99.0%) were included in the safety and ITT analysis sets and 628 (87.8%) were included in the PP analysis set. The majority (n=64) of the 80 subjects excluded from the PP analysis set were due to discontinuation of study drug prior to the Week 48 analysis window for reasons other than lack of efficacy.

7.1.1.2.10. Major protocol violations/deviations

A total of 133 important protocol deviations occurred in 114 subjects during the study. The number and types of important protocol deviations was similar between the 2 treatment groups, except that there were more deviations involving violations of inclusion/exclusion criteria in the ATV/r+TVD group (36 such deviations) than in the QUAD group (21 such deviations), and more deviations involving incorrect dispensing of study drug in the ATV/r+TVD group (11 such deviations) than in the QUAD group (7 such deviations). Overall, the majority of these important protocol deviations (57 out of 133 deviations) were for inclusion/exclusion criteria violations, and for non- adherence (49 [27 in QUAD group and 22 in ATR group] out of 133 deviations), which was defined as a subject with less than 70% adherence at any visit based on pill count[21].

7.1.1.2.11. Baseline data

Overall, demographic and baseline disease characteristics were similar between the 2 treatment groups. The majority of subjects were male (90.4%) and white (74.4%). The mean (range) age was 38 years (19 to 72 years). The mean (SD) baseline HIV-1 RNA level was 4.81 (0.613) $\log_{10}$ copies/mL, CD4 count was 370 (170.1) cells/µL, and CD4% was 21.4% (8.29). The median CD4 count was 357 cells/µL. Overall, 58.9 % of subjects had baseline HIV-1 RNA ≤ 100,000 copies/mL and 82.3% of subjects had CD4 counts ≤ 500 cells/µL .

[21] Adherence to study drug was calculated based on pill count. Non-adherence was defined as <70% adherence, and was considered as important protocol deviations.

7.1.1.2.12. Results for the primary efficacy outcome

Analysis of the primary efficacy outcome in the ITT analysis set showed that 89.5% (316 of 353) of subjects in the QUAD group and 86.8% (308 of 355) of subjects in the ATV/r+TVD group had virologic success (Table 8.).

Table 8. GS-US-236-0103: Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis) (ITT Analysis Set)

HIV-1 RNA Category	QUAD (N=353)	ATV/r+TVD (N=355)	QUAD vs. ATV/r+TVD p-value[a]	Difference in Percentages (95.2% CI)[b,c]
Virologic Success at Week 48				
HIV-1 RNA < 50 copies/mL	316 (89.5%)	308 (86.8%)	0.22	3.0% (-1.9% to 7.8%)
Virologic Failure at Week 48	19 (5.4%)	19 (5.4%)		
HIV-1 RNA >= 50 copies/mL	7 (2.0%)	8 (2.3%)		
Discontinued Study Drug Due to Lack of Efficacy	4 (1.1%)	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[d]	8 (2.3%)	11 (3.1%)		
No Virologic Data in Week 48 Window[e]	18 (5.1%)	28 (7.9%)		
Discontinued Study Drug Due to AE/Death	11 (3.1%)	18 (5.1%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	7 (2.0%)	9 (2.5%)		
Missing Data During Window but on Study Drug	0	1 (0.3%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA stratum.

b Difference in percentages of virologic success and its 95.2% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.

c At each of the 2 IDMC meetings, an alpha penalty of 0.001 was applied; therefore, for the primary endpoint analysis, a 95.2% CI (corresponding to an alpha level of 0.048) was constructed to preserve the overall alpha level of 0.05. As such, the primary analysis CI is described as a 95% CI.

d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.

e Week 48 window is between Day 309 and 378 (inclusive).

The baseline HIV-1 RNA stratum-weighted difference in the percentage of subjects with virologic success was 3.0% (95% CI: −1.9% to 7.8%). As the lower limit of the 2-sided 95% CI of the difference in response rate was greater than the prespecified −12% non-inferiority margin, the primary efficacy outcome analysis was deemed to have demonstrated that the QUAD was non-inferior to ATV/r+TVD. As the lower limit of the 95% CI was not greater than 0, and the difference between treatment groups was not statistically significant (p=0.22), superiority of QUAD over ATV/r+TVD was not demonstrated.

Percentages of subjects with virologic failure at Week 48 were similar between the 2 treatment groups (Table 8 above). At Week 48, 5.4% (19/353) of subjects in the QUAD group compared with 5.4% (19/355) of subjects in the ATV/r+TVD group had virologic failure.

7.1.1.2.13. Results for other efficacy outcomes

· Additional analyses on the primary efficacy endpoint

A secondary analysis of the primary efficacy endpoint based on the PP analysis set and a series of sensitivity analyses based on the ITT analysis set were done to evaluate the robustness of the primary analysis of the primary endpoint.

Results of the analysis of the primary efficacy endpoint on the PP analysis set showed non-inferiority of QUAD compared to ATV/r+TVD. At Week 48, 97.5% (310/318) of subjects in the QUAD group and 97.7% (303/310) of subjects in the ATV/r+TVD group had virologic success. The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success was -0.1% (95% CI: −2.6% to 2.4%), indicating that QUAD was non-inferior to ATV/r+TVD for the PP analysis set.

Sensitivity analyses results were consistent with the primary efficacy outcome results. The first sensitivity analysis of the primary endpoint excluded study drug discontinuations not related to virologic response and included all HIV-1 RNA data for late discontinuation. At Week 48, 91.0% (315/353) of subjects in the QUAD group and 89.0% (308/355) of subjects in the ATV/r+TVD group had virologic success. The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success was 2.2% (95% CI: −2.3% to 6.7%), indicating that QUAD was non-inferior to ATV/r+TVD using the first sensitivity analysis.

The second sensitivity analysis of the primary endpoint considered study drug discontinuations not related to virologic response as virologic successes and included all HIV-1 RNA data for late discontinuation. At Week 48, 89.3% (322/353) of subjects in the QUAD group and 89.3% (317/355) of subjects in the ATV/r+TVD group had virologic success. The HIV-1 RNA stratum-weighted difference in the percentage of subjects with virologic success was 2.1% (95% CI: −2.3% to 6.5%), indicating that QUAD was non-inferior to ATV/r+TVD using the second sensitivity analysis.

The third sensitivity analysis of the primary endpoint evaluated the impact of stratification factors (HIV-1 RNA level and region) on the treatment effect at Week 48. Response rates between the 2 treatment groups when not accounting for any factors or when accounting for region, were the same as those observed for the primary endpoint analysis (when stratification was done for baseline HIV-1 RNA levels) i.e. 89.5% and 86.8 % in the QUAD and ATV/r+TVD groups, respectively. Calculated odds ratios (QUAD to ATV/r+TVD) were similar: 1.33 (95% CI: 0.84 to 2.12) when accounting for baseline HIV-1 RNA level, 1.35 (95% CI: 0.84 to 2.15) when accounting for region, and 1.30 (95% CI: 0.82 to 2.06) when not accounting for any factors, indicating that the treatment effect for the primary endpoint was not confounded by baseline HIV-1 RNA level or region.

· Secondary efficacy endpoint

The secondary efficacy endpoint for this 48-Week analysis was the achievement and maintenance of confirmed HIV-1 RNA < 50 copies/mL through Weeks 48 as defined by the time to loss of virologic response (TLOVR) algorithm.

The TLOVR analysis results were consistent with the results of the snapshot analysis (primary efficacy outcome), showing that 86.1% (304/353) of subjects in the QUAD group and 84.8% (301/355) of subjects in the ATV/r+TVD group had confirmed HIV-1 RNA < 50 copies/mL through Week 48. The HIV-1 RNA stratum-weighted difference in the percentages of responders at Week 48 was 1.6% (95% CI: −3.6% to 6.8%), indicating that QUAD was non-inferior to ATV/r+TVD using the TLOVR analysis.

In the Kaplan-Meier (KM) analysis of TLOVR, separation in the KM curves was seen at baseline, with a higher percentage of subjects in the ATV/r+TVD group (8%) who were never suppressed compared to the QUAD group (6%). The KM curves converged with time, and by Week 48, there were similar percentages of subjects with loss of virologic response in each treatment group (16% and 17% in the QUAD and ATV/r+TVD groups, respectively, overall p-value = 0.48).

· Tertiary efficacy endpoints

Tertiary efficacy endpoints were pure virologic failure with HIV-1 RNA cut-off at 50 copies/mL by Week 48 (ITT analysis set), the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by 2 different missing data imputation methods (M=F and M=E methods)

(ITT and PP analysis sets), the change from baseline in HIV-1 RNA (log10 copies/mL) at Week 48 (ITT analysis set), and the change from baseline in CD4 cell count and CD4% at Week 48 (ITT and PP analysis sets).

In the pure virologic failure analysis, the percentages of subjects who had pure virologic response through Week 48 were similar in both treatment groups: 86.1% (304/353) and 84.8% (301/355) of subjects in the QUAD and ATV/r+TVD groups, respectively.

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using M = F and M = E imputation methods were similar between treatment groups, in both the ITT and PP datasets. In the M = F analysis (ITT dataset), at Week 48, the percentage of subjects with plasma HIV-1 RNA levels < 50 copies/mL was 91.5% (323/353) in the QUAD group and 88.2% (313/355) in the ATV/r+TVD group. The stratum weighted difference in response rates between treatment groups (QUAD − ATV/r+TVD) was 3.5% (95% CI: −1.0% to 8.0%; p=0.12), indicating that QUAD was non-inferior to ATV/r+TVD using the M = F method. In the M = E analysis (ITT dataset), at Week 48, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL was 96.7% (323/334) in the QUAD group and 96.9% (313/323) in the ATV/r+TVD group. The stratum-weighted difference in response rates between treatment groups was −0.0% (95% CI: −2.8% to 2.8%; p=0.98), indicating that QUAD was non-inferior to ATV/r+TVD using the M = E method. Similar results were obtained in the analyses on the PP dataset[22].

Mean (SD) baseline HIV-1 RNA levels were 4.82 (0.607) $\log_{10}$ copies/mL and 4.80 (0.619) $\log_{10}$ copies/mL in the QUAD and ATV/r+TVD groups, respectively. At Week 48, the mean (SD) changes from baseline in HIV-1 RNA were similar in the 2 treatment groups: −3.09 (0.640) $\log_{10}$ copies/mL in the QUAD group and −3.07 (0.637) $\log_{10}$ copies/mL in the ATV/r+TVD group. The difference in least-squares means (LSMs) was 0.02 (95% CI: −0.05 to 0.09). No test of statistical significance was reported in the CSR. The change from baseline in plasma HIV-1 RNA levels for the ITT analysis set is presented.

Mean (SD) baseline CD4 cell counts were 364 (180.6) cells/μL and 375 (158.9) cells/μL in the QUAD and ATV/r+TVD groups, respectively. At Week 48, the mean (SD) increases from baseline in CD4 cell count were similar in the 2 treatment groups: 207 (164.2) cells/μL in the QUAD group and 211 (160.3) cells/μL in the ATV/r+TVD group. The difference in LSMs from an analysis of variance (ANOVA) model was -6 (95% CI: -31 to 18). This difference was not statistically significant (p = 0.61). Results were similar for the PP analysis set. The change from baseline in CD4 cell count for the ITT analysis set is presented graphically.

In the ITT analysis set, mean (SD) baseline CD4% was 21.0% (8.47) in the QUAD group and 21.8% (8.11) in the ATV/r+TVD group. At Week 48, the mean (SD) increases from baseline in CD4% were 9.4% (4.97) in the QUAD group and 9.9% (5.05) in the ATV/r+TVD group. The difference in LSMs was −0.6 (95% CI: −1.4 to 0.2). No test of statistical significance was reported in the CSR.

· Subgroup analysis of primary efficacy endpoint

The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (snapshot analysis) by subgroup are presented**.** Subgroup analyses showed generally comparable pattern of virologic success to those observed for the primary endpoint, with the point estimate of treatment difference in virologic success >0 (i.e. in favour of QUAD) in all the subgroups, except for the subgroup of patients who were females (n=68), where it was -1.2 %. The lower limit of the 95% CI of the difference in response rate in the subgroup analyses was greater than the prespecified non-inferiority margin of -12% in all the subgroups, except for the subgroup of patients who

[22] In the PP dataset, the percentage of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48 (M = F) was 97.5% (310 of 318 subjects) in the QUAD group and 97.7% (303 of 310 subjects) in the ATV/r+TVD group. The percentage of subjects with plasma HIV-1 RNA levels < 50 copies/mL at Week 48 (M = E) was 98.4% (310 of 315 subjects) in the QUAD group and 97.7% (303 of 310 subjects) in the ATV/r+TVD group.

were females (where it was -20.6%). Homogeneity tests performed for the primary endpoint did not show a significant difference in treatment effects between subgroups.

7.1.1.2.14. Resistance analyses

A total of 20 subjects (2.8%; 20/708) met the virologic failure criteria for inclusion in the RAP. The distribution of the RAP was similar between the 2 treatment groups, with 3.4% of subjects (12/353) analysed in the QUAD group and 2.3% of subjects (8/355) analysed in the ATV/r+TVD group.

In the QUAD group, 5 subjects (5 of 353, 1.4%) had emergent resistance to a study drug. Four of these 5 subjects developed reverse transcriptase resistance (RT-R) mutations. Four of these 5 subjects also developed integrase strand transfer inhibitor resistance (INSTI-R) mutations. None of these subjects developed primary Protease Inhibitors resistance (PI-R) mutations. No subjects within the RAP in the ATV/r+TVD group had emergent resistance to a study drug.

Comments: Overall, demographic and baseline disease characteristics were similar between the 2 treatment groups. The overall mean and median CD4 counts of 370 and 357 cells/μL, respectively, and the overall percentage of subjects with CD4 counts ≤ 500 cells/μL of 82.3% suggested that the study population was clinically relevant, as current treatment guidelines for treatment of HIV infection recommend initiation of ARV treatment when CD4 cell counts are <500 cells/μL[23].

The virologic response rates in the primary, secondary and tertiary endpoint analyses are summarised in Table 9 below.

Table 9. GS-US-236-0103. virologic response rates in the primary, secondary and tertiary endpoint analyses

	Percentage with virologic response (n/N)		Baseline HIV-1 RNA stratum-weighted difference^ (95%CI)
	QUAD group	ATV/r+TVD group	
Primary efficacy outcome (i.e. primary efficacy endpoint in ITT dataset)	89.5% (316/353)	86.8% (308/355)	3.0% (−1.9% to 7.8%)
Primary efficacy endpoint in PP dataset	97.5% (310/318)	97.7% (303/310)	-0.1% (−2.6% to 2.4%)
Sensitivity analyses of primary efficacy endpoint			
Exclude study drug discontinuations not related to virologic response and include all HIV-1 RNA data for late discontinuation	91.0% (315/353)	89.0% (308/355)	2.2% (−2.3% to 6.7%)
Consider study drug discontinuations not related to virologic response as virologic successes and include all HIV-1	89.3% (322/353	89.3% (317/355)	2.1% (−2.3% to 6.5%)

[23] National Institutes of Health, Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, Jan 10th 2011.

	Percentage with virologic response (n/N)		Baseline HIV-1 RNA stratum-weighted difference^ (95%CI)
	QUAD group	ATV/r+TVD group	
RNA data for late discontinuation			
Sensitivity analysis on effect of stratification factors			
- Stratification factor of baseline HIV-1 RNA level	89.5% (316/353)	86.8% (308/355)	1.33 (0.84 to 2.12) *
- Stratification factor of region	89.5% (316/353)	86.8% (308/355)	1.35 (0.84 to 2.15) *
- No stratification factor	89.5% (316/353)	86.8% (308/355)	1.30 (0.82 to 2.06) *
TLOVR analysis	86.1% (304/353)	84.8% (301/355)	1.6% (−3.6% to 6.8%)
Pure virologic failure analysis	86.1% (304/353)	84.8% (301/355)	NA
M = F analysis	91.5% (323/353)	88.2% (313/355)	3.5% (−1.0% to 8.0%)
M = E analysis	96.7% (323/334)	96.9% (313/323)	−0.0% (−2.8% to 2.8%)

^ QUAD minus ATV/r+TVD, *values are calculated odds ratio (95%CI), NA= not available

Comments

The efficacy results showed that the analysis outcome of non-inferiority of QUAD versus ATV/r+TVD obtained in the primary efficacy outcome was supported by other analyses, including analysis in the PP dataset, analysis using the TLVOR algorithm, and analysis using different imputation methods.

Virologic response measured in terms of decrease in HIV-1 RNA levels from baseline at Week 48 was also similar between treatment groups (mean change from baseline of −3.09 and −3.07 $\log_{10}$ copies/mL in the QUAD and ATV/r+TVD groups, respectively). Drug effect measured in terms of immunological response was not statistically significantly different between the 2 treatment groups (mean increases from baseline at Week 48 in CD4 cell count of 207 and 211 cells/μL in the QUAD and ATV/r+TVD groups, respectively; p=0.61)

Subgroup analyses generally supported the primary efficacy results. The point estimates of treatment difference in virologic success were >0 (i.e. in favour of QUAD) in all the subgroups, except for the subgroup of patients who were females. The lower limits of the 95% CI of the difference in response rate in the subgroup analyses were all greater than the prespecified non-inferiority margin of -12% in all the subgroups, except for the subgroup of patients who were females. However, the 95% CI of the difference in response rate in this subgroup was very wide (-20.6% to 18.3%), reflecting the small sample size in this subgroup (n=24, versus n=292 for the subgroup of male patients). In addition,

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

With regards to emergent study drug resistance, out of 12 subjects tested in the QUAD group, 4 subjects developed RT-R mutations, 4 subjects developed INSTI-R mutations, and none developed PI-R mutations. This is comparable with resistance analyses results in Study GS-US-236-0102, where out of 14 subjects tested in the QUAD group, 8 subjects developed RT-R mutations, 7 subjects developed INSTI-R mutations, and none developed PI-R mutations. However this compares adversely with the results in the ATV/r+TVD group, where out of the 8 subjects tested, none developed emergent resistance to a study drug. Within the QUAD group, the percentage of patients with emergent RT-R mutations was 1.1 % (4 out of 353), and that for emergent INSTI-R mutations was 1.1% (4 out of 353).

7.1.2. Other efficacy studies

7.1.2.1. Study GS-US-236-0104

Study GS-US-236-0104 was a Phase 2, double-dummy, randomised, double-blind, multicentre, active-control study evaluating the safety and efficacy of the QUAD STR versus Atripla (ATR) in 71 HIV-1 infected, ARV treatment-naive adult subjects (≥ 18 years of age). This study was conducted to provide an estimation of the response rate of HIV-1 RNA < 50 copies/mL of QUAD, in order to allow for the planning of the Phase 3 studies. This is a multicentre study where subjects were enrolled in a total of 30 study sites in the United States. The study start date (first subject screened) was 30th March 2009. The study was ongoing in an open-label extension phase at the time of this submission, and data through Week 96 were presented in the CSR submitted. The date of last subject observation for this CSR was 17th May 2011.

The primary objective of this study was to evaluate the efficacy of QUAD STR (EVG/COBI/FTC/TDF) versus ATR STR (EFV/FTC/TDF) in HIV-1 infected, ARV treatment-naïve adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 24. The secondary study objectives were to evaluate the efficacy of QUAD STR versus ATR STR in HIV-1 infected, ARV treatment-naïve adult subjects at Week 48, and to evaluate the safety and tolerability of the 2 STRs through 48 weeks of treatment.

Subjects enrolled in this study were HIV-1 infected, ARV treatment-naive adults (≥ 18 years of age) who had plasma HIV-1 RNA levels ≥ 5000 copies/mL and CD4 cell count > 50 cells/μL at screening, with no prior use of any approved or experimental anti-HIV drug and with no NRTI, NNRTI or primary PI resistance mutations.

Subjects were randomised in a 2:1 ratio to 1 of 2 treatment groups: QUAD STR once daily and placebo for ATR once daily, or ATR STR once daily and placebo for QUAD once daily. Randomisation was stratified by HIV-1 RNA level (≤ 100000 copies/mL or > 100000 copies/mL) at screening. Subjects were treated with double-blind study drug for 48 weeks. At the subsequent visit (Week 60), subjects were offered the option of participating in an open-label, single-arm study extension in which all subjects were treated with QUAD STR.

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24. The secondary efficacy endpoints were the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48, virologic outcomes at Weeks 24 and 48 using the FDA-defined snapshot analysis and HIV-1 RNA < 50 copies/mL[24], and the changes from baseline in HIV-1 RNA (log10 copies/mL) and CD4 cell count and percentage at Weeks 24 and 48.

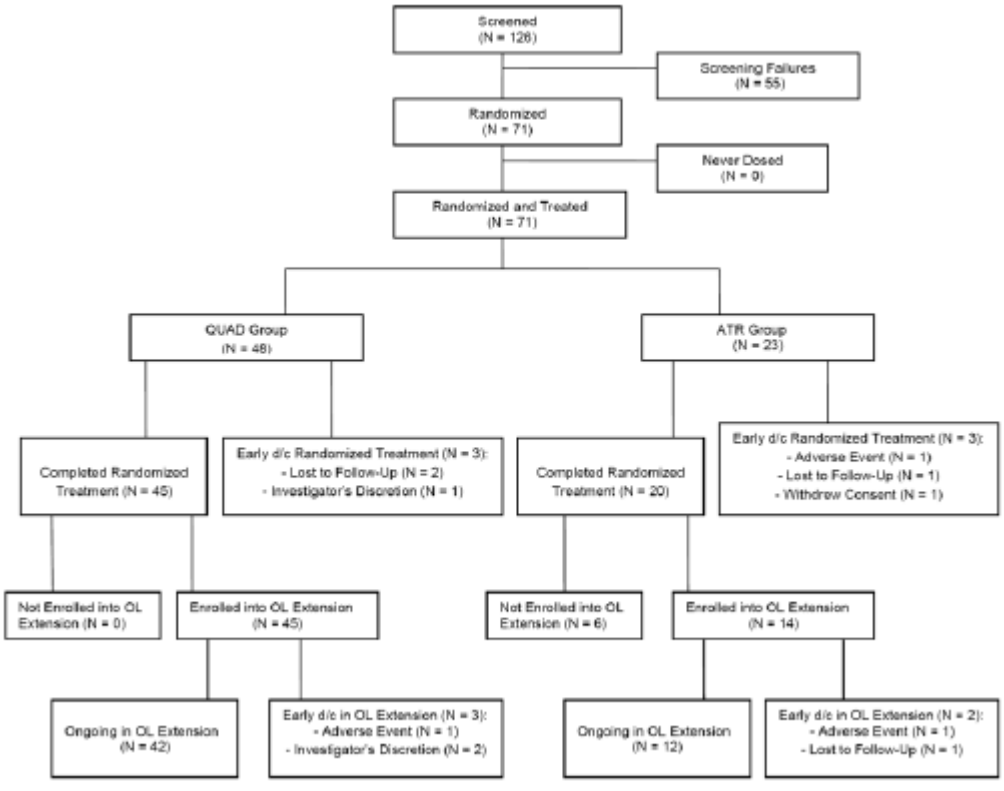
[24] In the snapshot analyses for the Week 24 and Week 48 virologic outcomes, visit window was defined as from study Day 141 to study Day 196 (inclusive) for Week 24, and from study Day 309 to study Day 378 (inclusive) for Week 48, respectively.

The intent-to-treat (ITT) analysis set was the primary analysis set for efficacy analyses in the randomised phase. The primary analysis for the primary efficacy endpoint was analysed using the missing = failure (M = F) method. Secondary analyses used missing data or ARV therapy switch equals failure (M/S=F) and missing = excluded (M=E) methods.

A sample size of 50 subjects in the QUAD treatment group was chosen to allow estimation of the response rate of HIV-1 RNA < 50 copies/mL at Week 24 for QUAD STR, in order to allow for the planning of Phase 3 studies. As the randomisation was in a 2:1 ratio, this would give a total sample size of 75 subjects. It was estimated that this total sample size of 75 subjects randomised in a 2:1 ratio would have a very low power of 26% to evaluate non-inferiority with respect to the response rate of HIV-1 RNA < 50 copies/mL at Week 24, assuming a response rate of 84% for both treatment groups and a non-inferiority margin of 0.12. The sponsor has stated in the protocol that in view of this, non-inferiority of the two treatment regimens would not be formally evaluated in this study.

A total of 71 subjects were enrolled in the study. Although this was 4 subjects fewer than the sample size planned (75 subjects), the sponsor has stated that this smaller study sample size was expected to have limited impact on the estimation of the response rate of HIV-1 RNA < 50 copies/mL at Week 24, which was the reason for conducting this study. Disposition of study subjects is presented below:

Figure 3. Study GS-US-236-0104 subject disposition



OL= open-label

Of the 71 randomised and treated subjects, 65 completed study treatment in the randomised phase (45 in the QUAD group and 20 in the ATR group). Fifty-nine subjects entered the open-label extension phase and received treatment with the QUAD STR. Among these 59 subjects, 45 had been initially randomised to the QUAD STR (labelled as QUAD/QUAD group in the CSR) and 14 had been initially randomised to ATR (labelled as ATR/QUAD group in the CSR).

Overall, demographic characteristics were similar between the 2 treatment groups. The majority of the patients were males (91.5%) and white (71.8%). Subjects had a mean age of 36 years (range of 19-56 years). The mean (SD) baseline HIV-1 RNA value was 4.59 $\log_{10}$ copies/mL, CD4 count was 403 (170.1) cells/µL, and CD4% was 23.1 (8.32). The median CD4 count was 394 cells/µL. Overall, 77.5% of subjects had baseline HIV-1 RNA ≤ 100,000 copies/mL, and 71.8 % of subjects had CD4 counts ≤ 500 cells/µL. Baseline mean viral load and CD4 percentage were similar between both treatment groups. However, the mean baseline CD4 count was lower in the QUAD group compared to that in the ATR group (378 cells/µL and 454 cells/µL in the QUAD and ATR groups, respectively; p=0.048).

Results of the primary and secondary endpoint analyses are summarised in Table 10 below.

Table 10. Study GS-US-236-0104 Results of the primary and secondary endpoint analyses

			QUAD versus ATR	
	QUAD n/N (%)	**ATR n/N (%)**	**p-value**	**Baseline HIV-1 RNA stratum-weighted difference* (95% CI)**
Week 24- percentage of subjects with HIV-1 RNA < 50 copies/mL				
Missing = Failure (primary efficacy outcome)				
HIV-1 RNA < 50 copies/mL	43/48 (89.6%)	20/23 (87.0%)	0.72	2.8% (−14.5% to 20.1%)
95% CI	77.3% to 96.5%	66.4% to 97.2%		
Missing/ARV Switch = Failure				
HIV-1 RNA < 50 copies/mL	43/48 (89.6%)	19/23 (82.6%)	0.39	7.2% (−11.7% to 26.0%)
95% CI	77.3% to 96.5%	61.2% to 95.0%		
Missing = Excluded				
< 50 copies/mL	43/45 (95.6%)	20/21 (95.2%)	0.90	0.7% (−13.4% to 14.8%)
95% CI	84.9% to 99.5%	76.2% to 99.9%		
Week 48- percentage of subjects with HIV-1 RNA < 50 copies/mL				
Missing = Failure				
< 50 copies/mL	43/48 (89.6%)	20/23 (87.0%)	0.72	2.8% (−15.1% to 20.8%)
95% CI	77.3% to 96.5%	66.4% to 97.2%		
Missing/ARV Switch = Failure				
< 50 copies/mL	43/48 (89.6%)	19/23 (82.6%)	0.39	7.2% (−12.1% to 26.5%)

			QUAD versus ATR	
	QUAD n/N (%)	**ATR n/N (%)**	**p-value**	**Baseline HIV-1 RNA stratum-weighted difference* (95% CI)**
95% CI	77.3% to 96.5%	61.2% to 95.0%		
Missing = Excluded				
< 50 copies/mL	43/45 (95.6%)	20/21 (95.2%)	0.90	0.7% (−13.5% to 15.0%)
95% CI	84.9% to 99.5%	76.2% to 99.9%		
Virologic Success at Week 24 using Snapshot Analysis and HIV-1 RNA < 50 copies/mL				
	QUAD (N=48)	ATR (N=23)	p-value	Difference in Percentages (95% CI)
HIV-1 RNA < 50 copies/mL	43 (89.6%)	20 (87.0%)	0.73	2.7% (-15.4% to 20.9%)
Virologic Success at Week 48 using Snapshot Analysis and HIV-1 RNA < 50 copies/mL				
	QUAD (N=48)	ATR (N=23)	p-value	Difference in Percentages (95% CI)
HIV-1 RNA < 50 copies/mL	44 (91.7%)	19 (82.6%)	0.26	9.2% (-9.9% to 28.3%)

* QUAD minus ATR

Results of analyses of virologic suppression in the open-label period is summarised in Table 11 below.

Table 11. Study GS-US-236-0104: Results of analyses of virologic suppression in the open-label period

Open label period- percentage of subjects with HIV-1 RNA < 50 copies/mL		
	QUAD/QUAD n/N (%)	**ATR/QUAD n/N (%)**
Baseline of open-label period (Study Week 60)		
Missing = Failure		
HIV-1 RNA < 50 copies/mL	0/46 (0%)	13/14 (92.9%)
95% CI	0.0% to 7.7%	66.1% to 99.8%

Open label period- percentage of subjects with HIV-1 RNA < 50 copies/mL		
	QUAD/QUAD n/N (%)	ATR/QUAD n/N (%)
Missing/ARV Switch = Failure		
HIV-1 RNA < 50 copies/mL	0/46 (0%)	13/14 (92.9%)
95% CI	0.0% to 7.7%	66.1% to 99.8%
Missing = Excluded		
HIV-1 RNA < 50 copies/mL	0/46 (0%)	13/14 (92.9%)
95% CI	0.0% to 7.7%	66.1% to 99.8%
Open-label Week 24 (Study Week 84)		
Missing = Failure		
HIV-1 RNA < 50 copies/mL	43/46 (93.5%)	12/14 (85.7%)
95% CI	82.1% to 98.6%	57.2% to 98.2%
Missing/ARV Switch = Failure		
HIV-1 RNA < 50 copies/mL	43/46 (93.5%)	11/14 (78.6%)
95% CI	82.1% to 98.6%	49.2% to 95.3%
Missing = Excluded		
HIV-1 RNA < 50 copies/mL	43/45 (95.6%)	12/13 (92.3%)
95% CI	84.9% to 99.5%	64.0% to 99.8%
Open label Week 36 (Study Week 96)		
Missing = Failure		
HIV-1 RNA < 50 copies/mL	NA	12/14 (85.7%)
95% CI	NA	57.2% to 98.2%
Missing/ARV Switch = Failure		
HIV-1 RNA < 50 copies/mL	NA	12/14 (85.7%)
95% CI	NA	57.2% to 98.2%

Open label period- percentage of subjects with HIV-1 RNA < 50 copies/mL		
	QUAD/QUAD n/N (%)	ATR/QUAD n/N (%)
Missing = Excluded		
HIV-1 RNA < 50 copies/mL	NA	12/12 (100.0%)
95% CI	NA	73.5% to 100.0%
Open label Week 40		
Missing = Failure		
HIV-1 RNA < 50 copies/mL	42/46 (91.3%)	NA
95% CI	79.2% to 97.6%	NA
Missing/ARV Switch = Failure		
HIV-1 RNA < 50 copies/mL	40/46 (87.0%)	NA
95% CI	73.7% to 95.1%	NA
Missing = Excluded		
HIV-1 RNA < 50 copies/mL	42/44 (95.5%)	NA
95% CI	84.5% to 99.4%	NA

NA= not available

Baseline plasma HIV-1 RNA was similar between treatment groups (4.59 and 4.58 $\log_{10}$ copies/mL in the QUAD and ATR groups, respectively). The mean (SD) change from baseline at Week 24 was −2.87 (0.578) $\log_{10}$ copies/mL in the QUAD group and −2.88 (0.586) $\log_{10}$ copies/mL in the ATR group (p = 0.63). The mean (SD) change from baseline at Week 48 was −2.89 (0.570) $\log_{10}$ copies/mL in the QUAD group and −2.71 (0.933) $\log_{10}$ copies/mL in the ATR group (p = 0.32).

The mean (SD) change from baseline in CD4 count at Week 24 was 161 (141.1) cells/μL in the QUAD group and 117 (143.7) cells/μL in the ATR group (p = 0.27). The mean change from baseline in CD4 count at Week 48 was 240 (172.8) cells/μL in the QUAD group and 166 (158.5) cells/μL in the ATR group (p = 0.10). The mean (SD) change from baseline in CD4% at Week 24 was 7.2% (4.26) in the QUAD group and 8.2% (4.41) in the ATR group (p = 0.41). The mean (SD) change from baseline in CD4% at Week 48 was 9.1% (4.73) in the QUAD group and 9.9% (5.00) in the ATR group (p = 0.53).

In the open label period, the mean (SD) change from baseline[25] in HIV-1 RNA at open-label Week 96 in the QUAD/QUAD group (n=44), was −2.86 (0.625) log10 copies/mL. The mean (SD) change from baseline in CD4 cell count at open-label Week 96 in the QUAD/QUAD group (n=44) was 336 (227.3) cells/μL, and the corresponding mean (SD) change from baseline in CD4% was 11.0% (6.70). In the open label period, at open-label Week 36 in the ATR/QUAD group (n=12), the mean (SD) change from open-label baseline in HIV-1 RNA, was -0.02 (0.086) log10

[25] The baseline used was the HIV-1 RNA levels at open-label baseline visit (i.e. Study Week 60)

copies/mL, the mean (SD) change from open-label baseline in CD4 count was 152 (161.5) cells/μL, and the mean (SD) change from open-label baseline in CD4% was 2.3% (2.89). Data for the ATR/QUAD group was not available for the period beyond open-label Week 36.

Of the 71 randomised and treated subjects, 3 subjects (4.2%) (2 in the QUAD group and 1 in the ATR group) were analysed for resistance development. Samples were submitted for genotypic and phenotypic analysis of the reverse transcriptase (RT), protease (PR), and integrase (IN) genes. One subject in the QUAD group developed IN mutations at Week 84. No data were available for the RT and PR genes for this subject due to assay failure, which the sponsor stated was likely due to the low viral load at that time point. This subject had suppression of HIV-1 RNA to < 50 copies/mL, 3 weeks later and also at Week 96 without any change in the ARV regimen. No resistance was detected in the other 2 subjects.

Comments: The overall demographic and general baseline disease characteristics were similar between the 2 treatment groups except for mean baseline CD4 count, which was lower in the QUAD group (378 cells/μL) compared to that in the ATR group (454 cells/μL) (p=0.048). It is noted that the immunological response measured was the change from baseline of CD4 counts, and hence this difference in baseline levels would not have directly affected the immunological response endpoint. However, the difference might reflect a greater baseline immunological suppressed state of patients in the QUAD group compared to the ATR group. It is unclear how this might have affected the accuracy of the analysis results. However, this needs to be considered in the context that this was a Phase II non-pivotal efficacy/safety study with a small sample size, which purpose for the current submission was to provide some preliminary indicative efficacy and safety data on the long-term use of QUAD beyond 48 weeks.

The virologic response rates in the primary and secondary endpoint analyses in the randomised phase, presented previously in the Table on *Study GS-US-236-0104: Results of the primary and secondary endpoint analyses*, above, showed that although the difference in virologic response rates between the 2 treatment groups were all not statistically significant, the lower limit of the 95% CI were all below the non-inferiority margin of -12% (i.e. failed to demonstrate non-inferiority of QUAD versus ATR), except for the analysis of the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the Missing/ARV Switch = Failure imputation method, where it was close to -12%, at-11.7%, and the analysis at Week 48 using snapshot analysis, where it was -9.9%. However this needs to be taken in the context that this study was not powered to evaluate non-inferiority of QUAD versus ATR, but to obtain an estimation of the response rate of HIV-1 RNA < 50 copies/mL at Week 24 for QUAD STR.

The virologic response rate in the QUAD group at Week 48 using snapshot analysis and HIV-1 RNA < 50 copies/mL was comparable to those obtained in Study GS-US-236-0102 and Study GS-US-236-0103 (virologic response rate of 89.5%, 87.6% and 91.7% in GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104, respectively).

Virologic response measured in terms of decrease in HIV-1 RNA levels from baseline was similar between treatment groups at Week 24 and Week 48. The mean change from baseline at Week 48 of HIV-1 RNA levels in the QUAD group was comparable to those obtained in Study GS-US-236-0102 and Study GS-US-236-0103 (change from baseline of −2.99, −3.09 and -2.89 $\log_{10}$ copies/mL in Study GS-US-236-0102, Study GS-US-236-0103 and Study GS-US-236-0104, respectively).

Drug effect measured in terms of immunological response was not statistically significantly different between the 2 treatment groups at Week 24 and 48. The mean change from baseline at Week 48 of CD4 counts in the QUAD group was comparable to those obtained in Study GS-US-236-0102 and Study GS-US-236-0103 (change from baseline of 239, 207 and 240 cells/µL in Study GS-US-236-0102, Study GS-US-236-0103 and Study GS-US-236-0104, respectively).

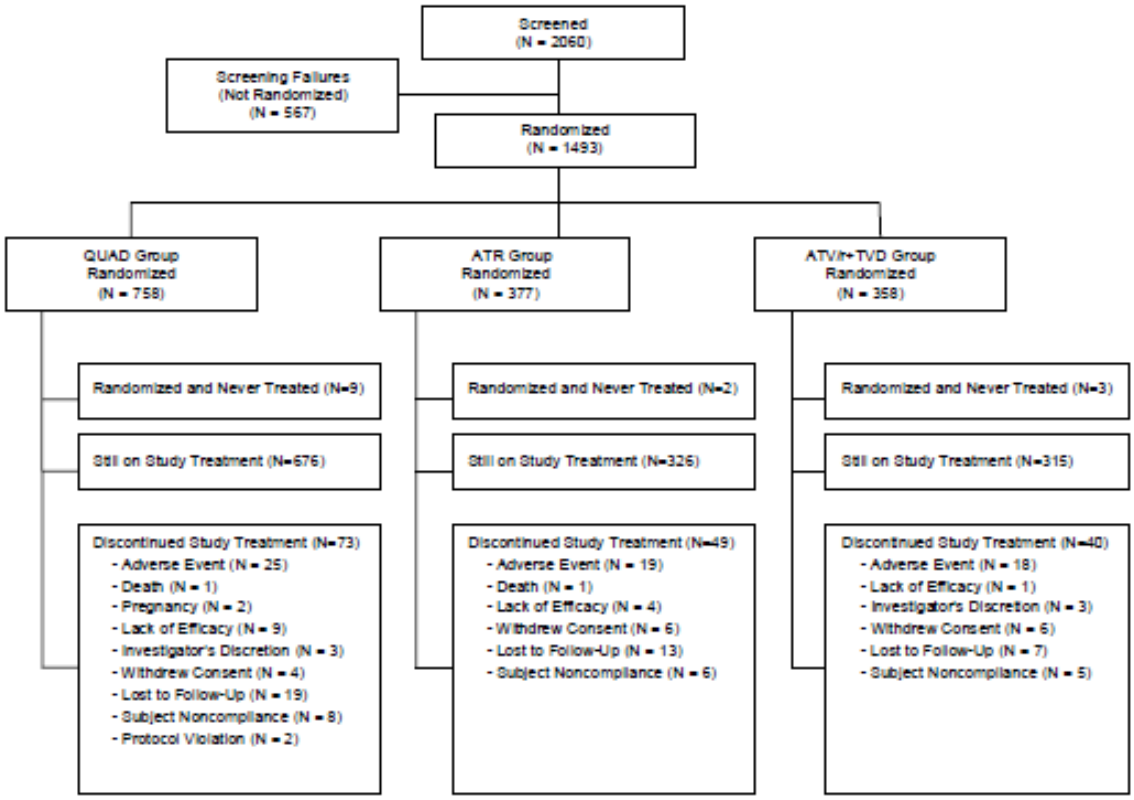
Interpretation of results in the open-label phase was difficult due to the small sample size (n= 46 in QUAD/QUAD group and n=14 in ATR/QUAD group). In particular, comparison of results between the QUAD/QUAD and ATR/QUAD group could not be meaningfully analysed or interpreted, due to the small sample sizes, as well as the fact that 13 out of 14 patients in the ATR/QUAD group already had HIV-1 RNA levels < 50 copies/mL at the start of the open-label period. Results in the QUAD/QUAD group suggested that in patients who were on QUAD in the randomised phase and who continued on QUAD in the open-label phase, there was further and sustained suppression of HIV-1 RNA levels. None of the 46 patients in the QUAD/QUAD group had HIV-1 RNA levels < 50 copies/mL at the start of the open-label period (Study Week 60). The percentage of subjects with HIV-1 RNA < 50 copies/mL increased to between 93.5% to 95.6% at open-label Week 24 (Study Week 84), and remained high at between 87.0% to 95.5% at open-label Week 40 (Study Week 100).

Analyses on the change from baseline in HIV-1 RNA levels in the QUAD/QUAD group showed that there was a further mean change in HIV-1 RNA levels from Study Week 60 to Study Week 156 (open-label Week 96) of −2.86 log10 copies/mL. During the same period, there was a further mean change from open-label baseline in CD4 cell count of 336 cells/µL. These results suggested that both virological and immunological responses were sustained beyond 48 weeks of QUAD dosing.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

In the clinical summary of efficacy in module 2 of this submission, the sponsor has provided a pooled analysis of efficacy results of Study GS-US-236-0102, Study GS-US-236-0103 and Study GS-US-236-0104. Pooled subject disposition is presented in the flow chart below:

Figure 4. Subject disposition: pooled analysis



Of the 1493 randomised subjects, 1479 were included in the pooled ITT analysis set, consisting of 749 subjects who were randomised to receive QUAD STR, 375 who were randomised to receive ATR, and 355 who were randomised to receive ATV/r+TVD.

The primary efficacy endpoint for the pooled ITT analysis set was the percentage of subjects with virologic success (HIV-1 RNA < 50 copies/mL) at Week 48, as defined by the FDA snapshot analysis algorithm. Virologic outcomes at Week 48 using snapshot analysis for individual studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104 are presented side by side in Table 12. For ease of reference, and the pooled data are presented in Table 13.

Table 12. GS-US-236-0102, 0103, and 0104: Individual Study Data for Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis, ITT Analysis Set)

	236-0102		236-0103		236-0104	
	QUAD (N=348)	ATR (N=352)	QUAD (N=353)	ATV/r + TVD (N=355)	QUAD (N=48)	ATR (N=23)
Virologic Success at Week 48[a]						
HIV-1 RNA < 50 copies/mL	305 (87.6%)	296 (84.1%)	316 (89.5%)	308 (86.8%)	44 (91.7%)	19 (82.6%)
Difference in Percentages[b]	3.6%		3.0%		9.2%	
(95% CI)	(-1.6% to 8.8%)		(-1.8% to 7.7%)		(-9.9% to 28.3%)	
p-value[c]	0.17		0.22		0.26	
Virologic Failure at Week 48	25 (7.2%)	25 (7.1%)	19 (5.4%)	19 (5.4%)	4 (8.3%)	3 (13.0%)
HIV-1 RNA >= 50 copies/mL	13 (3.7%)	11 (3.1%)	7 (2.0%)	8 (2.3%)	1 (2.1%)	1 (4.3%)
Discontinued Study Drug Due to Lack of Efficacy	4 (1.1%)	2 (0.6%)	4 (1.1%)	0	0	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	8 (2.3%)	12 (3.4%)	8 (2.3%)	11 (3.1%)	3 (6.3%)	2 (8.7%)
No Virologic Data in Week 48 Window	18 (5.2%)	31 (8.8%)	18 (5.1%)	28 (7.9%)	0	1 (4.3%)
Discontinued Study Drug Due to AE/Death	10 (2.9%)	19 (5.4%)	11 (3.1%)	18 (5.1%)	0	1 (4.3%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	8 (2.3%)	11 (3.1%)	7 (2.0%)	9 (2.5%)	0	0
Missing Data during Window but on Study Drug	0	1 (0.3%)	0	1 (0.3%)	0	0

a Week 48 window is between Day 309 and 378 (inclusive).
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted Mantel-Haenszel (MH) proportion.
c P-values for treatment comparisons were from the Cochran-Mantel-Haenszel (CMH) test stratified by baseline HIV-1 RNA stratum.
d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.

Table 13. GS-US-236-0102, 0103, and 0104: Pooled Data for Virologic Outcome at Week 48 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Analysis, ITT Analysis Set)

	QUAD		ATR	ATV/r+TVD
	236-0102,0103,0104 (N=749)	236-0102,0104 (N=396)	236-0102,0104 (N=375)	236-0103 (N=355)
Virologic Success at Week 48[a]				
HIV-1 RNA < 50 copies/mL	665 (88.8%)	349 (88.1%)	315 (84.0%)	308 (86.8%)
QUAD vs. ATR				
Difference in Percentages[b]	5.1%	4.1%		
(95% CI)	(0.7% to 9.4%)	(-0.8% to 9.1%)		
p-value[c]	0.016	0.096		
QUAD vs. ATV/r+TVD				
Difference in Percentages	1.9%			
(95% CI)	(-2.3% to 6.1%)			
p-value[c]	0.37			
Virologic Failure at Week 48	48 (6.4%)	29 (7.3%)	28 (7.5%)	19 (5.4%)
HIV-1 RNA >= 50 copies/mL	21 (2.8%)	14 (3.5%)	12 (3.2%)	8 (2.3%)
Discontinued Study Drug Due to Lack of Efficacy	8 (1.1%)	4 (1.0%)	2 (0.5%)	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	19 (2.5%)	11 (2.8%)	14 (3.7%)	11 (3.1%)
No Virologic Data in Week 48 Window	36 (4.8%)	18 (4.5%)	32 (8.5%)	28 (7.9%)
Discontinued Study Drug Due to AE/Death	21 (2.8%)	10 (2.5%)	20 (5.3%)	18 (5.1%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	15 (2.0%)	8 (2.0%)	11 (2.9%)	9 (2.5%)
Missing Data during Window but on Study Drug	0	0	1 (0.3%)	1 (0.3%)

a Week 48 window is between Day 309 and 378 (inclusive).
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c P-values for treatment comparisons were from the CMH test stratified by baseline HIV-1 RNA stratum.
d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, and pregnancy.

The pooled data from Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104 showed that the percentages of subjects having virologic success (ITT dataset) at Week 48 were 88.8% (665/749) in the pooled QUAD group, 84.0% (315/375) in the pooled ATR group, and 86.8%

(308/355) in the ATV/r+TVD group. The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success between the QUAD and ATR group was 5.1% (95% CI: 0.7% to 9.4%), with the lower limit of the 95% CI > 0. The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success between the QUAD group and the ATV/r + TVD group was 1.9% (95% CI: −2.3% to 6.1%), with the lower-bound of the 95% CI < 0, but above the specified non-inferiority margin of -12%.

The sponsor also analysed the data of pooled QUAD versus pooled control (ATR in studies GS-US-236-0102 and GS-US-236-0104, and ATV/r+TVD in study GS-US-236-0103). The percentage of subjects with virologic success (HIV-1 RNA < 50 copies/mL) at Week 48, as defined by the FDA snapshot analysis algorithm was 88.8% (665/749) in the poled QUAD group, compared with 85.3% (623/730) in the pooled control group. The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success between the pooled QUAD and pooled control group was 3.5% (95% CI: 0.1% to 7.0%).

Pooled subgroup analysis was also done, where the primary efficacy endpoint of virologic response (HIV-1 RNA < 50 copies/mL, snapshot analysis algorithm) was analysed for each of the following subgroups using the ITT analysis set: baseline HIV-1 RNA level (copies/mL; ≤ 100 000 and > 100 000), age (< 40 and ≥ 40 years), sex (male and female), race (white and non-white), and baseline CD4 group (≤ 350 and > 350 cells/μL).

Pooled subgroup analyses showed that the point estimates of treatment difference in virologic success were >0 (i.e. in favour of QUAD) in all the pooled subgroups, except for the pooled subgroup of patients who were females, where it was -0.2%. The lower limits of the 95% CI of the difference in response rate were greater than the prespecified −12% non-inferiority margin in all the pooled subgroups, except for the pooled subgroup of patients who were females, where it was -13.3%. Homogeneity tests of the treatment effects between subgroups performed for pooled study data for virologic success at Week 48 (HIV-1 RNA < 50 copies/mL, snapshot analysis) showed no significant differences in treatment effects between subgroups**.**

Comments: Pooled analysis of the 3 studies is appropriate as the study designs were similar. In all 3 studies, subjects were ARV treatment-naive, HIV-1 infected adult subjects with HIV-1 RNA ≥ 5000 copies/mL at screening. In all 3 studies, randomisation was stratified by HIV-1 RNA at screening (≤ 100 000 copies/mL or > 100 000 copies/mL). Overall, demographic and baseline disease characteristics were also similar among the 3 studies. In all 3 studies, the majority of subjects were male (89.0%, 90.4% and 91.5% in studies GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104, respectively), and white (63.0%, 74.4% and 71.8% in studies GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104, respectively). The mean (range) age was 38 years (18 to 67 years), 38 years (19 to 72 years), and 36 years (range of 19-56 years) in studies GS-US-236-0102, GS-US-236-0103 and GS-US-236-0104, respectively. The mean baseline HIV-1 RNA value were 4.76 , 4.81 and 4.59 $\log_{10}$ copies/mL in studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104, respectively. Mean baseline CD4 count were 386, 370 and 403 cells/μL ,respectivelyand median baseline CD4 count were 380, 367 and 394 cells/μL, respectively. Overall, 66.6% of subjects had baseline HIV-1 RNA ≤ 100 000 copies/mL in study GS-US-236-0102, compared with 58.9 % of subjects in study GS-US-236-0103, and 77.5% of subjects in study GS-US-236-0104. The percentage of subjects with CD4 counts ≤ 500 cells/μL was 78.7%, 82.3% and 71.8% in studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104, respectively.

Pooled virological response results were consistent with those in the individual studies. The percentage of subjects with virologic success (HIV-1 RNA < 50 copies/mL) at Week 48, as defined by the FDA snapshot analysis algorithm was 88.8% in the pooled QUAD group, compared with 87.6% in the QUAD group in

Study GS-US-236-0102, 89.5% in Study GS-US-236-0103, and 91.7% in Study GS-US-236-0104. The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success between the pooled QUAD and pooled ATR group, and that between the pooled QUAD group and the pooled ATV/r + TVD group were consistent with the results in the 2 pivotal Phase III studies in that the lower limits of the 95% CI were above the specified non-inferiority margin of -12%[26]. Pooling of both active controls also gave similar results, where the HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success between the pooled QUAD and pooled control group was 3.5% (95% CI: 0.1% to 7.0%).

7.2. Evaluator's conclusions on clinical efficacy for the proposed indication of QUAD as a complete regimen for the treatment of HIV infection in adults

Overall, in the 2 Phase III registration trials, the conclusion from the primary efficacy analyses that there was non-inferiority in the virologic efficacy of QUAD STR compared with ATR or ATV/r+TVD was appropriate. The study designs of both Phase III registration trials are sound. Inclusion and exclusion criteria are in line with recommendations on the study population in the TGA-adopted EMA guideline on the clinical development of medicinal products for the treatment of HIV infection, and study primary endpoints are in agreement with current HIV research guidelines and recommendations. The choices of active control ARV drug regimen of ATR in Study GS-US-236-0102 and of ATV/r+TVD in Study GS-US-236-0103 are appropriate as both ARV drug regimens are recommended first-line treatment regimen for ARV treatment-naive HIV-1 infected patients, in accordance with current treatment guidelines.

In each of the 2 Phase III studies, demographic and baseline disease characteristics were similar between treatment groups. The majority of subjects in each study had CD4 counts ≤ 500 cells/μL, and median CD4 counts were 380 and 367 cells/μL in studies GS-US-236-0102 and GS-US-236-0103, respectively, suggesting clinical relevance of the study population, as current treatment guidelines for treatment of HIV infection recommend initiation of ARV treatment when CD4 cell counts are <500 cells/μL.

Primary efficacy outcomes demonstrated non-inferiority of QUAD versus ATR or ATV/r+TVD. Secondary and tertiary endpoints analyses showed that the conclusion of non-inferiority of QUAD versus ATR or ATV/r+TVD obtained in the respective primary efficacy outcomes was supported by other analyses, including analysis in the PP dataset, analysis using the TLVOR algorithm, and analysis using different imputation methods. Virologic response measured in terms of decrease in HIV-1 RNA levels from baseline, and drug effect measured in terms of immunological response were both consistent with the primary efficacy outcome: virologic response measured in terms of decrease in HIV-1 RNA levels from baseline at Week 48 was similar between treatment groups in both studies, while drug effect measured in terms of immunological response was statistically significant in favour of QUAD over ATR, and did not show any statistically significant difference between QUAD and ATV/r+TVD.

Subgroup analyses in the 2 Phase III studies generally supported the respective primary efficacy results. In both studies, homogeneity tests performed for the primary endpoint did not show a significant difference in treatment effects between subgroups. In both studies, the lower limits of the 95% CI of the difference in response rate in the subgroup analyses were all greater than the prespecified −12% non-inferiority margin in all the subgroups, except for the subgroup of

[26] The HIV-1 RNA stratum-weighted difference in the percentages of subjects with virologic success between the pooled QUAD and pooled ATR group was 5.1% (95% CI: 0.7% to 9.4%), compared with 3.6% (95% CI: -1.6% to 8.8%) in Study GS-US-236-0102. The corresponding difference in percentage between the pooled QUAD group and the pooled ATV/r + TVD group was 1.9% (95% CI: −2.3% to 6.1%), compared with 3.0% (95% CI: -1.8% to 7.7%) in Study GS-US-236-0103.

patients who were females (-15.5% and -20.6% in studies GS-US-236-0102 and GS-US-236-0103, respectively). However, the 95% CI of the difference in response rate in this subgroup was very wide in both studies (-15.5% to 20.1% in study GS-US-236-0102 and -20.6% to 18.3% in study GS-US-236-0103) reflecting the small sample size in this subgroup (n=41 and n=24 in studies GS-US-236-0102 and GS-US-236-0103, respectively), which makes interpretation of the results difficult.

In the small Phase II study, Study GS-US-236-0104, although the results in the primary and secondary endpoint analyses in the randomised phase mostly failed to demonstrate non-inferiority of QUAD versus ATR, the analysis at Week 48 using the FDA snapshot analysis algorithm (a secondary endpoint in this study) yielded results suggesting non-inferiority of QUAD versus ATR. *These results need to be taken in the context that this study was not powered to evaluate non-inferiority of QUAD versus ATR, but to obtain an estimation of the response rate of HIV-1 RNA < 50 copies/mL at Week 24 for QUAD STR.*

The virologic response rate in the QUAD group at Week 48 using snapshot analysis was comparable to those obtained in Study GS-US-236-0102 and Study GS-US-236-0103, as was the mean change from baseline at Week 48 of HIV-1 RNA levels and CD4 counts in the QUAD group, providing some evidence of consistency in the virological and immunological response rates of QUAD.

Results in the open-label phase of Study GS-US-236-0104 suggested that in patients who were on QUAD in the randomised phase and who continued on QUAD in the open-label phase (i.e. > 60 weeks of QUAD), there was further and sustained suppression of HIV-1 RNA levels and increase in CD4 cell count, suggesting that both virological and immunological responses were sustained beyond 48 weeks of QUAD dosing. The sample size was small and inadequate for definitive evaluation of long-term efficacy, but gave a preliminary indication of potential long-term efficacy.

Pooled efficacy analysis is appropriate as the study designs of the 3 studies were similar and baseline demographic and disease characteristics of the study populations were similar. Pooled efficacy analysis results were consistent with the individual study results, showing non-inferiority of pooled QUAD group versus pooled ATR group, of pooled QUAD group versus pooled ATV/r + TVD group, and of pooled QUAD versus pooled active control group.

The main issues with regards to the efficacy results were the emergent study drug resistance results, and the rationale for the doses of the EVG of QUAD. With regards to emergent study drug resistance, in Study GS-US-236-0102, although the proportions of patients who developed emergent RT-R mutations were similar between the QUAD and ATR groups, seven out of the 8 subjects in the QUAD group who were tested for study drug resistance developed INSTI-R mutations, compared with none in the ATR group. In Study GS-US-236-0103, out of 12 subjects tested in the QUAD group, 4 subjects developed RT-R mutations, and 4 subjects developed INSTI-R mutations, while in the ATV/r+TVD group, out of the 8 subjects tested, none developed emergent resistance to a study drug. Although the number of patients analysed for emergent study drug resistance were too small for meaningful statistical analysis, the above results suggest that development of INSTI-R mutations may be an issue with the use of QUAD, compared to the active controls. This is, however, within expectations, as neither ATR nor ATV/r+TVD contain an INSTI, whereas the EVG component of QUAD is an INSTI. This also needs to be taken in the context that the calculated percentage of patients in the QUAD group with emergent INSTI-R mutations was low: 2.0% in Study GS-US-236-0102, and 1.1% in Study GS-US-236-0103[27].

[27] assuming that subjects who did not show virologic failure, and hence not tested for study drug resistance, did not have the resistance mutations

With regards to the rationale for the doses of the EVG of QUAD, in describing the justification for choice of dose of EVG, the sponsor has stated that in study GS-US-183-0105, RTV-boosted EVG of 125mg dose formulation was used, and that study GS-US-183-0140 showed that the 125 mg dose and the 150 mg dose provided bioequivalent EVG exposures. No rationale was given for the choice of 150mg instead of 125mg of EVG.

8. Clinical safety

8.1. Studies providing evaluable safety data

The principal clinical safety data in this submission were derived from the 2 Phase III studies (GS-US-236-0102 and GS-US-236-0103) and supported by the Phase 2 study, Study GS-US-236-0104.

The sponsor has provided a pooled safety analysis (using pooled safety data up to Week 48 plus the available data up to the respective cut-off dates for Studies GS-US-236-0102 and GS-US-236-0103, and up to Week 60 [i.e. randomised phase] for Study GS-US-236-0104) in the clinical summary of safety data, in addition to individual safety data of the 3 studies in the respective CSRs.

It is considered by the evaluator that a pooled analysis is appropriate as the study designs of the 3 studies were similar apart from the active control used. In this evaluation, the pooled safety analysis as well as the safety data in the open-label phase of Study GS-US-236-0104 will be presented.

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies (GS-US-236-0102 and GS-US-236-0103), the following safety data were collected:

- General adverse events (AEs)

All AEs that occurred from study screening visit onwards and throughout the duration of the study, including the follow-up period, were recorded as AEs. AEs were elicited by spontaneous reporting. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA).

- AEs of particular interest

Renal and bone safety parameters were considered to be 'of interest' in the 2 Phase III studies. Renal parameters were prespecified to be of interest as the prescribing information of Viread (TDF), has identified renal impairment as potentially associated with TDF. Bone parameters were prespecified to be of interest because bone toxicity has been associated with TDF administration.

- Laboratory tests, as listed below, were performed at all scheduled study visits.
  - Urinalysis
  - Urine pregnancy test (for females of childbearing potential only)
  - Urine for additional phosphate and creatinine testing
  - Chemistry profile: Liver function test (alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyltransferase [GGT], total bilirubin, direct and indirect bilirubin, total protein, albumin, lactate dehydrogenase [LDH], creatine phosphokinase [CPK]), renal function test (bicarbonate, urea, calcium, chloride, creatinine, phosphorus, fractional excretion of phosphate, cystatin C, magnesium, potassium, sodium), uric acid, and amylase

- Metabolic assessments: fasting glucose and lipid panel
- Estimated GFR according to the Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and Cystine C (CysC) clearance methods
- Hematology profile: complete blood count (CBC)

8.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.1.3. Dose-response and non-pivotal efficacy studies

Study GS-US-236-0104 provided safety data on use of QUAD beyond 48 weeks.

8.1.4. Other studies evaluable for safety only

8.1.4.1. Clinical Pharmacology Studies

Studies GS-US-183-0128 and GS-US-216-0107 were thorough QT/QTc studies of EVG and COBI, respectively. Study GS-US-216-0121 evaluated the effect of COBI on estimates of renal function. The safety results of these studies have been described in earlier sections in this report.

8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.3. Patient exposure

Exposure in the pooled safety analysis set in Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104 is summarised in Table 14 below. Overall, 749 subjects received QUAD in these studies, 375 subjects received ATR, and 355 subjects received ATV/r+TVD. The median duration of exposure to study drug was 48.4 weeks in the QUAD group, 58.9 weeks in the ATR group, and 48.1 weeks in the ATV/r+TVD group.

Table 14. GS-US-236-0102, 0103, 0104: Duration of Exposure to Study Drug (Safety Analysis Set)

	QUAD 236-0102, 0103, 0104 (N=749)	ATR 236-0102, 0104 (N=375)	ATV/r + TVD 236-0103 (N=355)
Total Exposure to Study Drug (Weeks)[a, b]			
N	749	375	355
Mean (SD)	50.3 (12.12)	50.1 (15.77)	46.8 (13.21)
Median	48.4	58.9	48.1
Q1, Q3	47.9, 60.0	48.1, 60.1	46.1, 51.0
Min, Max	0.1, 64.6	0.1, 69.0	0.6, 62.6
Total Exposure to Study Drug			
> 4 Weeks (28 days)	737 (98.4%)	359 (95.7%)	342 (96.3%)
> 8 Weeks (56 days)	731 (97.6%)	357 (95.2%)	339 (95.5%)
> 12 Weeks (84 days)	727 (97.1%)	347 (92.5%)	334 (94.1%)
> 16 Weeks (112 days)	715 (95.5%)	342 (91.2%)	332 (93.5%)
> 24 Weeks (168 days)	707 (94.4%)	336 (89.6%)	328 (92.4%)
> 32 Weeks (224 days)	697 (93.1%)	334 (89.1%)	323 (91.0%)
> 40 Weeks (280 days)	688 (91.9%)	331 (88.3%)	316 (89.0%)
> 48 Weeks (336 days)	509 (68.0%)	283 (75.5%)	185 (52.1%)
> 60 Weeks (420 days)	164 (21.9%)	111 (29.6%)	52 (14.6%)

a Duration of exposure to study drug was the number of weeks between the first dose and the last dose of study drug.

b If the last dose date was completely missing (eg, lost to follow-up) or a subject was still on study drug, the maximum of study drug start and end dates, clinic and laboratory visit dates excluding the 30-day follow-up visit date was used to impute the last dose date.

The safety analysis set in the open-label phase of Study GS-US-236-0104 (called the "All QUAD" group) consisted of 62 subjects (48 subjects in the QUAD/QUAD group and 14 subjects in the ATR/QUAD group). The median exposure was 96.1 weeks in the QUAD/QUAD group and 37.2 weeks in the ATR/QUAD group.

Comments: Overall, the amount of exposure to QUAD is adequate to evaluate the safety profile of the drug. In the 2 Phase III trials, 509 HIV1-infected patients were exposed to QUAD for at least 48 weeks. Longer-term safety data was derived from the open-label phase of the Phase II study, where subjects were exposed to QUAD beyond 48 weeks, but the sample size was small.

8.4. Adverse Events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pooled safety analysis, Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

A summary of AEs reported in the pooled safety analysis set in Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104 is presented in Table 15.

Table 15. GS-US-236-0102, 0103, 0104: Overall Summary of Adverse Events

	QUAD 236-0102, 0103, 0104 (N=749)	ATR 236-0102, 0104 (N=375)	ATV/r + TVD 236-0103 (N=355)
Subjects Experiencing Any Treatment-Emergent Adverse Event	694 (92.7%)	355 (94.7%)	333 (93.8%)
Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event	414 (55.3%)	206 (54.9%)	220 (62.0%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event	92 (12.3%)	41 (10.9%)	48 (13.5%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event	343 (45.8%)	250 (66.7%)	203 (57.2%)
Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event	97 (13.0%)	98 (26.1%)	60 (16.9%)
Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event	20 (2.7%)	15 (4.0%)	13 (3.7%)
Subjects Experiencing Any Treatment-Emergent Serious Adverse Event	69 (9.2%)	25 (6.7%)	31 (8.7%)
Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event	5 (0.7%)	7 (1.9%)	2 (0.6%)
Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	26 (3.5%)	19 (5.1%)	18 (5.1%)
Subjects Who Had Treatment-Emergent Death[a]	1 (0.1%)	2 (0.5%)	3 (0.8%)

a Treatment-emergent death refers to the death occurred between the first dose date and the last dose date plus 30 days (inclusive).

Overall, the percentage of subjects experiencing any treatment-emergent AEs was similar among the treatment groups (92.7% [694/ 749], 94.7% [355/ 375], and 93.8% [333/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively). A lower percentage of subjects in the QUAD group compared with the ATR or ATV/r + TVD groups experienced any study drug-related treatment-emergent AE (45.8% [343/ 749], 66.7% [250/ 375], and 57.7% [203/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively), but the difference was not tested for statistical significance. A higher percentage of subjects in the QUAD group compared with the ATR or ATV/r + TVD groups experienced any treatment-emergent serious adverse events (SAEs) (9.2% [69/ 749], 6.7% [25/ 375], and 8.7% [31/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively), but the difference was not tested for statistical significance. The percentage of subjects experiencing any study drug-related SAEs was comparable among the treatment groups (0.7% [5/ 749], 1.9% [7/ 375], and 0.6% [2/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively)

Data on treatment-emergent AEs reported for at least 5% of subjects in any treatment group is provided. The most frequently reported AEs in the QUAD group were diarrhoea (22.7%, 170 subjects), nausea (19.5%, 146 subjects), and headache (14.6%, 109 subjects); in the ATR group were abnormal dreams (27.5%, 103 subjects), dizziness (23.7%, 89 subjects), and diarrhoea (18.7%, 70 subjects); and in the ATV/r+TVD group were diarrhoea (27.3%, 97 subjects), nausea (19.4%, 69 subjects), and upper respiratory tract infection (16.3%, 58 subjects). AEs with a

higher percentage of subjects in the QUAD group than in the ATR group and ATV/r+TVD groups were in the System Organ Classification (SOC) of Musculoskeletal and Connective Tissue

Disorders (21.4% [160/ 749], 16.3% [61/ 375], and 15.5% [55/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively), and in the AE Preferred Term (PT) of Back Pain (5.6% [42/ 749], 3.7% [14/ 375], and 3.7% [13/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively).

Data on treatment-emergent Grade 3 (severe) or 4 (life-threatening) AEs reported for at least 1% of subjects in any treatment group is provided. Grade 3 and 4 AEs were reported for similar percentages of subjects in each treatment group (12.3% [92/ 749], 10.9% [41/ 375], and 13.5% [48/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively). Grade 3 and 4 AEs reported for > 1% of subjects in any treatment group were diarrhoea (0.4% [3 subjects], 0 subjects, and 1.1% [4 subjects] in the QUAD, ATR and ATV/r+TVD groups, respectively) and depression (0.7% [5 subjects], 1.6% [6 subjects], and 0.6% [2 subjects] in the QUAD, ATR and ATV/r+TVD groups, respectively).

8.4.1.2. All QUAD group

Any treatment-emergent AE was reported for 91.9% of subjects (57 subjects). AEs considered related to study drug by the investigator were reported for 41.9% of subjects (26 subjects). Any SAE was reported for 8.1% of subjects (5 subjects). No SAE was considered related to study drug by the investigator. Any Grade 3 or 4 AE was reported for 9.7% of subjects (6 subjects). Grade 3 or 4 AEs considered related to study drug were reported for 1 subject (1.6%). Two subjects (3.2%) discontinued study drug due to an AE.

The most frequently reported AEs were diarrhoea (24.2%, 15 subjects), followed by bronchitis, upper respiratory tract infection, and headache (each reported for 17.7%, 11 subjects). With regards to Grade 3 or 4 AEs in the All QUAD group, in addition to the events in the randomised phase, Grade 3 or 4 AEs reported in the All QUAD group were appendicitis (1 subject in the QUAD/QUAD group), hepatitis C (1 subject in the ATR/QUAD group), hepatic steatosis and hepatosplenomegaly (both in 1 subject in the QUAD/QUAD group), and peroneal nerve palsy (1 subject in the QUAD/QUAD group) The AEs of hepatic steatosis and hepatosplenomegaly were considered related to study drug by the investigator and resulted in discontinuation of study drug.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pooled safety analysis, Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

Treatment-emergent AEs considered by the investigator to be related to study drug reported for at least 1% of subjects in any treatment group is summarised in Table 16.

Table 16. GS-US-236-0102, 0103, 0104: Treatment-Emergent Adverse Events Considered Related to Study Drug Reported for at Least 1% of Subjects in Any Treatment Group (Safety Analysis Set)

	QUAD 236-0102, 0103, 0104 (N=749)	ATR 236-0102, 0104 (N=375)	ATV/r + TVD 236-0103 (N=355)
Number of Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event[a, b, c]	343 (45.8%)	250 (66.7%)	203 (57.2%)
Eye Disorders	5 (0.7%)	7 (1.9%)	51 (14.4%)
Ocular Icterus	2 (0.3%)	0	47 (13.2%)
Gastrointestinal Disorders	205 (27.4%)	90 (24.0%)	111 (31.3%)
Abdominal Distension	8 (1.1%)	3 (0.8%)	8 (2.3%)
Abdominal Pain	7 (0.9%)	4 (1.1%)	5 (1.4%)
Constipation	8 (1.1%)	5 (1.3%)	3 (0.8%)
Diarrhoea	86 (11.5%)	40 (10.7%)	57 (16.1%)
Dry Mouth	5 (0.7%)	6 (1.6%)	3 (0.8%)
Dyspepsia	10 (1.3%)	3 (0.8%)	6 (1.7%)
Flatulence	15 (2.0%)	1 (0.3%)	26 (7.3%)
Gastrooesophageal Reflux Disease	3 (0.4%)	3 (0.8%)	4 (1.1%)
Nausea	113 (15.1%)	31 (8.3%)	47 (13.2%)
Vomiting	14 (1.9%)	5 (1.3%)	9 (2.5%)
General Disorders and Administration Site Conditions	56 (7.5%)	45 (12.0%)	32 (9.0%)
Asthenia	4 (0.5%)	1 (0.3%)	5 (1.4%)
Fatigue	37 (4.9%)	29 (7.7%)	20 (5.6%)
Feeling Abnormal	4 (0.5%)	4 (1.1%)	2 (0.6%)
Feeling Drunk	0	4 (1.1%)	0
Hepatobiliary Disorders	1 (0.1%)	2 (0.5%)	34 (9.6%)
Jaundice	0	1 (0.3%)	30 (8.5%)
Metabolism and Nutrition Disorders	21 (2.8%)	14 (3.7%)	16 (4.5%)
Decreased Appetite	11 (1.5%)	7 (1.9%)	8 (2.3%)
Nervous System Disorders	91 (12.1%)	111 (29.6%)	43 (12.1%)
Dizziness	21 (2.8%)	75 (20.0%)	15 (4.2%)
Headache	53 (7.1%)	15 (4.0%)	22 (6.2%)
Somnolence	9 (1.2%)	26 (6.9%)	4 (1.1%)
Psychiatric Disorders	105 (14.0%)	136 (36.3%)	29 (8.2%)
Abnormal Dreams	65 (8.7%)	98 (26.1%)	12 (3.4%)
Anxiety	4 (0.5%)	8 (2.1%)	1 (0.3%)
Depression	3 (0.4%)	13 (3.5%)	3 (0.8%)
Disorientation	1 (0.1%)	4 (1.1%)	0
Insomnia	22 (2.9%)	29 (7.7%)	5 (1.4%)
Nightmare	4 (0.5%)	6 (1.6%)	2 (0.6%)
Sleep Disorder	5 (0.7%)	4 (1.1%)	3 (0.8%)
Skin and Subcutaneous Tissue Disorders	39 (5.2%)	61 (16.3%)	33 (9.3%)
Acne	0	0	4 (1.1%)
Night Sweats	5 (0.7%)	2 (0.5%)	6 (1.7%)
Pruritus	5 (0.7%)	11 (2.9%)	2 (0.6%)
Rash	14 (1.9%)	28 (7.5%)	10 (2.8%)
Rash Generalised	0	4 (1.1%)	1 (0.3%)
Rash Maculo-Papular	2 (0.3%)	5 (1.3%)	3 (0.8%)
Vascular Disorders	2 (0.3%)	4 (1.1%)	4 (1.1%)
Hot Flush	1 (0.1%)	4 (1.1%)	2 (0.6%)

a Adverse events were coded using MedDRA 14.0.

b System organ class (SOC) and high level term (within each SOC) were presented alphabetically, and preferred term was presented by decreasing order based on the total frequencies.

c Multiple AEs were counted only once per subject for each system organ class, high level term and preferred term, respectively.

A lower percentage of subjects in the QUAD group (45.8%; 343/749) compared with the ATR (66.7%; 250/375) or ATV/r+TVD (57.2%; 203/355) groups reported any AE considered to be

related to study drug by the investigator. The most frequently reported AEs considered related to study drug by the investigator in the QUAD group were nausea (15.1%, 113 subjects), diarrhoea (11.5%, 86 subjects), and abnormal dreams (8.7%, 65 subjects); in the ATR group were abnormal dreams (26.1%, 98 subjects), dizziness (20.0%, 75 subjects), and diarrhoea (10.7%, 40 subjects); and in the ATV/r+TVD group were diarrhoea (16.1%, 57 subjects), ocular icterus (13.2%, 47 subjects), and nausea (13.2%, 47 subjects).

Treatment-related AEs with a higher incidence in the QUAD group compared to the ATR and ATV/r+TVD groups were nausea (15.1% [113/ 749], 8.3% [31/ 375], and 13.2% [47/ 355], in the pooled QUAD, ATR, and ATV/r + TVD groups, respectively), and headache (7.1% [53/ 749], 4.0% [15/ 375], and 6.2% [22/ 355], in the pooled QUAD, ATR, and ATV/r + TVD groups, respectively).

8.4.2.1.1. All QUAD group

In the All QUAD group, AEs considered related to study drug by the investigator were reported for 41.9% of subjects (26 subjects) The most frequently reported AEs considered related to study drug by the investigator were diarrhoea (8.1%, 5 subjects), fatigue (6.5%, 4 subjects) and abnormal dreams (6.5%, 4 subjects).

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pooled safety analysis, Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

In the pooled safety analysis, 6 treatment-emergent deaths were reported (1, 2 and 3 subjects in the QUAD, ATR and ATV/r+TVD groups, respectively). The death by suicide for 1 subject in the ATR group was considered related to study drug by the investigator. No other deaths were considered to be related to study drug by the investigator.

A higher percentage of subjects in the pooled QUAD group compared with the pooled ATR and ATV/r+TVD groups experienced any treatment-emergent SAEs (9.2% [69/ 749], 6.7% [25/ 375], and 8.7% [31/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively). No individual SAE was reported in more than 1% of subjects in any treatment group. The difference observed between the QUAD and ATR and ATV/r + TVD groups was mainly due to differential incidences of SAEs in the SOC of Infections and Infestations (occurring in 4.7% [35/ 749], 1.9% [7/ 375], and 3.7% [13/ 355] of subjects in the QUAD, ATR, and ATV/r + TVD groups, respectively). None of the SAEs in this SOC in the QUAD group were considered by the investigator to be related to study drug.

The overall incidence of SAEs considered related to study drug by the investigator was similar among the 3 treatment groups (0.7% [5/ 749], 1.9% [7/ 375], and 0.6% [2/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively). No individual SAE considered related to study drug by the investigator was reported for more than 1 subject in any treatment group. The SAEs considered related to study drug by the investigator in the QUAD group were liver injury, drug hypersensitivity, Burkitt's lymphoma, headache, and depression; in the ATR group were abdominal pain, pyrexia, headache, grand mal convulsion, syncope, completed suicide, suicide attempt, dyspnea, exertional dyspnea, and maculopapular rash; and in the ATV/r+TVD group were impetigo and drug eruption.

8.4.3.2. All QUAD group

No subjects died in the All QUAD group. SAEs were reported for 5 subjects (8.1%). SAEs reported in the All QUAD group were appendicitis (1 subject in the QUAD/QUAD group), peroneal nerve palsy (1 subject in the QUAD/QUAD group), and hepatitis C (1 subject in the ATR/QUAD group). No SAEs were considered to be related to study drug by the investigator.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pooled safety analysis, Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

In the pooled safety analysis set, the percentage of subjects who discontinued due to an AE was comparable between treatment groups (3.5% [26/ 749], 5.1% [19/ 375], and 5.1% [18/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively). No individual AE that resulted in study drug discontinuation was reported in more than 1% of subjects in the QUAD treatment group.

8.4.4.1.1. All QUAD group

In the All QUAD group in Study GS-US-236-0104, AEs that resulted in study drug discontinuation were reported for 2 subjects (3.2%). The AEs of hepatic steatosis and hepatosplenomegaly for 1 subject in the QUAD/QUAD group, and of abdominal distension for the other subject in the ATR/QUAD group were considered to be related to study drug by the investigator.

Comments: On AEs: Overall, there were no significant concerns of note in the incidences of AEs with administration of QUAD. In the pooled safety analysis, the percentage of subjects experiencing any treatment-emergent AEs was similar between QUAD and each of the 2 active controls, ATR and ATV/r+TVD, but there was a lower percentage of subjects in the QUAD group compared with the ATR or ATV/r+TVD group who reported any treatment-emergent AE considered to be related to study drug by the investigator. A higher percentage of subjects in the pooled QUAD group compared with the pooled ATR and ATV/r+TVD groups experienced any treatment-emergent SAEs, but the overall incidence of SAEs considered related to study drug by the investigator was similar among the 3 treatment groups. The number of treatment-emergent deaths was smaller in the pooled QUAD group than in the ATR or ATV/r+TVD group. The percentage of subjects who discontinued due to an AE was comparable among the 3 treatment groups.

The most frequently reported treatment emergent AEs in the pooled QUAD group were diarrhoea (22.7%, 18.7% and 27.3% in the pooled QUAD, ATR and ATV/r + TVD groups, respectively), nausea (19.5%, . 13.3% and 19.4%, respectively), and headache (14.6%, 10.1% and 12.4%, respectively), while the most frequently reported study drug- related AEs in the QUAD group were nausea (15.1%, 8.3% and 13.2%, respectively), diarrhoea (11.5%, 10.7% and 16.1%, respectively), and abnormal dreams (8.7%, 26.1% and 3.4%, respectively).

Results in the All QUAD group showed that in patients who continued on, or were switched to QUAD, the incidences of AEs remained stable, as presented in Table 17 below:

Table 17. Incidences of AEs

	Pooled QUAD group*	All QUAD group**
Any treatment-emergent AE	92.7%	91.9%
Any study drug-related treatment-emergent AE	45.8%	41.9%
Any SAE	9.2%	8.1%
Any study drug-related SAE	0.7%	0%

	Pooled QUAD group*	All QUAD group**
Any Grade 3 or 4 AE	12.3%	9.7%
Any study drug-related Grade 3 or 4 AE	2.7%	1.6%
Discontinuation of study drug due to an AE	3.5%	3.2%

** pooled safety data from Studies GS-US-236-0102, GS-US-236-0103, and randomised phase of GS-US-236-0104*
*** safety data from open-label phase of Study GS-US-236-0104*

The most-frequently reported AE in the All QUAD group was diarrhoea (24.2% of subjects), and this is consistent with the results in the pooled QUAD group, where the most-frequently reported AE was also diarrhoea, occurring in 22.7% of subjects. The most frequently reported study drug-related AEs in the All QUAD group were diarrhoea (8.1%, 5 subjects), fatigue (6.5%, 4 subjects) and abnormal dreams (6.5%, 4 subjects). This is consistent with the results in the pooled QUAD group, where the most-frequently reported study drug-related AEs were nausea (15.1%), diarrhoea (11.5%) and abnormal dreams (8.7%). Study drug-related AE of fatigue occurred in 4.9% of subjects in the pooled QUAD group.

8.4.5. Adverse events of interest

Renal events were evaluated as prespecified AEs[28] of interest because renal toxicity has been associated with tenofovir (TFV) or TDF administration, and because COBI has been shown to increase serum creatinine by inhibiting proximal tubular secretion of creatinine, leading to a decrease in estimated GFR but not actual GFR (aGFR). Renal events were not considered AEs of interest for EVG or FTC. Bone fracture events were also evaluated as prespecified AEs of interest because bone toxicity has been associated with TFV or TDF administration. Bone fractures were not considered AEs of interest for EVG, COBI, or FTC.

8.4.5.1. Pooled safety analysis, Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

In the pooled safety analysis set, 6 subjects reported a renal AE of interest (5 subjects [0.7%] in QUAD group, 1 subject [0.3%] in ATR group and 0 subjects in ATV/r+TVD group; p = 0.67 for comparison of QUAD versus ATR, and p = 0.18 for comparison of QUAD versus ATV/r+TVD). All 6 of the renal AEs of interest were reported in Study GS-US-236-0102.

The most frequently reported renal AE was renal failure, which occurred in 4 of the 5 subjects in the QUAD group and in 1 subject in the ATR group. No subject required dialysis or other forms of renal replacement therapy during the study. Two out of these 4 subjects with renal failure had discontinuation of study drug due to the renal AE. An AE of Fanconi syndrome (Grade 3) was reported for one subject in the QUAD group. This AE led to discontinuation of study drug. The sponsor has stated that the AE improved by laboratory assessment following discontinuation of study drug, but was reported to be ongoing at the time of the last study visit.

With regards to renal events leading to discontinuation of study drug, in Study GS-US-236-0102, five subjects (all in the QUAD group) discontinued study drug due to renal AEs. Three of these subjects had renal AEs of interest as described in the preceding paragraph (2 for renal failure, and 1 for Fanconi's syndrome), and the other 2 subjects discontinued study drug for AEs of 'blood creatinine increased'. Serum creatinine increases improved after discontinuation of study drug. In Study GS-US-236-0103, 2 subjects, 1 each in the QUAD and ATV/r+TVD groups,

[28] A prespecified AE search was conducted using the following MedDRA preferred terms: Fanconi syndrome, Fanconi syndrome acquired, renal failure, acute renal failure, and renal tubular disorder.

discontinued study drug due to renal AEs. The subject in the QUAD group discontinued study medication for an AE of "mild blood creatinine increased," and the subject in the ATV/r+TVD group discontinued study medication for nephrotoxicity. No subjects discontinued study drug due to renal AEs in Study GS-US-236-0104.

The sponsor has provided summary details of the 12 subjects who experienced a renal AE of interest, discontinued study drug due to renal AEs, or had notable renal laboratory abnormalities.

In the pooled safety analysis, bone fractures were reported for similar percentages of subjects in each treatment group (10 subjects [1.3%] in QUAD group, 6 subject [1.6%] in ATR group and 6 subjects [1.7%] in ATV/r+TVD group; p = 0.79 for comparison of QUAD versus ATR, and p = 0.60 for comparison of QUAD versus ATV/r+TVD). The majority of the reported fractures occurred due to traumatic injury. Non-traumatic fractures were reported for 1 subject in each group in Study GS-US-236-0103. The subject in QUAD group had a history of vitamin D deficiency and had a foot fracture diagnosed by radioisotope bone scan on Day 239, while the subject in the ATV/r+TVD group had thoracic vertebral fracture diagnosed by dual-energy x-ray absorptiometry (DEXA) before receiving study drug on Day 1.

8.4.5.2. All QUAD group

No renal AEs of interest or fractures were reported in the All QUAD group in Study GS-US-236-0104.

Comments

On AEs of interest: The results suggested that renal AE could be a potential concern with administration of QUAD. The incidence of renal AE of interest was higher in the pooled QUAD group (5 subjects, 0.7%) than in the ATR (1 subject 0.3%) or ATV/r+TVD group (0 subject), the majority of which were renal failure (4 out of the 5 subjects in the QUAD group). The percentage of patients who discontinued study drug due to renal AEs was also higher in the pooled QUAD group (6 subjects, 0.8%) compared to the ATR (0 subject) or ATV/r+TVD group (1 subject, 0.3%).

However, the renal AEs and the abnormal renal parameters appeared to be reversible after drug discontinuation, and none of the 4 subjects with renal failure in the QUAD group required dialysis or other forms of renal replacement therapy during the study. Two out of these 4 subjects with renal failure had discontinuation of study drug due to the renal AE, and in both subjects, renal laboratory changes normalised after discontinuation of QUAD. Among the 2 subjects with AE of renal failure who continued on the study drug, 1 subject had serum creatinine improvement subsequently, although the AE of renal failure was reported to be ongoing at the time of the last study visit. The other subject had an AE of renal failure reported on Day 57, but had no confirmed renal laboratory abnormalities at any study visit, and the AE of renal failure was reported as resolved on Day 59.

In the remaining subject out of the 5 subjects with renal AEs in the pooled QUAD group, the renal AE reported was that of Grade 3 Fanconi syndrome (renal tubular injury with hypophosphatemia). This AE led to discontinuation of study drug, following which there was improvement of the AE by laboratory assessment, although the AE was reported to be ongoing at the time of the last study visit.

Out of the 6 subjects in the pooled QUAD group who had discontinuation of study drug due to renal AEs, 1 subject had discontinuation of study drug for Fanconi syndrome and 2 subjects for renal failure, as described in the preceding paragraphs, and another 3 subjects for increased serum creatinine. In all of these 3 subjects, renal laboratory changes improved after discontinuation of QUAD,

although in 2 of the subjects, the AE of blood creatinine increased was reported to be ongoing at the time of the last study visit.

In the pooled safety analysis, bone fractures were reported for similar percentages of subjects in each treatment group. No renal AEs of interest and no fractures were reported in the All QUAD group, suggesting that the incidence of renal AEs of potential concern in the QUAD group was not increased with prolonged use.

8.5. Laboratory tests

In the pooled safety analysis, the majority of subjects had at least 1 treatment-emergent laboratory abnormality reported (99.5% [745/ 749], 99.2% [372/ 375], and 99.2% [352/ 355], in the QUAD, ATR, and ATV/r + TVD groups, respectively). The majority of the abnormalities reported were Grade 1 or Grade 2 in severity (72.9% [543/ 745], 68.3% [254/ 372], and 31.0% [109/ 352], in the QUAD, ATR, and ATV/r + TVD groups, respectively). Treatment-emergent Grade 3 or Grade 4 abnormalities were reported less frequently in the QUAD group than in the ATR group or the

ATV/r+TVD group, with 12.1% of subjects in the QUAD group with Grade 3 abnormalities, compared with 14.0% in the ATR group and 52.0% in the ATV/r+TVD group. The percentage of subjects who had Grade 4 laboratory abnormalities was 3.9 % in the QUAD group, compared with 9.7% in the ATR group and 15.9% in the ATV/r+TVD group.

The most frequently reported Grade 3 or 4 abnormalities in the QUAD group were abnormalities in lipase (8.1% Grade 3, 3.2% Grade 4, n = 62[29]), creatine kinase (3.5% Grade 3, 1.7% Grade 4, n = 745), and hematuria (2.8% Grade 3, n = 745). In the ATR group, the corresponding incidences were: abnormalities in lipase (13.9% Grade 3, 2.8% Grade 4, n = 36), creatine kinase (4.0% Grade 3, 6.7% Grade 4, n = 372), and hematuria (1.3% Grade 3, n = 372). In the ATV/r+TVD group, the corresponding incidences were: abnormalities in lipase (18.2% Grade 3, 3.0% Grade 4, n = 33), creatine kinase (2.8% Grade 3, 4.5% Grade 4, n = 352) and hematuria (2.3% Grade 3, n = 352).

In the All QUAD group, the majority of subjects had at least 1 treatment-emergent laboratory abnormality reported (96.8%; 60/62). The majority of the abnormalities reported were Grade 1 or Grade 2 in severity (72.6%; 45/62). Treatment-emergent Grade 3 or 4 abnormalities were reported for 16.7% of subjects (10 out of 60 subjects, Grade 3 for 7 subjects and Grade 4 for 3 subjects). The most frequently reported Grade 3 or 4 abnormality was increased creatine kinase (10.0%; 6/60).

8.5.1. Liver function

8.5.1.1. Pooled safety analysis, Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

A summary of liver enzyme abnormalities in the pooled safety analysis is presented. There were no significant liver function abnormalities of concern in the pooled QUAD group compared to the other pooled treatment groups.

8.5.1.1.1. All QUAD group

There were no significant liver function abnormalities of concern in the All QUAD group.

[29] The denominator used to calculate the percentages was n, which was the number of subjects in the safety analysis set with at least one postbaseline laboratory value for each test.

8.5.2. Kidney function

8.5.2.1. Pooled safety analysis, Studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104

In the pooled safety analysis, increases in median values for serum creatinine in the QUAD group were noted at about Week 2 (median change from baseline at Week 2 was 0.09 mg/dL). At Week 24, median change of serum creatinine from baseline was 0.13 mg/dL, and remained stable through Week 48 (median change from baseline at Week 48 was 0.13 mg/dL). A similar pattern of change in serum creatinine was seen in the ATV/r+TVD group but the increases from baseline were smaller than those seen in the QUAD group (median change of serum creatinine from baseline at Week 2 was 0.05 mg/dL, and that at Week 48 was 0.08 mg/dL). There were no notable changes from baseline in median values for serum creatinine in the ATR group.

Glomerular Filtration Rate (GFR) was estimated using 3 methods: Cockcroft-Gault (CG) method, Modification of Diet in Renal Disease (MDRD) method and the Cystatin C-derived (Cys) method.

In the pooled safety analysis, baseline median estimated GFR (eGFR) calculated using the CG method ($eGFR_{CG}$) were comparable among the treatment groups (114.2 ml/min/1.73m^2, 114.4 ml/min/1.73m^2 and 114.7 ml/min/1.73m^{2}in the QUAD, ATR and ATV/r+TVD groups, respectively). There was a decrease in median $eGFR_{CG}$ in the QUAD group, with a median change from baseline at Week 48 of -13.5 ml/min/1.73m^2. The median change from baseline of $eGFR_{CG}$ at Week 48 was −3.0 ml/min/1.73m^2 and −9.5 ml/min/1.73m^2 in the ATR and ATV/r+TVD groups, respectively.

Estimated GFR calculated using the MDRD method ($eGFR_{MDRD}$) were consistent with those observed for $eGFR_{CG}$. However, results for estimated GFR calculated using the Cystatin-C method (cysGFR) showed increases from baseline in all treatment groups. Baseline median cysGFR were 98.4, 96.4, and 93.2 ml/min/1.73m^2 in the QUAD, ATR and ATV/r+TVD groups, respectively. Median changes from baseline at Week 48 were 8.5, 15.5, and 10.2 mL/min/1.73m^2 in the QUAD, ATR and ATV/r+TVD groups, respectively.

In the pooled safety analysis treatment-emergent proteinuria was observed for a higher percentage of subjects in the QUAD group compared with the ATR or ATV/r+TVD groups

(38.1% [284/745], 28.8% [107/372], and 24.1% [85/352] in the QUAD, ATR and ATV/r+TVD groups, respectively). Proteinuria was predominantly Grade 1 in severity. Grade 3 proteinuria was reported in 2 subjects (0.3%) in the QUAD group, and 1 subject (0.3%) in the ATV/r+TVD group. No subject in the ATR group had Grade 3 proteinuria. No subject in any of the treatment groups had Grade 4 proteinuria.

The sponsor had performed additional exploratory analyses to assess baseline and post-baseline urine protein relative to actual values reported (negative, trace, +1, +2, +3, +4). Among subjects with no protein in the urine at baseline, similar percentages of subjects in each treatment group had confirmed proteinuria (trace or worse) during study treatment (38.6% [186/482], 42.9% [109/254], and 36.3% [85/234] in the QUAD, ATR and ATV/r+TVD groups, respectively).

Median values for serum phosphorus were within normal ranges throughout studies GS-US-236-0102, GS-US-236-0103, and GS-US-236-0104. In Study GS-US-236-0102, hypophosphatemia of any grade was observed in 8.3% (29 subjects) of subjects in the QUAD group compared with 4.5% (16 subjects) of subjects in the ATR group. Of these subjects, 1 subject in the QUAD had Grade 3 hypophosphatemia. The subject continued to receive study drug and repeat testing 3 days after the reported Grade 3 abnormality showed a return to normal levels. In Study GS-US-236-0103 hypophosphatemia of any grade was observed in 4.8% (n=17) of subjects in the QUAD group compared with 6.3% (n=22) of subjects in the ATV/r+TVD group. No subjects in the QUAD group, and 2 subjects in the ATV/r+TVD group, had Grade 3 hypophosphatemia. In the randomised phase of Study GS-US-236-0104, 1 subject in the

QUAD group had Grade 2 hypophosphatemia reported and 1 subject in the ATR group had Grade 1 hypophosphatemia reported. None of these serum phosphorus abnormalities were reported as AEs.

In Study GS-US-236-0102, there were small increases in median values for urine fractional excretion of phosphate[30] in both the QUAD and ATR groups, but more in the QUAD than ATR group. The baseline median urine fractional excretion of phosphate was comparable in both treatment groups, 10.0% and 9.6% in the QUAD and ATR groups, respectively. In the QUAD group, the median change from baseline was 2.3% at Week 2 and was then stable within a range of 1.0% to 2.3% through Week 48. In the ATR group, the median change from baseline was 0.8% at Week 2 and was then stable within a range of 0.5% to 1.0% through Week 48. The maximum median urine fractional excretion of phosphate in the QUAD group was 12.4% (at Week 48) and 10.8% in the ATR group (at Week 2).

Similar results were seen in Study GS-US-236-0103 between the QUAD and ATV/r+TVD groups. The baseline median urine fractional excretion of phosphate was comparable between the 2 treatment groups, 9.5% and 10.1% in the QUAD and ATV/r+TVD groups, respectively. In the QUAD group, the median change from baseline was 2.4% at Week 2 and was then stable within a range of 2.3% to 2.7% through Week 48. In the ATV/r+TVD group, the median change from baseline was 1.9% at Week 2 and was then stable within a range of 1.3% to 1.7% through Week 48. The maximum median urine fractional excretion of phosphate in the QUAD group was 12.6% (at Week 4) and 12.2% in the ATV/r+TVD group (at Week 2).

Urine phosphate was not assessed in Study GS-US-236-0104.

8.5.2.1.1. All QUAD group

In the All QUAD group in Study GS-US-236-0104, there was a small increase in median values for serum creatinine, consistent with that seen in the randomised phase, and consistent in both the QUAD/QUAD and ATR/QUAD groups. At Week 2 (of open-label phase), median change of serum creatinine from open-label baseline in the All QUAD group was 0.08 mg/dL, reaching 0.15 mg/dL at Week 16, and remaining at around this value through to Week 72.

In the All QUAD group in Study GS-US-236-0104, there was a decrease in median values for $eGFR_{CG,}$ consistent with that seen in the randomised phase, and consistent in both the QUAD/QUAD and ATR/QUAD groups. Baseline median $eGFR_{CG}$ was 119.4 ml/min/1.73m^2 in the open-label period, and median change from open-label baseline of $eGFR_{CG}$ at Week 2, 24 and 48 were -10.0, -14.6, and -17.6 ml/min/1.73m^2, respectively.

In the All QUAD group in Study GS-US-236-0104, Grade 1 proteinuria was reported for 28.3% (17/60) of subjects and Grade 2 proteinuria was reported for 3.3% (2/60) of subjects. No Grade 3 or 4 proteinuria was reported. In the All QUAD group, 1 subject had Grade 2 hypophosphatemia reported.

Comments On laboratory parameters: The main laboratory abnormalities of concern pertain to renal laboratory parameters. The pooled safety analysis showed greater increases in median values for serum creatinine in the QUAD group compared to the ATR and ATV/r+TVD groups (change from baseline of serum creatinine at Week 48 of 0.13mg/dL in the pooled QUAD group, compared with 0.08mg/dL in the ATV/r+TVD group and no notable change in the ATR group). This was associated with a corresponding greater decrease in median $eGFR_{CG}$ and $eGFR_{MDRD}$ in the pooled QUAD group compared to the ATR and ATV/r+TVD groups (change from baseline of $eGFR_{CG}$ at Week 48 of -13.5 ml/min/1.73m^{2}in the pooled QUAD group, compared with −3.0 ml/min/1.73m^2 and −9.5

[30] Phosphate homeostasis is chiefly regulated at the level of the proximal renal tubule. The fractional excretion of phosphate is often used as an investigation of renal tubular phosphate handling.

ml/min/1.73m^2 in the ATR and ATV/r+TVD groups, respectively). However, results for estimated GFR calculated using the cystatin-C method (cysGFR) showed increases from baseline in all the treatment groups.

The use of cystatin C to measure GFR compared to the use of serum creatinine is still a matter of debate and research[31]. However, the advantage of cystatin C over creatinine is that creatinine can be affected by multiple other factors such as muscle mass, diet, gender and age. In addition, creatinine undergoes both renal glomerular filtration as well as tubular secretion, and some drugs (e.g. cimetidine) have been known to lead to increased measured serum creatinine by inhibiting tubular secretion of creatinine. Cystatin C does not undergo tubular secretion, and is freely filtered by the glomeruli without proximal tubular secretion. Measurements of cysGFR can help evaluate whether the effect of a drug on serum creatinine reflects a true change in GFR (thus suggesting an adverse effect on renal function) or could have an alternative explanation, such as interaction with the tubular secretion of creatinine. The sponsor has stated in this submission that biopharmaceutic studies on the COBI component of QUAD showed that COBI appeared to inhibit proximal tubular secretion of creatinine. The results in the pooled safety analysis, showing increase in serum creatinine and decrease in $eGFR_{CG}$ but not cysGFR in the QUAD group, suggested that the raised serum creatinine levels and reduced $eGFR_{CG}$ could be due to the inhibition of tubular secretion of creatinine by COBI, and not reflecting a nephrotoxic effect of QUAD.

In the assessment of possible nephrotoxic effect via measurements of proteinuria, results in the pooled safety analysis showed that treatment-emergent proteinuria was observed in a higher percentage of subjects in the QUAD group compared with the ATR or ATV/r+TVD groups. However, proteinuria was predominantly Grade 1 in severity and Grade 3 proteinuria was reported in only 2 subjects in the QUAD group and no subject reported grade 4 proteinuria. In addition, among subjects with no proteinuria at baseline, the percentage of subjects who had confirmed proteinuria during study treatment was similar among the treatment groups.

Hypophosphatemia can be a manifestation of proximal renal tubular injury, and study results showed that the percentage of subjects with hypophosphatemia in the QUAD group was higher than that in the ATR group in Study GS-US-236-0102, but lower than that in the ATV/r+TVD group in Study GS-US-236-0103. However most of the hypophosphatemia were of grades 1 or 2, and out of subjects on QUAD in both studies, only 1 subject had Grade 3 hypophosphatemia. None of these serum phosphorus abnormalities were reported as AEs.

Urine fractional excretion of phosphate can also be increased in proximal renal tubular injury, and study results showed that the median increases from baseline of urine fractional excretion of phosphate at Week 48 was greater in the QUAD group compared to those in the ATR group in Study GS-US-236-0102, and those in the ATV/r+TVD group in Study GS-US-236-0103. However, the increases from baseline in the QUAD groups were small, of up to 2.3% through to Week 48 in Study GS-US-236-0102, and 2.7% in Study GS-US-236-0103. In addition, the maximum median urine fractional excretion of phosphate were comparable between the QUAD groups and the respective active controls, and were 12.4% and 12.6% in Study GS-US-236-0102 and Study GS-US-236-0103, respectively.

[31] Stevens LA, et. al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis.* 2008 Mar;51(3):395-406.

There is no definite clinical agreement on what degree of increase from baseline in urine fractional excretion of phosphate is considered abnormal, as renal excretion of phosphate is involved in phosphate homeostasis and varies according to the amount of phosphate that has been ingested and that needs to be excreted in order to maintain homeostasis. Under normal physiologic condition, the urine fractional excretion of phosphate varies between 5% and 20%. The clinical measurement of urine fractional excretion of phosphate is usually utilised in diagnosing the causes of hypophosphatemia, where a value of greater than 5-15% in the presence of hypophosphatemia is indicative of renal phosphate wasting[32].

In the ALL QUAD group, where subjects continued on QUAD, or were switched to QUAD after Week 60, there was further increase in median serum creatinine of up to 0.15mg/dL at Week 16 of open-label phase (Study Week 76), then remaining stable through to Week 72 of open-label phase (Study Week 132). This was associated with a further change from baseline of $eGFR_{CG}$ of up to -17.6 ml/min/1.73m^{2}at Week 48 of open-label phase (Study Week 108). In the All QUAD group, cysGFR was not measured, thus not allowing evaluation of whether the further increase in serum creatinine and further drop in $eGFR_{CG}$ was due to nephrotoxic effect, or the effect of COBI on the proximal tubular secretion of creatinine. There were no significant concerns with regards to incidence of proteinuria or hypophosphatemia in the All QUAD group.

8.5.3. Bone Mineral Density

Bone mineral density (BMD) was assessed in a subset of subjects at selected sites in Study GS-US-236-0103, because bone toxicity has been associated with TFV or TDF administration. DEXA scans were performed to measure percentage changes from baseline in BMD. The mean percentage decreases from baseline in BMD at the lumbar spine and hip was comparable between the QUAD

ATV/r+TVD groups (changes at Week 48 at the lumbar spine was -2.63% in the QUAD group versus -3.33% in the ATV/r+TVD group; changes at Week 48 at the hip was -3.06% in the QUAD group versus -3.88% in the ATV/r+TVD group). The differences between treatment groups were not statistically significant.

8.5.4. Electrocardiograph

There were no notable electrocardiograph abnormalities of concern in studies GS-US-236-0102, GS-US-236-0103 and Study GS-US-236-0104.

8.6. Post-marketing experience

Not Applicable

8.7. Evaluator's overall conclusions on clinical safety

Overall, there were no significant concerns of note in the incidences of AEs with administration of QUAD. The most frequently reported study drug- related AEs in the QUAD group were nausea, diarrhoea and abnormal dreams. Results in the All QUAD group showed that in patients who continued on, or were switched to QUAD, the incidences and types of AEs remained stable.

There were no particular concerns raised with regards to the AE of special interest of bone fractures. Although the incidence of renal AEs of interest as well as the percentage of patients

[32] Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. Am J Med. 2005;118:1094-101.

who discontinued study drug due to renal AEs, were higher in the pooled QUAD group than in the ATR or ATV/r+TVD group, the renal AEs and the abnormal renal parameters appeared to be reversible after drug discontinuation, and none of the 4 subjects with renal failure in the QUAD group required dialysis or other forms of renal replacement therapy during the study. It is also noted that the reporting of the AE of renal failure was based on renal laboratory abnormalities (raised serum creatinine and reduced eGFR), and analysis of renal laboratory parameters showed that although there were greater increases in median values for serum creatinine and a greater decrease in median $eGFR_{CG}$ in the pooled QUAD group compared to the ATR and ATV/r+TVD groups, there were no corresponding decreases from baseline of cysGFR, suggesting that the raised serum creatinine levels and reduced $eGFR_{CG}$ could be due to the inhibition of tubular secretion of creatinine by COBI, and not reflecting an actual nephrotoxic effect of QUAD.

The main concern pertaining to the laboratory safety results is with regards to hypophosphatemia and urine fractional excretion of phosphate. The percentage of subjects with hypophosphatemia was higher in the QUAD group than in the ATR group in Study GS-US-236-0102. However, it was lower in the QUAD group than in the ATV/r+TVD group in Study GS-US-236-0103, and most of the hypophosphatemia were of grades 1 or 2 in severity. The median increases from baseline of urine fractional excretion of phosphate at Week 48 was greater in the QUAD group compared to those in the ATR group in Study GS-US-236-0102, and those in the ATV/r+TVD group in Study GS-US-236-0103. However, the increases from baseline were small, of up to 2.7% through to Week 48, and the maximum median urine fractional excretion of phosphate were comparable between the QUAD groups and the respective active controls. The maximum median urine fractional excretion of phosphate in the QUAD groups were 12.4% and 12.6% in Study GS-US-236-0102 and Study GS-US-236-0103, respectively, falling within the normal range of 5% and 20%. Urine fractional excretion of phosphate was not measured in Study GS-US-236-0104, thus no results for beyond Week 48 was available.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefit of QUAD in the proposed usage is as an alternative Single Tablet Regimen (STR), combining an INSTI with an N(t)RTI backbone, for the treatment of ARV treatment-naive HIV-1 infected adult patients. Current treatment guidelines recommend that initial treatment for ARV treatment-naive HIV-1 infected patients should involve 2 N(t)RTIs (e.g. FTC and TDF) and either an NNRTI (e.g. EFV or rilpivirine), a boosted protease inhibitor (PI), or an INSTI. Currently in Australia, raltegravir is the only INSTI approved for use in adults. It requires twice-daily dosing regimen, and is not formulated as an STR with an N(t)RTI combination. Currently in Australia, there are 2 STRs approved for once-daily administration in the treatment of HIV-1 infection, and both combine an NNRTI with an N(t)RTI backbone of FTC and TDF: Atripla (FTC/TDF/ EFV) and Eviplera (FTC/TDF/ rilpivirine). No approved STRs exist that combine an INSTI with an N(t)RTI backbone. The QUAD STR has a role as an alternative treatment for patients who cannot tolerate NNRTIs or boosted PIs, while allowing for a simplified drug regimen which can improve compliance and reduce the risk of development of drug resistance.

Efficacy results showed that the use of QUAD STR in the treatment of ARV treatment-naive HIV-1 infected adult patients with baseline HIV-1 RNA ≥ 5000 copies/mL, led to approximately 89% of patients achieving virologic levels of < 50 HIV-1 copies/mL at Week 48, as defined by the FDA snapshot analysis algorithm. When benchmarked against treatment guidelines-recommended first-line ARV drug of ATR STR or ARV drug regimen of ATV/r+TVD, this proportion of virologic response of QUAD was found to be non-inferior to those of ATR STR or ATV/r+TVD.

In addition, efficacy results in patients who were on QUAD for more than 48 weeks showed that there was further and sustained suppression of HIV-1 RNA levels and increase in CD4 cell count, suggesting that both virological and immunological responses were sustained beyond 48 weeks of QUAD dosing.

9.2. First round assessment of risks

The risks of QUAD in the proposed usage are:

· the potential adverse effect on the renal system

In the 2 pivotal Phase III registration studies, safety results showed that the incidence of renal AE of interest as well as the percentage of patients who discontinued study drug due to renal AEs, were higher in the pooled QUAD group than in the ATR or ATV/r+TVD group. In addition, the majority of the renal AEs of interest in the QUAD group were that of renal failure.

However, the renal AEs and the abnormal renal parameters appeared to be reversible after drug discontinuation, and none of the subjects with renal failure in the QUAD group required dialysis or other forms of renal replacement therapy during the study. This also needs to be considered in the context that the renal adverse events and abnormal laboratory parameters can be monitored and detected by routine laboratory tests. It is also noted that the reporting of the AE of renal failure was based on renal laboratory abnormalities (raised serum creatinine and reduced eGFR), and analysis of renal laboratory parameters showed that although there were greater increases in median values for serum creatinine and a greater decrease in median $eGFR_{CG}$ in the pooled QUAD group compared to the ATR and ATV/r+TVD groups, there were no corresponding decreases from baseline of cysGFR, suggesting that the raised serum creatinine levels and reduced $eGFR_{CG}$ could be due to the inhibition of tubular secretion of creatinine by COBI, and not reflecting an actual nephrotoxic effect of QUAD.

In the 2 pivotal Phase III registration studies, the median increase from baseline of urine fractional excretion of phosphate, used as a measure of proximal renal tubular injury, was greater at Week 48 in the QUAD group compared to those in the ATR or ATV/r+TVD group. However, the increases from baseline were small, of up to 2.7% through to Week 48, and the maximum median urine fractional excretion of phosphate were comparable between the QUAD groups and the respective active controls. In addition, the maximum median urine fractional excretion of phosphate in the QUAD groups of 12.4% and 12.6% in Study GS-US-236-0102 and Study GS-US-236-0103, respectively, fell within the normal range of 5% and 20%. This was also not associated with significant concerns regarding the incidence of hypophosphatemia, with safety results showing that the percentage of subjects with hypophosphatemia in the QUAD group, although higher than that in the ATR group, was lower than that in the ATV/r+TVD group, and that most of the hypophosphatemia were of grades 1 or 2 in severity.

· the emergence of resistance to INSTI

Study results suggested that development of INSTI-R mutations may be an issue with the use of QUAD, compared to the active controls of ATR and ATV/r+TVD. This, however, is within expectations, as neither ATR nor ATV/r+TVD contains an INSTI, whereas the EVG component of QUAD is an INSTI. The calculated percentage of patients in the QUAD group with emergent INSTI-R mutations was low: 2.0% in Study GS-US-236-0102, and 1.1% in Study GS-US-236-0103 (assuming that subjects who did not show virologic failure, and hence not tested for study drug resistance, did not develop the resistance mutations). The proportions of patients who developed emergent RT-R mutations were similar between the QUAD and ATR groups, but higher in the QUAD group compared to the ATV/r+TVD group, although the number of patients analysed for emergent study drug resistance was too small for meaningful statistical analysis

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of QUAD, given the proposed usage, is favourable.

- Efficacy results showed that the use of QUAD STR in the treatment of ARV treatment-naive HIV-1 infected adult patients with baseline HIV-1 RNA ≥ 5000 copies/mL, led to approximately 89% of patients achieving virologic levels of < 50 HIV-1 copies/mL at Week 48, as defined by the FDA snapshot analysis algorithm. When benchmarked against treatment guidelines-recommended first-line ARV drug of ATR STR or ARV drug regimen of ATV/r+TVD, this proportion of virologic response of QUAD was found to be non-inferior to those of ATR STR or ATV/r+TVD.
- Preliminary efficacy results in patients who were on QUAD for more than 48 weeks suggested that there was further and sustained suppression of HIV-1 RNA levels and increase in CD4 cell count, suggesting that both virological and immunological responses were sustained beyond 48 weeks of QUAD dosing.

The main risks involve the potential adverse effect on the renal system and the emergence of resistance to INSTI with the use of QUAD.

- potential adverse effect on the renal system

Although safety results showed that there was a higher incidence of renal AE of interest in the QUAD group than in the ATR or ATV/r+TVD group, and that the majority of these renal AEs of interest in the QUAD group were renal failure, the reporting of these AEs of renal failure was based on renal laboratory abnormalities (raised serum creatinine and reduced eGFR). Analysis of renal laboratory parameters showed that although there were greater increases in median values for serum creatinine and a greater decrease in median $eGFR_{CG}$ in the QUAD group compared to the ATR or ATV/r+TVD groups, there were no corresponding decreases from baseline of cysGFR. This raised the possibility that the increased serum creatinine levels and reduced $eGFR_{CG}$ could be due to the inhibition of tubular secretion of creatinine by COBI, and not reflecting an actual nephrotoxic effect of QUAD, and that the renal AEs were triggered when the raised serum creatinine and reduced eGFR were noted. In addition, the renal AEs and the abnormal renal parameters appeared to be reversible after drug discontinuation. It is also taken into consideration that the renal adverse events and abnormal laboratory parameters can be monitored and detected by routine laboratory tests.

Overall, the potential risk of adverse effect on the renal system with the use of QUAD is not considered to be high, given that safety results suggested that the renal AEs and abnormal renal laboratory parameters detected in the studies may be reflecting the effect of COBI on tubular secretion of creatinine rather than an actual nephrotoxic effect of QUAD, and given that it is monitorable and reversible. It is also noted that appropriate precautions are stated in the proposed Product Information (PI) that "It is recommended that creatine clearance be estimated in all patients prior to initiating therapy with THEQUAD. Routine monitoring of estimated creatine clearance and serum phosphorus should be performed during THEQUAD therapy in patients with renal impairment." and that "THEQUAD should be avoided with concurrent or recent use of a nephrotoxic agent."

- emergence of resistance to INSTI with the use of QUAD

With regards to the emergence of resistance to ARVs, there are no significant concerns that the rate of emergence of RT-T mutations was higher with the use of QUAD compared to ATR or ATV/r+TVD. However, results suggested that INSTI-R mutations may be an issue with the use of QUAD, compared to the active controls of ATR and ATV/r+TVD. This, however, is within expectations, as neither ATR nor ATV/r+TVD contains an INSTI, whereas the EVG component of QUAD is an INSTI with the use of QUAD. The degree to which the INSTI resistance mutations which was found to emerge with the use of QUAD will lead to resistance to other INSTIs is not known. Additional data needs to be collected with regards to cross-resistance in this relatively

new class of ARV medications. However, it is noted that the percentage of patients in the QUAD group in the Phase III studies with emergent INSTI-R mutations was low, at between 1 to 2%.

Overall, the benefit-risk balance of QUAD is positive, and meets the EMA guideline on the clinical development of medicinal products for the treatment of HIV infection, which recommended that a "convincingly demonstrated non-inferior benefit-risk at 48 weeks versus a well recognised reference product may serve as a basis for approval"[33]. With study results showing that efficacy is comparable with that of ATR and of ATV/r+TVD, both recognised reference ARV drug or drug regimens for the treatment of ARV treatment-naive HIV-1 infected adult patients, and with a safety profile that does not raise significant concerns, QUAD has a role as an alternative treatment option for HIV-1 infected treatment-naïve adult patients who cannot tolerate NNRTIs or boosted PIs.

10. First round recommendation regarding authorisation

It is recommended that the application for registration of QUAD, for the proposed indication of treatment of HIV-1 infection in ARV treatment-naïve adult patients be approved, subject to a satisfactory response to the recommended changes to the PI.[34]

However, it is recommended that the indications of QUAD be further clarified, from the original proposed text of

> "THEQUAD is indicated as a complete regimen for the treatment of HIV infection in adults who have no known mutations associated with resistance to the individual components of THEQUAD"

to

"THEQUAD is indicated as a complete regimen for the treatment of HIV-1 infection in ARV treatment-naive adults aged 18 years and over, who have no known mutations associated with resistance to the individual components of QUAD."

It is noted that at the time of submission of this clinical dossier, the 2 pivotal phase III studies and the Phase II study were both ongoing. It is recommended that the sponsor submit the results of these studies as soon as they are completed.

11. Clinical questions

11.1. Pharmacokinetics

a. Although EVG has the potential for stereoisomeric forms there were no studies on the possible inter-conversion of isomers *in vivo*. Was this issue addressed in pre-clinical studies and inter-conversion ruled out?

b. In assessing the drug interaction potential of the QUAD reliance has been placed on *in vitro* assessments and some *in vivo* studies with 'model' substrates. There have been few *in vivo* studies with medications used to treat possible co-morbid, non-virus related conditions. Given the effect of COBI on renal function and the potential use of lithium in HIV patients, and its known effect on renal function, has a study been conducted to examine this interaction? A study using the QUAD rather than any of the

[33] European Medicines Agency. Guideline on the clinical development of medicinal products for the treatment of HIV infection. 20 Nov 2008.
[34] The sections on the PI and CMI are not included in this Extract from the CER

components would seem to be potentially more useful in deciding the clinical significance of any such interaction effects found.

11.2. Pharmacodynamics

a. Has the potential PD interaction with the QUAD and alcohol been considered? Perhaps an *in vivo* study assessing the effects on cognitive and psychomotor performance would be useful.

11.3. Efficacy

Please justify the dose for EVG in the formulation of QUAD.

In describing the justification for choice of dose of EVG, the sponsor has stated that in study GS-US-183-0105, RTV-boosted EVG of 125mg dose formulation was used, and that study GS-US-183-0140 showed that the 125 mg dose and the 150 mg dose of EVG provided bioequivalent EVG exposures. No rationale was given for the choice of 150mg instead of 125mg of EVG.

12. Second round evaluation of clinical data submitted in response to questions

The sponsor provided its response to the s31 clinical questions. This was reviewed by the TGA internally and considered acceptable (see *Addendum*, below)

13. Second round benefit-risk assessment

The risk-benefit assessment provided by the Round 1 evaluators under section 9 above is considered final with respect to this clinical evaluation report.

14. Second round recommendation regarding authorisation

The recommendation with respect to market authorisation made by the Round 1 evaluators under section 10 is considered final with respect to this evaluation report.

15. References

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http://jama.ama-assn.org/content/304/3/321.full.pdf (accessed 20th March 2012)

16. Addendum

16.1. ROUND 2: Review of sponsor's response to s31 clinical questions

Pharmacokinetics

TGA Question

Although EVG has the potential for stereoisomeric forms there were no studies on the possible inter-conversion of isomers in vivo. Was this issue addressed in pre-clinical studies and inter-conversion ruled out?

Sponsor's response:

The *in vivo* interconversion of elvitegravir (EVG) to the (R)-enantiomer (JTP-65381) was evaluated in a study in rats and dogs. JTP-65381 was not detected in rat and dog plasma after oral administration of EVG. Additionally, the chiral center in the EVG molecule (i.e. the (*S*)-enantiomer) is not inter-convertible because of the relatively high pKa value of the proton on the chiral center contained in the valinol moiety and the strong connective bonds between the stereogenic center and the appending groups. Thus, the chiral center is not labile and formation of the (*R*)-enantiomer starting from EVG is highly unlikely. Stability study results support this assessment as the (*R*)-enantiomer of EVG has not been detected under long term and accelerated conditions. Thus, based on the results from the pre-clinical study in rats and dogs, and the chemical knowledge and understanding of the pathways necessary for epimerization of chiral centers to occur, the chemical activity of the chiral center in the EVG molecule, and the chemical stability data for EVG, the potential inter-conversion of isomers *in vivo* is highly unlikely therefore, clinical studies evaluating the inter-conversion are not considered necessary.

TGA Evaluator's comment

The response is considered acceptable.

TGA Question

In assessing the drug interaction potential of the QUAD reliance has been placed on in vitro assessments and some in vivo studies with 'model' substrates. There have been few in vivo studies with medications used to treat possible co-morbid, non-virus related conditions. Given the effect of COBI on renal function and the potential use of lithium in HIV patients, and its known effect on renal function, has a study been conducted to examine this interaction? A study using the QUAD rather than any of the components would seem to be potentially more useful in deciding the clinical significance of any such interaction effects found.

Sponsor's response

The assessment of drug interaction potential between QUAD and concomitant medications that may be used to treat co-morbidities in HIV-1 infected patients is based on a thorough evaluation of the relevant ADME properties of each of the components, including the investigational agents elvitegravir and cobicistat, and the marketed agents tenofovir DF and emtricitabine. These overall recommendations are consistent with the approach taken for other antiretroviral agents (ARV) which are used as part of an ARV regimen (along with concomitant medications if necessary).

This approach is also consistent with the European Guidelines: *Guideline on the investigation of Drug Interactions* (EMA/CHMP/EWP/125211/2010) and the US Guideline for Industry *Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations (February 2012)* for evaluation of drug interactions.

Following oral administration, lithium is excreted almost entirely by the kidney, via glomerular filtration**.** Study GS-US-216-0121 (Module 5) demonstrated that COBI affects the estimated glomerular filtration rate (eGFR), which is calculated based on serum creatinine (an endogenous agent that is both filtered and secreted) and not the actual GFR (aGFR), as assessed by clearance of iohexol, a exogenous marker that is eliminated almost exclusively by filtration. The mechanism of change in eGFR has been elucidated to be a transporter mediated interaction between COBI and creatinine (i.e. inhibition of primarily the MATE-1 transporter-mediated secretion of creatinine by COBI). Therefore it is unlikely for COBI to undergo clinically relevant interactions with lithium.

Elvitegravir, the other investigational component of QUAD, is minimally eliminated in urine (and not as unchanged parent), and is not associated with changes in GFR. The pharmacokinetic properties of the marketed NRTI components of QUAD, tenofovir DF and emtricitabine, have been well established, and the exposures of tenofovir DF and emtricitabine with QUAD are comparable to those historically observed upon their administration as individual agents with other ARVs. Mechanistically, these agents are not expected to affect lithium pharmacokinetics. From a drug interaction perspective, the clinical experience with QUAD and lithium is expected to be consistent with that when lithium is coadministered with other ARV regimens, including ritonavir-boosted protease inhibitors used in combination with tenofovir DF and/or emtricitabine.

In summary, the totality of data indicates that it is unlikely for COBI or any other component of QUAD to undergo clinically relevant interactions with lithium.

TGA evaluator's comment

The response is considered acceptable.

Pharmacodynamics

TGA Question

Has the potential PD interaction with the QUAD and alcohol been considered? Perhaps an in vivo study assessing the effects on cognitive and psychomotor performance would be useful.

Sponsor's response

There are no relevant interactions expected between the components of QUAD and alcohol that may affect alcohol pharmacokinetics. The metabolism of alcohol is mediated by alcohol dehydrogenase and also by CYP2E1. These enzymes are not considered to be affected by the components of QUAD, including COBI. In particular, the substrate and inhibitor specificities of these enzymes are restrictive, such that COBI (based on molecular weight) is not expected to interact with these enzymes. Further data with a structurally related molecule ritonavir indicate the lack of inhibition of CYP2E1. Report JTK303-AD-027 demonstrates that EVG, when tested as an inhibitor of CYP2E1 *in vitro* had no effect (IC50 > 30 µg/mL). Report JTK303-AD-027 was provided to TGA in Module 4. In the absence of a PK-driven interaction between QUAD and alcohol, a PD interaction is considered unlikely.

TGA evaluator's comment

The response is considered acceptable

Efficacy

TGA Question

Please justify the dose for EVG in the formulation of QUAD. In describing the justification for choice of dose of EVG, it is stated that in study GS-US-183-0105, RTV-boosted EVG of 125mg dose formulation was used, and that study GS-US-183-0140 showed that the 125 mg dose and the 150 mg dose of EVG provided bioequivalent EVG exposures. No rationale was given for the choice of 150mg instead of 125mg of EVG.

The dose of EVG (150 mg) was selected based on results from GS-US-183-0101, as well as a Phase 2 study in heavily treatment-experienced HIV-1 infected subjects (GS-US-183-0105), and a Phase 1 biopharmaceutics/formulation study (GS-US-183-0140). The reports for these studies were provided to TGA in Module 5.

During the development program of elvitegravir, a Phase 1 study to evaluate the relative bioavailability of the various formulations of ritonavir-boosted elvitegravir was performed in Study GS-US-183-0121. Study GS-US-183-0121 was ongoing at the time of the Category 1 submission for QUAD, however is provided in response to the above question. Among the formulations tested, this study demonstrated that EVG 125 mg Test Formulation 2 provided ~10% lower EVG exposures compared to the Reference Formulation used in the Phase 2 Study GS-US-183-0105. Accordingly, a higher dose of EVG 150 mg using Test Formulation 2 was evaluated further in Study GS-US-183-0140 as a potential Phase 3 and proposed commercial formulation.

Study GS-US-183-0140 then demonstrated that the newer EVG formulation 150 mg in boosted condition provides bioequivalent EVG exposures relative to the Phase 2 tablet of boosted-EVG 125 mg, including EVG trough concentrations, resulting in the selection of 150 mg of the newer EVG formulation as the dose and formulation for the Phase 3 study and commercial use of the stand-alone tablet for boosted-EVG 150 mg, and for the formulation of QUAD.

Pharmacokinetic results (Study GS-US-183-0121) are below.

Table 18. Study GS-US-183-0121. Statistical comparison of EVG and RTV pharmacokinetic parameters for test versus reference treatments (PK analysis set)

	EVG (N = 21)				
EVG Plasma PK Parameter	EVG/r Reference A	EVG/r Test Formulation 1 B	EVG/r Test Formulation 2 C	GMR (%) (90% CI)	
				B vs. A	C vs. A
C_{max} (ng/mL)	934.1 (65)	730.4 (56)	813.7 (50)	79.7 (68.5, 92.7)	91.9 (78.8, 107.0)
$AUC_{0\text{-}last}$ (ng•h/mL)	12,652.9 (59)	9925.7 (58)	10,577.1 (50)	79.2 (69.6, 90.1)	87.2 (76.6, 99.3)
AUC_{inf} (ng•h/mL)	13,384.5 (57)	10,969.6 (57)	11,653.9 (50)	82.7 (72.6, 94.2)	90.1 (79.0, 102.7)
	RTV (N = 21)				
RTV Plasma PK Parameter	EVG/r Reference A	EVG/r Test Formulation 1 B	EVG/r Test Formulation 2 C	GMR (%) (90% CI)	
				B vs. A	C vs. A
C_{max} (ng/mL)	491.4 (51)	417.2 (42)	497.4 (46)	87.1 (76.3, 99.3)	105.0 (92.0, 119.9)
$AUC_{0\text{-}last}$ (ng•h/mL)	3362.9 (40)	3155.6 (44)	3373.1 (42)	92.0 (85.1, 99.5)	101.0 (93.4, 109.3)
AUC_{inf} (ng•h/mL)	3464.1 (38)	3250.6 (43)	3542.6 (42)	91.6 (84.9, 98.9)	102.3 (94.7, 110.4)

TGA evaluator's comment

The sponsor's response is considered acceptable.

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