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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Kimberly Martin, D.O., MPH
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Established Name	Elvitegravir
(Proposed) Trade Name	Vitekta®
Therapeutic Class	HIV-1 Integrase Inhibitor
Applicant	Gilead Sciences, Inc.

Formulation(s)	85mg and 150mg tablets
Dosing Regimen	85mg or 150mg daily in combination with ritonavir and other antiretroviral agents
Indication(s)	Treatment of HIV-1 infection in treatment-experienced adults
Intended Population(s)	Adults

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Commonly used terms will be abbreviated in this document, as indicated below:

AE: Adverse Event
ARV: Antiretroviral
ATV: Atazanavir
BR: Background ARV regimen
COBI: Cobicistat
DLV: Delavirdine
DRV: Darunavir
DTG: Dolutegravir
EFV: Efavirenz
EVG: Elvitegravir
FPV: Fosamprenavir
HIV: Human immunodeficiency virus
IAS-USA: International Antiviral Society-USA
IDV: Indinavir
LPV: Lopinavir
NFV: Nelfinavir
NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor
NPV: Nevirapine
NRTI: Nucleoside/Nucleotide Reverse Transcriptase Inhibitor
PI: Protease Inhibitor
PT: Preferred Term
RAL: Raltegravir
RTV: Ritonavir
SAE: Serious Adverse Event
SOC: System Organ Class
SQV: Saquinavir
TEAE: Treatment Emergent Adverse Event
TDF: Tenofovir disoproxil fumarate
TPV: Tipranavir

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The antiviral efficacy and safety data reviewed in the original NDA review by Russell Fleischer, PA-C and the updated safety information reviewed in this NDA resubmission support the recommendation that Vitekta® (elvitegravir, EVG), an HIV-1 integrase inhibitor, be approved as a choice for treatment of antiretroviral treatment experienced adults when co-administered with a ritonavir (RTV) boosted protease inhibitor and other antiretroviral (ARV) agents.

1.2 Risk Benefit Assessment

The initial NDA analysis found the risk benefit assessment to be acceptable. In this resubmission, only updated aggregate safety information was reviewed as datasets were not submitted. Therefore, all data is presented as submitted by the Applicant. The risk benefit analysis of the resubmission data was again found to be acceptable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

No new Postmarket Requirements and Commitments will be required.

2 Introduction and Regulatory Background

2.1 Product Information

Vitekta® is an anti-HIV integrase inhibitor that inhibits the integration of human immunodeficiency virus DNA into host chromosomal DNA. EVG was in-licensed by Gilead Sciences, Inc. from Japan Tobacco Company.

EVG is primarily and rapidly metabolized by cytochrome P450 3A (CYP3A4) thus limiting its exposure and subsequent antiviral activity. The Applicant proposed co-administration of EVG with RTV, which is a potent inhibitor of CYP3A that leads to increased bioavailability of EVG. RTV has antiviral activity on its own and when used at lower than therapeutic doses as a pharmacologic enhancer, must be co-administered with another protease inhibitor in order to protect against the emergence of protease associated resistance mutations.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently 28 drugs and 3 fixed-dose combinations of multiple drugs approved for the treatment of HIV-1 infection. Based on the mechanism of action on the life cycle of the human immunodeficiency virus, the drugs are classified into 6 HIV-1 drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 antagonists, and integrase inhibitors. Table 1 summarizes the approved antiretroviral drugs.

Table 1: Approved Antiretroviral Drugs

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx®/Videx EC®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavirdine	Rescriptor®
	Nevirapine	Viramune®
	Efavirenz (EFV)	Sustiva®
	Etravirine	Intelence®
	Rilpivirine	Edurant®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	fosamprenavir	Lexiva®
	Atazanavir (ATV)	Reyataz®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Tipranavir (TPV)	Aptivus®
	Darunavir (DRV)	Prezista®
Fusion/Entry Inhibitor	Enfuvirtide (ENF)	Fuzeon®
CCR5 receptor antagonist	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir	Isentress®
	Dolutegravir	Tivicay®

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The three single tablet fixed-dose combinations approved for treatment of HIV-1 infection are Atripla® (efavirenz/emtricitabine/ tenofovir) approved on 12 July 2006, Complera® (emtricitabine/rilpivirine/tenofovir) approved on 10 August 2011, and Stribild® (elvitegravir/tenofovir/emtricitabine/cobicistat) approved on 27 August 2012.

2.3 Availability of Proposed Active Ingredient in the United States

The drug substance/product is not approved or available in the United States but EVG active ingredient is readily available in the US as a component of Stribild®.

2.4 Important Safety Issues With Consideration to Related Drugs

Raltegravir, approved in the US in 2007 and dolutegravir, approved in 2013 are the only integrase inhibitors currently available for use as single drugs. Please see the initial EVG NDA review for full details of known safety issues with raltegravir.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Please see the initial NDA review for full details of the presubmission regulatory activities. The initial NDA was received on 2 July 2012 and after review, a Complete Response letter was issued on 26 April 2013 because of isolated facility inspection issues. At the time of the Complete Response, no clinical barriers to approval were identified and approval, contingent on successful completion of all pending facility inspections, was recommended. The following facility inspection deficiencies were forwarded to the Sponsor in the Complete Response letter:

1. During the current inspection of the Gilead Sciences (Foster City, CA) manufacturing facility for this application, FDA field investigators found significant deficiencies and discussed them with firm management. Firm management acknowledged these deficiencies in a letter dated 23 April 2013. Satisfactory resolution of significant deficiencies is required before this application may be approved.
2. During the inspection of the Gilead Sciences (Foster City, CA) manufacturing facility, FDA field investigators found significant concerns regarding the release and stability data presented in the NDA and in DMF 25187 because of lack of method validation of the test methods used to obtain this data. Before the application can be approved, the integrity of the drug substance and drug product release and stability data need to be assured by submission of a detailed explanation to reconcile the analytical methods submitted in the NDA and the DMF with those used at the Foster City manufacturing site.

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A pre-resubmission meeting was conducted on 22 January 2014 via teleconference to discuss the Applicant's proposal to address the comments in the Complete Response letter. Specifically, details of the third party evaluation and the corrective action plan to correct deficiencies found during the inspection of the Gilead Sciences (Foster City, CA) manufacturing facility were discussed.

2.6 Other Relevant Background Information

Elvitegravir is approved as a component of Stribild® (a fixed dose combination containing EVG, cobicistat (COBI), tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)) approved only for use in treatment naïve patients (NDA 203100). Cobicistat is a mechanism-based CYP3A inhibitor that enhances or "boosts" the exposure of CYP3A substrates, including EVG. A complete response letter was also issued for cobicistat on 16 April 2013 because of the documented inspection deficiencies at the Foster City, CA facility. The resubmission NDA for cobicistat was received on 28 March 2014 and is under review by Sarita Boyd, Pharm D.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The resubmission included aggregate safety data that was easily reviewable.

3.2 Compliance with Good Clinical Practices

Please see the initial NDA review for information related to Good Clinical Practice compliance.

3.3 Financial Disclosures

Please see the initial NDA review for information related to financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

As noted in Section 2.5, significant deficiencies were noted during the inspection of the production facility in Foster City, CA that led to the Complete Response Letter issued 26 April 2013.

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In the resubmission, these issues were rectified by removal of all data from the Foster City, CA facility. Please see the CMC review completed by Steve Miller, Ph.D. for full details.

4.2 Clinical Microbiology

No new Virology information submitted.

4.3 Preclinical Pharmacology/Toxicology

No new Preclinical Pharmacology/Toxicology information submitted.

4.4 Clinical Pharmacology

No new Clinical Pharmacology information submitted.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

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Table 2: Updated Clinical Trial Data Included in Resubmission

Study Number	Study Title	Submission	Data Cut Date ^a	
			Original NDA	Current Safety Update
GS-US-183-0145	A Multicenter, Randomized, Double-Blind, Double-Dummy, Phase 3 Study of the Safety and Efficacy of Ritonavir-Boosted Elvitegravir (EVG/r) Versus Raltegravir (RAL) Each Administered With a Background Regimen in HIV-1 Infected, Antiretroviral Treatment-Experienced Adults	Original NDA (NDA 203093, Sequence 0000, 27 June 2012) and 120-day Safety Update (NDA 203093, Sequence 0009, 25 October 2012)	31 October 2011 (Week 96 analysis)	01 July 2013 (interim analysis)
GS-US-183-0130	A Phase 2, Open-Label, Multicenter Study of the Safety of Ritonavir-boosted GS-9137 (GS-9137/r) Administered in Combination with Other Antiretroviral Agents for the Treatment of HIV-1 Infected Subjects	Original NDA (NDA 203093, Sequence 0000, 27 June 2012) and 120-day Safety Update (NDA 203093, Sequence 0009, 25 October 2012)	22 March 2011 (Week 192 analysis)	01 July 2013 (interim analysis)
GS-US-236-0102 ^b	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Efavirenz/Emtricitabine/ Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	Original NDA (NDA 203093, Sequence 0000, 27 June 2012) and 120-day Safety Update (NDA 203093, Sequence 0009, 25 October 2012)	26 July 2011 (Week 48 analysis/ ISS analysis)	29 May 2013 (Week 144 analysis/ ISS analysis)
GS-US-236-0103 ^b	A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Ritonavir-Boosted Atazanavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	Original NDA (NDA 203093, Sequence 0000, 27 June 2012) and 120-day Safety Update (NDA 203093, Sequence 0009, 25 October 2012)	01 September 2011 (Week 48 analysis/ ISS analysis)	05 July 2013 (Week 144 analysis/ ISS analysis)
GS-US-236-0104	A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Elvitegravir/Emtricitabine/Tenofovir Disoproxil Fumarate/GS-9350 Versus Atripla® (Efavirenz 600 mg/Emtricitabine 200 mg/Tenofovir Disoproxil Fumarate 300 mg) in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	Original NDA (NDA 203093, Sequence 0000, 27 June 2012) and 120-day Safety Update (NDA 203093, Sequence 0009, 25 October 2012)	17 March 2011 (Week 96 analysis)	01 July 2013 (interim analysis)
GS-US-183-0149	A Phase 1 Study to Evaluate the Bioavailability of Boosted Age-Appropriate Pediatric Elvitegravir (EVG) Tablet or Suspension Formulation Compared with Adult EVG 150 mg Tablets in Healthy Adult Volunteers	Submitted to IND 072177, Serial No. 426, 22 August 2013	None ^c	27 March 2013 (final analysis)
GS-US-216-0125	A Phase 1 Study Evaluating the Drug Interaction Potential Between Once-Daily Cobicistat-Boosted Elvitegravir and Methadone or Buprenorphine/Naloxone	Clinical Study Report (NDA 203100/S-004, Sequence 0068, 05 December 2012)	None ^c	20 June 2012 (final analysis)
GS-US-236-0118	A Phase 3 Single Arm Open-Label Safety Study of Cobicistat-containing HAART in HIV-1 Infected Patients with Mild to Moderate Renal Impairment	Clinical Study Report (NDA 203100/S-010, Sequence 0108, 15 November 2013)	None ^c	27 June 2013 (Week 48 analysis)
GS-US-236-0135	A Phase 1 Multiple-Dose Study Evaluating the Drug Interaction Potential Between Telaprevir and Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen (Part 1) or Ritonavir-Boosted Atazanavir plus Elvitegravir (Part 2) in Healthy Subjects	Not submitted to IND or NDA.	None ^c	20 June 2013 (final analysis)

- a The dates used to cut the adverse event eCRF data are presented.
b Data from Studies GS-US-236-0102 and GS-US-236-0103 were pooled.
c Data were not available at the time of the original EVG NDA.

Source: NDA 203093 Safety Update for NDA Resubmission, pages 8-9.

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5.2 Review Strategy

This review heavily references the initial review completed by Russell Fleischer, PA-C for many aspects of the review that were completed prior to the resubmission. Please see his review for full details of the initial analysis.

The review strategy for this NDA resubmission consisted of reviewing the new safety data accrued since the data cut dates for the pivotal Phase 3 trial (GS-US-183-0145, 31 October 2011) and the supportive Phase 2 trial (GS-US-183-0130, 22 March 2011). In this resubmission, both blinded trial and open label rollover data were submitted for Study GS-US-183-0145 but this review primarily highlights only open label rollover data as all of the blinded data has previously been reviewed. This review strategy was chosen given that the blinded portion of the trial was almost completed at the time of initial submission and final blinded data was submitted with the 120 day safety update.

Additionally, updated information was submitted and reviewed for trials GS-US-236-0104, a Phase 2 trial of Stribild® (EVG/FTC/TDF/COBI) versus Atripla® (EFV/FTC/TDF) in HIV-1 infected treatment naïve adults and GS-US-236-0135, a Phase 1 drug interaction study of telaprevir and Stribild® or ritonavir boosted atazanavir. Datasets were not included as part of this resubmission and as such, all data is taken from the Sponsor's submitted information.

In addition to the studies that were reviewed for this NDA resubmission, the sponsor submitted updated trial information for multiple other studies which have been reviewed or are currently being reviewed under multiple NDA numbers by various clinical and non-clinical reviewers. These include studies GS-US-216-0114 and GS-US-216-0105 which were re-submitted under NDA 203094, for the approval of cobicistat, and are being reviewed by Sarita Boyd, Pharm D. Studies GS-US-236-0102, GS-US-236-0103 and GS-236-0118, all submitted under NDA 203100 (Stribild®) and are currently under review by Dr. Prabha Viswanathan. Additionally, information was re-submitted for GS-US-183-0149, a Phase 1 bioavailability study of elvitegravir in pediatric subjects that was reviewed by Dr. Peter Miele. Lastly, new information was submitted for trial GS-US-216-0125, a Phase 1 drug interaction study between cobicistat boosted elvitegravir and methadone or buprenorphine/naloxone being reviewed by Vikram Arya, Ph.D. Please see the appropriate reviews for full details of these studies.

5.3 Discussion of Individual Studies/Clinical Trials

GS-US-236-0135: Phase 1, multiple-dose study evaluating the drug interaction potential between telaprevir and Stribild® (Part 1) or ritonavir-boosted atazanavir plus elvitegravir (Part 2) in healthy adults.

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GS-US-236-0104: Phase 2, randomized, double-blinded study of the safety and efficacy of Stribild® versus Atripla® in HIV-1 infected, antiretroviral treatment-naïve adults.

GS-US-183-0130: Phase 2, ongoing, rollover, open-label, multi-center, multiple dose, single-arm extension study designed to assess the safety of ritonavir boosted EVG, in combination with other ARV agents, in treatment-experienced HIV-1 infected adults and adolescents. Subjects were eligible for this study if they had completed a prior ritonavir boosted EVG treatment study without experiencing any dose-limiting toxicity; eligible subjects may or may not have received EVG in their prior study.

Subjects were enrolled in this extension study regardless of their baseline HIV-1 RNA level. Non-virologically suppressed subjects entering the study had, for the most part, failed prior ARV regimens and had limited treatment options available; these subjects were allowed in the current extension study even if they had been exposed to EVG in their prior study.

Genotyping was not performed at baseline, so subjects who met eligibility requirements were enrolled at the discretion of the investigator. The components of each subject's background ARV regimen were selected by the investigator without input from the Applicant. Background ARV regimens consisted of at least 2 agents, but were not to include the NNRTIs efavirenz (EFV), nevirapine (NPV), or delavirdine (DLV), or the PIs saquinavir (SQV), nelfinavir (NFV), or indinavir (IDV). Subjects who were receiving a RTV-boosted PI (PI/r) as part of their ARV regimen took the RTV dose and followed the dosing schedule indicated in the prescribing information for the PI. No additional RTV was administered. Subjects whose ARV regimen did not include RTV took RTV 100 mg once daily with their EVG dose. Subjects who were taking lopinavir/r (LPV/r) or atazanavir/r (ATV/r) as part of their ARV regimen received EVG 85 mg once daily due to an established drug-drug interaction with these agents; all other subjects received EVG 150 mg once daily.

GS-US-183-0145: Phase 3, multicenter, randomized, double-blind, double dummy study of the safety and efficacy of EVG boosted with ritonavir (EVG/RTV) versus raltegravir (RAL) each administered with a background regimen (BR) in HIV-1 infected, antiretroviral treatment-experienced subjects. Subjects were antiretroviral treatment experienced adults with plasma HIV-1 RNA levels >1000 copies/mL who had documented resistance from 2 or more different classes of antiretroviral agents or at least 6 months experience before screening with at least one antiretroviral agent and were fully susceptible to a selected PI.

Subjects were randomized 1:1 to one of the following treatment groups and treated in the blinded phase for 96 or more weeks:

- Group 1: EVG 150 mg (or 85 mg) once daily + RAL placebo twice daily + BR

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- Group 2: RAL 400 mg twice daily + EVG placebo once daily + BR

Due to known PK interactions, subjects who were receiving ATV or LPV as part of their BR were to receive a reduced EVG dose of 85 mg once daily if randomized to Group 1. The BR was constructed by the investigator based on viral resistance testing and was to be composed of a fully active RTV-boosted PI and a second active agent. The ritonavir dose used to pharmacologically boost EVG was based on the ritonavir-boosted PI that was required to be in the regimen. The fully active PI was defined by phenotypic resistance analysis.

For phenotypic susceptibility, fully active was defined as being below the lower clinical or biological cutoff. The following RTV-boosted PIs were allowed to be prescribed by the investigator as part of the BR: atazanavir (ATV), darunavir (DRV), fosamprenavir (FPV), lopinavir (LPV), or tipranavir (TPV). Subjects took their RTV dose based on the dosing schedule indicated in the prescribing information for the PI and no additional RTV was required to be taken with EVG.

Randomization was stratified by screening HIV-1 RNA level ($\leq 100,000$ c/mL or $> 100,000$ copies/mL) and the class of the second agent (NRTI vs other classes). During Week 2, a PK substudy was conducted at selected sites. Additionally, a trough PK sample (at Weeks 2, 12, 16, 24, and 48) and a post-dose sample (at Weeks 8, 20, 32, and 40) were collected for all subjects.

All subjects who remained on blinded study drug until their Unblinding Visit were given the option to participate in an extension phase of the study, during which EVG would be provided for an additional 144 weeks or until commercial approval was received in the applicable country (whichever occurred first). At Week 96, subjects originally randomized to RAL who elected to continue in the open-label extension phase would be switched to EVG. After Week 144, subjects were given the option to participate in another open-label extension phase of the study if commercial approval had not yet been obtained in the applicable country.

At the time this study was initiated, RAL was only indicated for use in treatment experienced subjects. Of note, the Applicant initially enrolled subjects in two identically designed studies that were later combined into a single study. To be eligible, subjects were to be antiretroviral treatment-experienced HIV-1 infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL and documented resistance, as defined by current International Antiviral Society-USA (IAS-USA) definitions, or at least 6 months experience prior to screening with 2 or more different classes of antiretroviral agents. Thus, subjects may have had resistance to 1 class and at least 6 months experience prior to screening with a second class of antiretroviral agents, or resistance to 2 classes of antiretroviral agents, or at least 6 months experience with the 2 classes of antiretroviral agents. Subjects may have also had resistance or at least 6 months

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experience prior to screening with 3 or more classes of antiretroviral agents. In addition, subjects were to have been on a stable antiretroviral regimen for at least 30 days prior to screening and up until the baseline visit and be eligible to receive one of the fully active RTV-boosted-PIs, based on the results of screening phenotype analysis provided by (b) (4), and an allowed second agent.

6 Review of Efficacy

The primary efficacy review was conducted during the initial review cycle, please see the initial clinical review and the Statistics review by Lei Nie, Ph.D. for full details.

Table 3 provides the efficacy information to be displayed in the label for subjects in Study GS-US-183-0145, as confirmed during the initial review.

Table 3: Virologic Outcomes of HIV-1 Infected Treatment-Experienced Adults in Study GS-US-183-0145 (Week 96^a Analysis)

	VITEKTA + protease inhibitor/ritonavir+ another antiretroviral drug (N=351)	Raltegravir + protease inhibitor/ritonavir+ another antiretroviral drug (N=351)
HIV-1 RNA <50 copies/mL^b	52%	53%
HIV-1 RNA ≥50 copies/mL^c	36%	31%
No Virologic Data at Week 96	12%	16%
Discontinued Study Drug Due to AE or Death ^d	3%	7%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL ^e	8%	9%
Missing Data During Window but on Study Drug	1%	1%

- The Week 96 analysis window is between Day 645 and 700 (inclusive).
- Difference (95% CI) of response rate is -0.5% (-7.9%, 6.8%) at Week 96.
- Includes subjects who had ≥50 copies/mL in the Week 96 window; subjects who discontinued early due to lack or loss of efficacy; subjects who had a viral load ≥50 copies/mL at the time of change in background regimen; subjects who discontinued for reasons other than an adverse event, death, or lack or loss of efficacy, and at the time of discontinuation had a viral value of ≥50 copies/mL.
- Includes subjects who discontinued due to adverse event or death at any time point from Day 1 through the time window, if this resulted in no virologic data on treatment during the specified window.
- Includes subjects who discontinued for reasons other than an adverse event, death, or lack or loss of efficacy; eg., withdrew consent, loss to follow-up, etc.

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7 Review of Safety

Safety Summary

The most common treatment emergent adverse events (TEAE) identified in the All EVG cohort portion of the Phase 3 trial and the Phase 2 open label EVG trial by System Organ Class (SOC) included Infections and Infestations and Gastrointestinal Disorders. In Study GS-US-183-0145, the most common adverse events (AE) by preferred term (PT) included diarrhea, upper respiratory infection, headache, nausea and back pain.

In Studies GS-US-183-0145 and GS-US-183-0130, 17 deaths in EVG subjects were reported as compared to 10 RAL treated subjects in Study GS-US-183-0145 only. None of the EVG deaths in either study were attributed to study drug by the investigator while 3 of the RAL treated subject deaths were felt to be possibly related to study drug. Twenty-six EVG treated subjects in Studies GS-US-183-0145 and GS-US-183-0130 discontinued study drug secondary to an adverse event with 8 of these events attributed to study drug. Fifteen RAL subjects discontinued study drug due to an AE in Study GS-US-183-0145 with 9 of these events felt to be secondary to study drug by the investigator.

Serious Adverse Events (SAE) were noted in 109 of 505 subjects (21.6%) in the All EVG cohort with a majority of new events occurring in the SOC of Infections and Infestations. During the blinded portion of Study GS-US-183-0145, 73 SAEs (20.6%) were reported with 4 events considered related to study drug as compared to 86 SAEs (24%) in RAL treated subjects with 7 events considered related to study drug. In Study GS-US-183-0130, 82 subjects (42.7%) had SAEs with 3 events attributed to study drug by the investigator.

During this re-submission review, psychiatric events of interest both in the previously submitted blinded portion and the newly submitted All EVG open label portion of Study GS-US-183-0145 and full data from GS-US-183-0130 were evaluated. Case report forms were evaluated for all psychiatric SAEs and discontinuations due to psychiatric events. Although a majority of psychiatric events were found to be confounded by previous history of psychiatric disorder/ psychiatric medication, illicit substance usage and/or significant life event at the time of SAE or discontinuation, similar psychiatric events have been seen in other integrase inhibitors and Stribild®. Because of the concern for psychiatric events occurring in these integrase inhibitor treated subjects, especially those with a pre-existing history of psychiatric illness, the label will be updated to contain similar language to the current Stribild® and raltegravir package inserts.

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7.1 Methods

The review of this safety update details open label rollover data from subjects in the All EVG cohort which consists of subjects previously randomized in the blinded portion of the trial to EVG or RAL who then continued in the open label EVG portion of the study. This All EVG cohort includes a denominator of 505 subjects; 354 subjects who received at least one dose of blinded EVG plus 151 RAL subjects who rolled over into open label EVG after 96 weeks. Of the 354 blinded EVG patients, 196 subjects continued into the open label portion of the trial. All EVG cohort adverse event data is cumulative and therefore includes the events which occurred during the blinded portion of the trial in addition to the new open label events.

Subjects in the All STB cohort were also included in the analysis of data from Study GS-US-236-0104. This cohort included all subjects who received at least one dose of Stribild® during the randomized or open label phases of the study. A total of 71 subjects were randomized and received at least one dose of study medication: 48 in the Stribild® group and 23 in the ATR group. Subjects were treated for 60 weeks in the randomized, double-blinded phase. At Week 60, all subjects were given the option to receive the Stribild® formulation in an open-label rollover study. Sixty two subjects were included in the All STB cohort: 48 subjects initially randomized to Stribild® and 14 ATR subjects who began open label Stribild®.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The principal source of safety data for the initial EVG review was taken from the Phase 3 Study GS-US-183-0145. Supportive safety information was provided from the Phase 1 Study GS-US-236-0101 and the Phase 2 Studies GS-US-236-105 and GS-US-183-130. Additional safety data was excerpted from the clinical review of Stribild® in which EVG is a component of this fixed dose combination.

In this safety update, updated safety information was reviewed as submitted by the sponsor for the Phase 3 Study, GS-US-183-0145 and the Phase 2 Study, GS-US-183-130. Additional information reviewed for safety analyses included submitted data from the Phase 2 Study GS-US-236-0104 and the Phase 1 Study, GS-US-236-0135.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using the MedDRA adverse event dictionary (Version 14.0 during the initial review and upgraded to MedDRA 16.0 for the safety update) and the Division of AIDS Table for Grading the Severity of Adult Adverse Events and Laboratory Abnormalities of the National Institutes of Health. Both systems are well established and acceptable as means for defining adverse clinical and laboratory events.

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7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

It was not possible to pool safety data as the Phase 2 and Phase 3 studies were conducted using different designs in different populations.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The dose and formulation selected for marketing are the EVG 85mg and 150 mg tablets. This formulation was used during the Phase 3 study, and as such is appropriate to assess the safety of the proposed dose and formulation intended for marketing.

Prior to this resubmission, a total of 629 HIV-1 infected subjects received from 10 days to 192 weeks of EVG. Of these, 361 subjects received the final formulation proposed for marketing for up to 96 weeks in the Phase 3 Study GS-US-183-145: 85 mg or 150 mg daily (depending on concomitant PI use). The safety database also includes long-term exposure data on 192 subjects (184 from prior EVG studies who received EVG and 30 from prior studies that had not received EVG) who received EVG for an additional 192 weeks in the long-term treatment Study GS-US-183-0130.

7.2.2 Explorations for Dose Response

No new analyses performed.

7.2.3 Special Animal and/or In Vitro Testing

No new information submitted.

7.2.4 Routine Clinical Testing

Routine clinical testing for adverse clinical and laboratory events was comprehensive. Adverse events, serious and non-serious, were collected beginning after the informed consent form was signed through the Safety follow-up assessment. Adverse events were recorded regardless of the suspected cause of the event. Study visits occurred at Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 (end of longest duration of dosing) and at Follow-up Weeks 4, 12 and 24. Unscheduled visits were conducted as needed to assess progression and/or resolution of events.

Safety evaluations included clinical laboratory assessments, clinical evaluation of vital signs, physical examinations, ECGs, and the subjective reporting of adverse events. For

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each adverse event, the following information was collected: description, classification of “serious” or “not serious,” date of first occurrence and date of resolution (if applicable), severity, causal relationship to study drug (possible, probable or definite), action taken, outcome, and concomitant or other treatment given. Similar requirements were in place for laboratory abnormalities as adverse events. Events were graded using the Applicant’s Grading Scale for Severity of Adverse Events and Laboratory Abnormalities as Grade 1 (mild), 2 (moderate), 3 (severe) and 4 (life-threatening).

7.2.5 Metabolic, Clearance, and Interaction Workup

No new analyses performed.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

RAL and DTG are the only other approved integrase inhibitors. The most common drug related AEs in both drugs include headache and insomnia. Both drugs include labeled warnings that hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction, including liver injury, have been reported. As noted above, psychiatric events have been reported in subjects taking integrase inhibitors or Stribild®. While events are often confounded by previous psychiatric history, illicit substance usage or life events, the raltegravir and Stribild® package inserts contain information pertaining to psychiatric events.

7.3 Major Safety Results

7.3.1 Deaths

Three deaths in EVG treated subjects were reported during the blinded portion of Study GS-US-183-0145. Two further deaths were recorded in the open label All EVG portion of the study. These included Subject 1622-4158 and Subject 2135-3251, please see below for clinical information pertaining to their deaths. Ten deaths in RAL treated subjects were reported during the blinded portion of the study. See Table 3 below for all of the deaths in Study GS-US-183-0145 with new deaths highlighted in bold.

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Table 4: Death Listings in GS-US-183-0145

Subject ID	Treatment Group	Cause of Death	Applicant's Assessment of Relatedness to Study Drug	Day of Last Study Drug	Study Day of Death
0566-3310*	EVG	Cardiac failure due to ischemic cardiomyopathy	No	Day 831	Day 831
0595-4154	EVG	Hepatic failure due to Hepatitis C	No	Day 187	Day 244
1555-4095*	EVG	Peritonitis due to Intestinal perforation	No	Day 263	Day 284
1622-4158*	EVG	Shock	No	Day 1310	Day 1311
2135-3251	EVG	Diffuse Large B cell lymphoma	No	Day 661	Day 1015
0359-3353*	RAL	Choking by foreign body	No	Day 226	Day 226
0637-3051*	RAL	Acute heroin intoxication	No	Day 288	Day 306
0744-3151	RAL	Hodgkin's lymphoma and sepsis	No	Day 676	Day 725
1543-3294	RAL	Cardiomegaly, mitral valve prolapse	No	Day 279	Day 312
1925-3341*	RAL	Trauma due to auto accident	No	Day 1	Day 5
2140-3229*	RAL	Severe autoimmune anemia	Yes	Day 37	Day 45
2493-3396*	RAL	Possible acute coronary event	Yes	Day 139	Day 147
2493-3472*	RAL	Cardiac arrest	Yes	Day 43	Day 44
3718-4100*	RAL	Non-Hodgkin's lymphoma	No	Day 485	Day 485
4024-4043*	RAL	Biliary sepsis related to small cell/neuroendocrine tumor	No	Day 1023	Day 1040

*Treatment-emergent: death event occurred after day 1 of dosing to <30 days after stopping study medication

Subject 1622-4158, a 46 year old white male with a history significant for virologic failure, CMV choreoretinitis, anxiety, polyneuropathy, Kaposi's sarcoma, esophageal candidiasis, cryptosporidium and depression, pneumonia and septic shock, and steatohepatitis. The subject was receiving darunavir, etravirine, clonazepam, trimethoprim/sulfamethoxazole, paroxetine, and metformin prior to randomization. He

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was randomized to elvitegravir and ritonavir on (b) (6). The patient was admitted to the emergency room presenting with respiratory distress and impairment of consciousness on (b) (6). He was placed on mechanical ventilation and a chest x-ray showed multifocal pneumonia. He was moved to the intensive care unit (ICU) where he presented with progressive desaturation and hemodynamic instability, respiratory metabolic acidosis and anuric renal failure. He developed refractory hypoxemia and hemodynamic instability and finally bradycardia and asystole. The patient died (b) (6). An autopsy was not performed. The cause of death was refractory shock and the investigator assessed the relationship to study drug for all events as not related.

Subject 2135-3251 was a 62 year old Hispanic male with a history significant for diabetes mellitus, hypertension, Hepatitis B and C, HIV lipodystrophy, common warts, and hypercholesterolemia. The subject was receiving metformin, lisinopril and pravastatin prior to randomization. He was randomized to elvitegravir and ritonavir on (b) (6) with a background regimen of etravirine and darunavir. The patient was hospitalized due to complaints of persistent hiccups, intermittent chest pain and stabbing localized to his left side and ribs lasting several hours, night fevers, night sweating, and a 15 pound weight loss in the last 3-4 months. Imaging obtained and showed splenomegaly, cholelithiasis, and lymphadenopathy that was consistent with a suspected lymphoma. Biopsy confirmed diffuse large B cell lymphoma. The patient received a cycle of treatment with cytarabine but had no response and died on (b) (6). The investigator assessed the relationship to study drug as not related.

Eleven subject deaths in Study GS-US-183-0130 were reported in the initial NDA submission. Causes of death included: subdural hematoma following recreational drug overdose, PCP resulting in respiratory failure, presumed autoerotic asphyxiation, perforated ulcer, colorectal carcinoma, sepsis, occlusive coronary arterial sclerosis with dilated cardiomyopathy, killed by strangulation, PML, Hodgkin's lymphoma, and advanced HIV disease. None of the deaths were considered related to study drug.

One new death was reported in Study GS-US-183-0130. Subject 2675-2036 was a 44 year old Hispanic male with a history significant for HIV disease, chronic hepatitis and Kaposi's sarcoma in both lower extremities treated with radiation in 1993. Concomitant medications included amitriptyline, lansoprazole, clonazepam, testosterone, alprazolam, fluticasone and acyclovir. The subject was receiving a background HIV regimen of tenofovir DF and darunavir. He was randomized to elvitegravir and ritonavir on (b) (6). In July of 2011 he complained of severe lumbar pain with lymph node biopsy later confirming Hodgkin's lymphoma. He expired on (b) (6). The investigator assessed the events of Hodgkin's lymphoma to be serious due to hospitalization but not related to study drug or study procedure, but rather related to study disease.

No deaths were reported in Studies GS-US-236-0104 or GS-US-236-0135.

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7.3.2 Nonfatal Serious Adverse Events

SAEs were experienced in a total of 109/505 (21.6%) subjects in the All EVG cohort of Study GS-US-183-0145. This includes 29 new subjects with a majority of new SAEs in the SOC of Infections and Infestations. Two new SAEs of interest occurred in the SOC of Psychiatric Disorders, including a suicide attempt and an episode of acute psychosis. During the blinded portion of the study, 73/354 (20.6%) of EVG subjects had a SAE compared to 86/358 (24%) of RAL subjects.

Four SAEs were reported as related to the study drug during the blinded portion of the study. Relatedness of SAEs in the All EVG cohort was not able to be determined from the aggregate information submitted although 2 new related SAEs were determined from a review of new case report forms. These included pancreatitis and acute myocardial infarction.

In Study GS-US-183-0130, 82 subjects (42.7%) experienced treatment emergent SAEs, an increase of ten subjects from the time of the original NDA submission. Of the newly experienced SAEs, an increase of more than 1% only occurred in the SAEs of atrial fibrillation (1.6% increase), myocardial infarction and acute myocardial infarction (combined 1.5%) and pneumonia (1.6%). None of the newly reported SAEs were classified as related to study drug.

In Study GS-US-236-0104, 9 subjects (14.5%) in the All STB cohort experienced treatment emergent SAEs, an increase of four subjects from the time of the original NDA submission. Of the newly experienced SAEs, three new SAEs were submitted in the SOC of Infections and Infestations and included 2 reports of appendicitis and one report of pneumonia. No information regarding relatedness of study drug was submitted for the events in GS-US-236-0104.

No SAEs were reported in Study GS-US-236-0135.

7.3.3 Dropouts and/or Discontinuations

Six EVG subjects discontinued study drug due to an adverse event in the initial blinded portion of Study GS-US-183-0145 as compared to 9 RAL treated subjects. In the All EVG cohort, 1 further subject discontinued study drug secondary to an AE of pancreatitis which was classified as related to study drug while two further subjects discontinued in Study GS-US-183-0130 (acute myocardial infarction and nausea). The SAE of nausea was classified as related to study drug while myocardial infarction was not. Two further subjects in Study GS-US-236-0104 discontinued study drug due to adverse events; one with hepatitis C and one with decreased creatinine clearance. No information was submitted regarding the relatedness of the discontinuation due to hepatitis C but the discontinuation secondary to decreased creatinine clearance was

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reported as secondary to study drug. Five subjects in Study GS-US-236-0135 discontinued study drug due to adverse events of maculopapular rash (4 subjects) and vomiting (1 subject). All of the events in Study GS-US-236-0135 were considered related to study drug.

7.3.4 Significant Adverse Events

Information on graded adverse events was not submitted with this re-submission. For information on significant adverse events please see the initial NDA review.

7.3.5 Submission Specific Primary Safety Concerns

Psychiatric adverse events have been evaluated in multiple studies of integrase inhibitors including the Stribild® and dolutegravir studies and post marketing analysis of raltegravir. For discussion of these evaluations please see Dr. Viswanathan's Stribild® review (NDA 203100-Supplement-10) and the dolutegravir review (NDA 204790) by Drs. Mullick, Carter and Belew.

During this re-submission review, psychiatric events of interest both in the previously submitted blinded portion and the newly submitted All EVG open label portion of Study GS-US-183-0145 and full data from GS-US-183-0130 were evaluated. Case report forms were evaluated for all psychiatric SAEs and discontinuations due to psychiatric events.

True comparison of psychiatric adverse events in EVG treated versus RAL treated subjects was challenging as these agents are both integrase inhibitors and as such may have a similar rate and pattern of psychiatric events. After review of psychiatric events in both treatment groups, a majority of events were found to be confounded by previous history of psychiatric disorder/psychiatric medication or illicit substance usage and/or significant life event at time of SAE or discontinuation.

In Study GS-US-183-0145, during the blinded portion of the study, 3 EVG subjects (0.8%) had SAEs of suicidal ideation while 4 RAL subjects (1.1%) had suicidal ideation SAEs. None were reported as related to study drug by the investigator. In the blinded portion of the study, 2 RAL subjects (0.6%) had SAEs of suicide attempt while 2 subjects (0.4%) on open label EVG in the All EVG cohort had SAEs of suicide attempts. None were reported as related to study drug by the investigator.

As can be seen from the following example, determination of study drug relatedness is challenging due to confounding psychiatric illnesses and life events which complicate the clinical cases.

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Subject 2880-5016: 16 year old HIV infected female enrolled in Study GS-US-183-0130 who commenced EVG on (b) (6). The subject had no history of mental illness but did carry a diagnosis of attention deficit hyperactivity disorder (ADHD). Her concomitant medications included sumatriptan and Adderall XR. She presented to a healthcare provider approximately 14 months after beginning study drug with symptoms of fearful, angry mood and was noted to have difficulties with decision making during the clinic visit. After the clinic visit, she attempted suicide with an overdose of prescription and over the counter medications. Multiple life stressors were reported by the investigator at the time of the event including previous parental death from HIV and environmental stressors of abuse in the home, change in caregiver, relocation and change of school. The suicide attempt was reported as not related to study drug but related to life stressors. No change in study drug was reported.

Common psychiatric AEs included depression in 32 blinded EVG subjects (9%), 33 RAL subjects (9.2%) and 41 All EVG subjects (8.1%) and insomnia in 26 blinded EVG subjects (7.3%), 21 RAL subjects (5.9%) and 36 All EVG subjects (7.1%).

No blinded EVG or All EVG subject discontinued study drug secondary to a psychiatric AE while one RAL subject discontinued due to substance abuse.

In Study GS-US-183-0130, 2 subjects (1%) each experienced SAEs of depression and mental status change. Neither event was related to study drug by the investigator. Common adverse events of depression, insomnia and anxiety were experienced in 31 (16.1%), 25 (13%), and 22 (11.5%) subjects, respectively. One subject discontinued due to mental status changes but the event was not related to study drug per the investigator.

No deaths were reported as related to psychiatric adverse events in either study.

Currently, the Raltegravir label includes the following statement:

Psychiatric events including depression (particularly in subjects with a pre-existing history of psychiatric illness), suicidal ideation and behaviors have been observed in treatment-naïve and treatment experienced subjects

The Stribild® label includes the following statement:

Additional adverse drug reactions observed with Stribild® included suicidal ideation and suicide attempt (0.3%), all in subjects with a pre-existing history of depression or psychiatric illness.

Despite the confounded nature of the reported events, similar psychiatric events have been seen in Stribild® and in other integrase inhibitors. Because of the concern for psychiatric events occurring in these integrase inhibitor treated subjects, especially

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those with a pre-existing history of psychiatric illness, the label will be updated to contain similar language to the current Stribild® and raltegravir package inserts.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

TEAEs were experienced in 446/505 (88.3%) subjects in the All EVG cohort of Study GS-US-183-0145. This includes 125 subjects experiencing new TEAEs with a majority of new TEAEs in the SOC of Infections and Infestations, Gastrointestinal Disorders and Musculoskeletal and Connective Tissue Disorders. The most commonly reported TEAEs in the All EVG cohort includes: diarrhea (28.3%), upper respiratory infection (20.6%), headache (11.3%), nausea (11.1%) and back pain (11.1%). In the SOC of interest, Psychiatric Disorders, 31 new TEAEs were reported including 9 new episodes of depression and 10 new episodes of insomnia. Data was not presented in this re-submission for other TEAEs in the SOC of Psychiatric Disorders. During the blinded portion of the study, 321/354 (90.7%) of EVG subjects had a TEAE compared to 320/358 (89.4%) of RAL subjects.

In Study GS-US-183-0130, 180 subjects (93.8%) experienced TEAEs, an increase of three subjects from the time of the original NDA submission. Of the newly experienced TEAEs, the SOC which accrued the most new TEAEs included Gastrointestinal Disorders, Psychiatric Disorders and Metabolism and Nutrition Disorders. The most commonly reported TEAEs in this study included upper respiratory infection (31.3%), diarrhea (24.5%), sinusitis (24.5%) and bronchitis (21.4%). In the SOC of interest, Psychiatric Disorders, 16 new TEAEs were reported including 10 new episodes of depression, 10 new episodes of insomnia and 5 new episodes of anxiety. Data was not presented in this re-submission for other TEAEs in the SOC of Psychiatric Disorders.

In Study GS-US-236-0104, 59 subjects (95.2%) in the All STB cohort experienced TEAEs, an increase of 2 subjects from the time of the original NDA submission. Of the newly experienced TEAEs, the SOC of Neoplasms Benign, Malignant and Unspecified, Renal and Urinary Disorders and Respiratory, Thoracic and Mediastinal Disorders accrued the most new TEAEs. Of note, the renal events in this study are not felt to be secondary to EVG but more likely secondary to other components of Stribild®.

Study GS-US-236-0135 paired Stribild® and telaprevir and thus attribution of TEAEs to EVG are not possible with the data presented.

7.4.2 Laboratory Findings

No new laboratory data submitted.

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7.4.3 Vital Signs

No new vital sign data submitted.

7.4.4 Electrocardiograms (ECGs)

No new ECG data submitted.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

No new immunogenicity data submitted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No information was submitted in this re-submission in regard to dose dependency and analysis was not possible on aggregate data.

7.5.2 Time Dependency for Adverse Events

Adverse events occurred at all times during open label treatment and no pattern of adverse events could be determined from aggregate data submitted.

7.5.3 Drug-Demographic Interactions

No new drug-demographic data submitted.

7.5.4 Drug-Disease Interactions

No new drug-disease data submitted.

7.5.5 Drug-Drug Interactions

Study GS-US-216-0125 evaluated the interaction of cobicistat boosted EVG and methadone or buprenorphine/naloxone and GS-US-236-0135 evaluated the interaction of Stribild® and telaprevir. Please see the Clinical Pharmacology review of these studies for full detail.

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7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new human carcinogenicity data was submitted. Preclinical testing demonstrated that EVG is not carcinogenic. Please see the original Pharmacology/Toxicology review by Pritam Verma, Ph.D. for full details.

7.6.2 Human Reproduction and Pregnancy Data

No new human reproduction or pregnancy data was submitted. One new pregnancy was reported in Study GS-US-183-0130 but this pregnancy ended in elective termination. No new pregnancies were reported in Studies GS-US-183-0145, GS-US-236-0104 or GS-US-236-0135.

Animal studies did not indicate direct or indirect harmful effects of EVG with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. Please see the original Pharmacology/Toxicology review by Pritam Verma, Ph.D. for full details.

7.6.3 Pediatrics and Assessment of Effects on Growth

No pediatric information was submitted with this re-submission. Please see the original review for details of the proposed pediatric investigational plan at the time of initial submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information submitted regarding overdose potential.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

EVG is currently approved in the EU, Norway, Iceland, Canada and Australia. EVG is a component of the fixed dose combination Stribild® which was approved in the US on 27 August 2012. Please see Dr. Viswanathan's Stribild® review (NDA 203100-Supplement-10) for full details of postmarket experience with the fixed dose combination.

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9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

Final labeling changes are pending at the time of this review but most labeling negotiations were completed prior to the Complete Response. As mentioned, we intend to include information similar to the Stribild® and raltegravir package inserts regarding Psychiatric AEs.

9.3 Advisory Committee Meeting

None.

9.4 Financial Disclosure Form

Please see the previously completed financial disclosure section of the initial NDA review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY C MARTIN

09/04/2014

LINDA L LEWIS

09/04/2014

I concur with Dr. Martin's review and conclusions.

Decisional Review for NDA 203093

Date	April 26, 2013
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA #	NDA 203093/Original Submission
Supp #	
Proprietary / Established (USAN) names	Vitekta [™] Elvitegravir (EVG)
Dosage forms / strength	EVG 85 mg once daily coadministered with: Atazanavir 300 mg/ritonavir 100 mg once daily Lopinavir 400 mg/ritonavir 100 mg twice daily EVG 150 mg once daily coadministered with: Darunavir 600 mg/ritonavir 100 mg twice daily Fosamprenavir 700 mg/ritonavir 100 mg twice daily Tipranavir 500 mg/ritonavir 200 mg twice daily
Proposed Indication(s)	For use in combination with other antiretroviral therapy for the treatment of HIV-1 infection in adults who are antiretroviral treatment-experienced (b) (4)
Action	Complete Response

1. Introduction to Review: This Division Director's memorandum provides an overview of NDA 203093 for Gilead Sciences' New Drug Application (NDA) for Vitekta (EVG), an integrase strand transfer inhibitor (INSTI) for use in combination with a ritonavir-boosted protease inhibitor (PI/r) for the treatment of HIV-1 infection in adults who are antiretroviral treatment-experienced (b) (4)

This decisional review summarizes clinical trial results from principle Phase 3 Trial 145 that was a multicenter, randomized, double-blind, double-dummy trial of the safety and efficacy of EVG in combination with PI/r and other antiretroviral agents (ARVs) compared to another INSTI, raltegravir in antiretroviral treatment-experienced adult patients who were able to construct a regimen utilizing a boosted protease inhibitor; other pertinent findings from the multidisciplinary reviews will be highlighted. Requested post-marketing studies and product labeling are also summarized.

2. Background/Regulatory History/Previous Actions/Foreign

Regulatory Actions/Division of Scientific Investigations (DSI) Status:

The NDA for EVG was submitted and received on June 27, 2012. EVG is an INSTI that requires concomitant administration with a fully active protease inhibitor in the treatment-experienced population to attempt to prevent emergence of resistance along with a potent CYP3A inhibitor such as ritonavir to increase EVG exposures

because EVG undergoes CYP3A-mediated hydroxylation. The dosage of EVG is 85 mg once daily when coadministered with atazanavir 300 mg/ritonavir 100 mg once daily or lopinavir 400 mg/ritonavir 100 mg twice daily. The dosage of EVG is 150 mg once daily when coadministered with darunavir 600 mg/ritonavir 100 mg twice daily, fosamprenavir 700 mg/ritonavir 100 mg twice daily or tipranavir 500 mg/ritonavir 200 mg twice daily.

EVG is also a component of STRIBILD, a fixed-dose combination of four drugs – EVG/cobicistat/emtricitabine/tenofovir disoproxil fumarate for use as a single treatment regimen in treatment-naïve HIV-1 infected patients; STRIBILD was approved in August 2012. CMC, non-clinical and clinical data from the STRIBILD NDA were also used to support the EVG NDA. EVG will only be indicated with a PI/r for a treatment-experienced population because there are no pharmacokinetic or clinical data evaluating VITEKTA with cobicistat as single entities compared to STRIBILD.

The application was granted a 10-month standard review because there are already multiple regimens available for treatment-experienced patients including an INSTI-based regimen with raltegravir (RAL).

Three clinical trial sites were audited by the Division of Scientific Investigations (DSI). The trial sites were selected for review based on the numbers of patients enrolled per site. Per Dr. Antoine El-Hage, DSI, applicable statutory requirements and FDA regulations governing the conduct of clinical trials and the protection of human subjects were followed.

3. Chemistry/Manufacturing/Controls (CMC): The CMC reviewers of the EVG NDA are: Drs. Celia Cruz, Milton Sloan, and Kareen Riviere. Drs. Rapti Madurawe and Sandra Suarez supervised the CMC review with Dr. Stephen Miller serving as CMC-Lead. The CMC team could not recommend approval of the EVG NDA at the time of completion of the CMC reviews due to the pending establishment evaluation. The Gilead Sciences (Foster City, CA) manufacturing facility site was subsequently inspected in April 2013. Some deficiencies identified during the inspection include, but are not limited to: 1) assay methods for commercial release and stability testing for EVG 85mg and 150mg were not validated adequately; 2) dissolution methods for commercial release and stability testing were not validated adequately; 3) (b) (4) test methods for release of EVG drug substance were not validated; 4) not all validation data for (b) (4) test methods for release and stability were available upon request; and 5) there were no validation reports for the release and stability test methods for the clinical and primary stability batches

Specifically, under 21 CFR 314.125 (b)(13), parts 210 and 211, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with current good manufacturing practice regulations. Further, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing,

or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability under 21 CFR 314.125 (b)(1). Thus, a withhold approval recommendation was made by the Office of Compliance. This forms the basis for the Complete Response regulatory decision.

4. Pharmacology/Toxicology: No new non-clinical data were submitted with this NDA. The EVG pharmacology and toxicology data have previously been reviewed during the STRIBILD NDA review by Drs. Pritam Verma and Mark Powley with supervisory concurrence by Dr. Hanan Ghantous. Their conclusions, as reflected in the product labeling are below.

Animal Data

EVG studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. In offspring from rat and rabbit dams treated with elvitegravir during pregnancy, there were no toxicologically significant effects on developmental endpoints. The exposures (AUC) at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 23 and 0.2 times higher than the exposure in humans at the recommended daily dose of 150 mg.

EVG is a pregnancy category B drug based on animal data as there are no adequate and well-controlled studies in pregnant women. The labeling states that healthcare providers are encouraged to register patients in the Antiretroviral Pregnancy Registry and monitor fetal outcomes of pregnant women exposed to Stribild. Further, because animal reproduction studies are not always predictive of human response, Stribild should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. EVG did not affect fertility in male and female rats at exposures approximately 16- and 30-fold higher exposures (AUC), respectively, than in humans at the therapeutic 150 mg daily dose.

The following wording related to EVG carcinogenicity and mutagenesis is included in product labeling:

Long-term carcinogenicity studies of were carried out in mice (104 weeks) and in rats for up to 88 weeks (males) and 90 weeks (females). No drug-related increases in tumor incidence were found. EVG was not genotoxic in the reverse mutation bacterial test (Ames test) and the rat micronucleus assay. In an *in vitro* chromosomal aberration test, EVG was negative with metabolic activation; however, an equivocal response was observed without activation.

5. Clinical Pharmacology: The Office of Clinical Pharmacology reviewers were Drs. Leslie Chinn, Dhananjay Marathe, Jeffry Florian and Islam Younis.

Sixteen clinical trials using EVR/r were submitted in the EVG NDA. Gilead Sciences also provided a right of reference to the STRIBILD NDA. The proposed dose of EVG depends upon the PI/r with which it is concurrently administered. For example, EVG 85 mg once daily is coadministered with atazanavir 300 mg/ritonavir 100 mg once daily or lopinavir 400 mg/ritonavir 100 mg twice daily. EVG 150 mg once daily is coadministered with darunavir 600 mg/ritonavir 100 mg twice daily, fosamprenavir 700 mg/ritonavir 100 mg twice daily, or tipranavir 500 mg/ritonavir 200 mg twice daily. The lower EVG dose of 85 mg is required due to UGT1A1/3- mediated pharmacokinetic interaction between EVG and lopinavir or atazanavir boosted with ritonavir. EVG should be taken with food because the boosted PIs require administration with food. Race and gender did not impact the pharmacokinetics of EVG/r.

Use of EVG/r in special populations is described in labeling. Specifically, no clinically relevant differences in EVG pharmacokinetics were observed between subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min) and healthy subjects in a clinical trial. No dose adjustment of EVG is required for patients with renal impairment. Further, in a clinical trial, no clinically relevant differences in elvitegravir pharmacokinetics were observed between subjects with moderate hepatic impairment (Child-Pugh Class B) and healthy subjects. Therefore, dosage adjustment of EVG is not necessary for patients with mild-to-moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of EVG has not been studied. With regard to co-infected patients, limited data from population pharmacokinetic analysis (N=56) indicated that hepatitis B and/or C virus infection had no clinically relevant effect on the exposure of EVG/r.

Since EVG is primarily metabolized by CYP3A, coadministration of EVG with drugs that induce CYP3A may result in decreased plasma concentrations of EVG and reduced therapeutic effect. The effects of coadministered drugs on the exposure of EVG/r are shown in Table 5 of labeling and the effects of EVG/r on the exposure of coadministered drugs are shown in Table 6 of labeling. No clinically significant interactions were observed between EVG and abacavir, emtricitabine, etravirine, famotidine, omeprazole, stavudine, tenofovir disoproxil fumarate, or zidovudine in drug interaction studies conducted with EVG/r. Established and potentially significant drug interactions are described in Table 4 in labeling. For example, there are no data available to make dosing recommendations for coadministration of EVG with doses of darunavir other than 600/100 mg twice daily.

A relatively flat exposure-response efficacy relationship was identified across EVG exposures (AUC_{tau} Q1-Q3 of 13641-21254 ng·hr/mL; C_{tau} Q1-Q3 of 1128-1584 ng/mL). No significant covariates, such as baseline viral load, were identified as predictive of response across the EVG exposures. No exposure-response relationships were observed between predicted EVG AUC_{tau} or C_{tau} and adverse events of interest.

The Applicant conducted a thorough QT study with EVG/r in 126 healthy subjects. This study was reviewed by the FDA's Interdisciplinary Review Team for QT Studies (IRT). The IRT concluded EVG's effect on QTc prolongation was below the threshold for regulatory concern and there appeared to be no clinically relevant effects on PR and QRS intervals.

(b) (4)

6. Clinical Virology: Please see extensive review by Dr. Sung Rhee with supervisory concurrence by Dr. Jules O'Rear. Resistance and cross-resistance wording appears in product labeling. Primary EVG resistance-associated integrase substitutions include T66A/I/K, E92G/Q, T97A, S147G, Q148H/K/R and N155H. In addition, E92A, F121C/Y, P145S, Q146I/L/R, and N155S substitutions were also occasionally observed in EVG virologic treatment failure subjects and were shown to confer reduced susceptibility to EVG. In treatment-experienced subjects from Study 145, emerging primary EVG resistance-associated substitutions T66A/I, E92G/Q, T97A, S147G, Q148R, or N155H were observed in 23 of the 74 subjects with evaluable genotypic data by week 96. Post-baseline virus isolates harboring primary EVG resistance-associated substitutions had median decreases in susceptibility to EVG of 8-fold (N=29, ranging from 2- to > 158-fold) and of 5-fold (N=26, ranging from 1- to > 58-fold) compared to wild-type reference HIV-1 and to their respective baseline isolates, respectively.

Cross-resistance within the INSTI class was observed. HIV-1 variants harboring EVG resistance substitutions remained susceptible to other drug classes. The following wording appears in product labeling:

EVG-resistant viruses showed varying degrees of cross-resistance in cell culture to RAL in the INSTI class depending on the type and number of substitutions in HIV-1 integrase. Of the primary EVG resistance-associated substitutions tested (T66A/I/K, E92G/Q, T97A, S147G, Q148H/K/R, and N155H), all but three (T66I, E92G, and S147G) conferred >1.5-fold reduced susceptibility to RAL when introduced individually into a wild-type virus by site-directed mutagenesis. Of the primary RAL resistance-associated substitutions tested (Y143C/H/R, Q148H/K/R, and N155H), all but one (Y143H) conferred > 2.5-fold reductions in susceptibility to EVG (above the biological cutoff for EVG).

7. Efficacy and Safety: Clinical and statistical reviews were conducted by Clinical Analyst Russell Fleischer and Dr. Lei Nie. Dr. Linda Lewis supervised the clinical review and Dr. Greg Soon provided secondary statistical review. The NDA for EVG is based on data from 702 subjects. The initial Phase 3 program consisted of two identically designed trials (Trials 144 and 145) in treatment-

experienced adult HIV-1 subjects that only differed by geographic location. These trials were later combined into a single trial, Trial 145. Supportive Phase 2 data, as well as data from the STRIBILD NDA were also reviewed.

Trial 145 was a randomized, double-blind, active-controlled trial, where subjects were randomized in a 1:1 ratio to receive either EVG (150 mg or 85 mg) once daily or raltegravir 400 mg twice daily, each administered with a background regimen (BR) containing a fully active PI/r and a second agent. The BR was selected by the investigator based on genotypic/phenotypic resistance testing and prior antiretroviral treatment history. Randomization was stratified by geographic area (US and Puerto Rico or Europe, Australia, Canada, and Mexico), screening HIV-1 RNA level ($\leq 100,000$ copies/mL or $>100,000$ copies/mL) and the class of the second agent (NRTI or other classes). The noninferiority margin was 10%. The protocol-defined primary endpoint was the percentage of subjects who achieved HIV-1 RNA < 50 copies/mL through treatment week 48, however 96-week efficacy data were reviewed for durability of efficacy and included in labeling in this ongoing 144-week trial.

Disposition of enrolled subjects was as follows: 724 randomized to EVG or RAL groups, 12 subjects never received study drugs, and 10 additional subjects were excluded from efficacy analyses due to multiple protocol violations at one site. This resulted in a final efficacy population of 351 subjects in each treatment arm. By week 96, approximately 40% of subjects discontinued from the trial. The most common reasons were noncompliance and lost-to-follow-up.

Treatment outcomes through 96 weeks are presented in Table 7 in labeling as highlighted below.

Table 7 Virologic Outcome of Randomized Treatment of Trial 145 at Week 96

	Week 96	
	EVG + BR (N=351)	RAL + BR (N=351)
HIV-1 RNA < 50 copies/mL	52%	53%
HIV-1 RNA ≥ 50 copies/mL	36%	31%
No Virologic Data at Week 96 Window	12%	16%
Discontinued Study Drug Due to AE or Death	3%	7%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	8%	9%
Missing Data During Window but on Study Drug	1%	1%

Results of this trial are comparable to other development programs in a similar population. This was a treatment-experienced population who had a mean duration of prior HIV-1 treatment of 9.4 years. Greater than one-third of subjects had an AIDS diagnosis. Only 17% of subjects had no known resistance mutations at baseline. Although about 80% of subjects had a baseline phenotypic and genotypic sensitivity score >2 , this could represent drugs with only partial susceptibility as the second agent. The second agent could have also come from the nucleoside class in addition to the requirement for susceptibility to a boosted PI. Notably, higher response rates were observed for the subgroup of subjects with baseline HIV RNA $\leq 100,000$ copies/ml (EVG 65.5% compared to 64.4% for RAL). Higher response rates were also observed for the subgroup of subjects with baseline CD4 count > 200 cells/mm³ (EVG 69.8% compared to 68.1% for RAL).

In Trial 145, immunologic benefits based on CD4 count were comparable between treatment arms. The mean increase from baseline in CD4+ cell count at Week 96 was 205 cells/mm³ in the EVG-treated subjects and 198 cells/mm³ in the RAL-treated subjects.

The drop-out rates for this trial over 96 weeks were higher than expected. Approximately one-third of subjects failed virologically. A likely explanation relates to the difficulty of taking a regimen requiring a ritonavir-boosted protease inhibitor. This conclusion is supported by the finding that the majority of samples sent for resistance testing in subjects who failed virologically had wild-type virus without any new HIV-1 mutations. This is also supported by the finding that 44% of subjects in Trial 145 had one or more EVG concentrations below the level of quantitation. Similar findings were seen in a trial of HIV-infected adolescents receiving 85 mg or 150 mg of EVG plus PI/r. Although the adolescents studied had exposures comparable to or slightly higher than those observed in adults, 8/9 subjects (88%) continuing the EVG regimen had multiple EVG concentration samples below the limit of quantification during the 48-week treatment phase, suggesting lack of continued adherence to the regimen.

Thirteen subjects died during Trial 145: 3 in the EVG arm and 10 in the RAL arm. Causes of death and relatedness to study drugs were assessed by the clinical reviewer and described in his review. Subjects receiving EVG died of ischemic cardiomyopathy, hepatic failure in the setting of chronic hepatitis C infection and peritonitis; none was thought to be related to EVG.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety assessment of EVG is primarily based on data from Trial 145, in which 712 HIV-1 infected, antiretroviral treatment-experienced adults received

EVG (N=354) or RAL (N=358), each administered with a background regimen consisting of a fully active PI/r and other antiretroviral agents for at least 96 weeks. The proportion of subjects who discontinued study treatment due to adverse events, regardless of severity, was 3% in the EVG group and 4% in the RAL group. The most common adverse reaction occurring in subjects receiving EVG in Study 145 was diarrhea. Also see Table 2 in product labeling for the frequency of adverse reactions occurring in at least 2% of subjects in any treatment group in Study 145. Treatment-emergent adverse drug reactions that occurred in less than 2% of subjects treated with EVG included abdominal pain, vomiting, dyspepsia, fatigue, depression, insomnia and rash. Suicidal ideation and suicide attempt occurred in less than 1% of patients receiving EVG, all of whom had a pre-existing history of depression or psychiatric illness.

Treatment-emergent laboratory abnormalities (Grades 3-4), occurring in at least 2% of subjects in either treatment group in Study 145, is presented in Table 3 in labeling and below.

Table 3 Laboratory Abnormalities (Grades 3-4) Reported in $\geq$ 2% of Subjects in Either Treatment Group in Study 145 (Week 96 analysis)

Laboratory Parameter Abnormality	EVG N=354	RAL N=358
ALT ($> 5.0 \times$ ULN)	2%	5%
AST ($> 5.0 \times$ ULN)	2%	6%
Total Bilirubin ($> 2.5 \times$ ULN)	6%	9%
GGT ($> 5.0 \times$ ULN)	3%	7%
Serum Amylase ^a ($> 2.0 \times$ ULN)	6%	6%
Total Cholesterol (> 300 mg/dL)	5%	5%
Creatine Kinase ($\geq 10.0 \times$ ULN)	6%	4%
Hematuria (> 75 RBC/HPF)	6%	7%
Neutrophils ($< 750/\text{mm}^3$)	3%	3%
Hyperglycemia (> 250 mg/dL)	5%	3%
Total Triglycerides (> 750 mg/dL)	5%	4%
Urine Glucose (4+)	4%	3%

a. For subjects with serum amylase $> 1.5 \times$ upper limit of normal, lipase test was also performed. The frequency of increased lipase (Grades 3-4) occurring in VITEKTA (N=66) and raltegravir (N=58) treatment groups was 14% and 7%, respectively.

8. Postmarketing Requirements (PMR): The following PREA PMR will be requested to address the development of EVG for the pediatric population:

We are waiving the pediatric study requirement for ages 0 to less than 4 weeks because necessary studies are impossible or highly impracticable because few patients in this age group will have need of a regimen intended for treatment-experienced patients and the co-administered protease inhibitors are not approved in this age group.

We are deferring submission of your pediatric study for ages 4 weeks to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

This required study is listed below.

2030-1 Evaluate the pediatric pharmacokinetics (PK), safety, and antiviral activity of once daily elvitegravir combined with a background regimen including a protease inhibitor coadministered with ritonavir in HIV-1 treatment-experienced pediatric subjects from 4 weeks to less than 18 years of age. Initial evaluation of elvitegravir exposure (when combined with a protease inhibitor/ritonavir) must be performed to allow dose selection and agreed upon with the FDA. Evaluation of longer term treatment with elvitegravir, plus background regimen including protease inhibitor/ritonavir, must assess treatment response on the basis of HIV-1 RNA virologic response and conduct safety monitoring over at least 24 weeks of dosing.

Protocol Submission: July 31, 2013
Trial Completion: April 31, 2017
Final Report Submission: November 31, 2017

(b) (4)

9. Advisory Committee: This NDA was not presented before the Antiviral Products Advisory Committee because it was the second INSTI in the class.

Conclusions and Recommendations: I am in agreement with the conclusions of the reviewers that the risk-benefit ratio favors approval of EVG as part of an antiretroviral regimen in HIV-1 infected treatment-experienced adults pending satisfactory resolution of facility inspection deficiencies and product quality concerns regarding the release and stability data contained in this NDA. Notably, although pivotal trial 145 demonstrated noninferiority to a RAL-based regimen, adherence to an EVG-based regimen in this patient population appears to be encumbered by the need for concomitant use of a ritonavir-boosted protease inhibitor.

This application will receive a complete response based on findings during a facility inspection that cannot be corrected during this review cycle and a recommendation to withhold approval by CDER's Office of Compliance.

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/s/

DEBRA B BIRNKRANT
04/26/2013

CLINICAL REVIEW

Application Type	NDA
Application Number	203093
Priority or Standard	Standard

Submit Date(s)	06/27/2012
Received Date(s)	07/02/2012
PDUFA Goal Date	04/27/2013
Division / Office	DAVP/OAP

Reviewer Name	Russell Fleischer, PA-C, MPH
Review Completion Date	03/21/2013

Established Name	Elvitegravir
Trade Name	Vitekta®
Therapeutic Class	HIV-1 Integrase Inhibitor
Applicant	Gilead Sciences, Inc.

Formulation(s)	85 and 150 mg tablets
Dosing Regimen	85 or 150 mg QD in combination with ritonavir and other antiretroviral agents
Indication	Treatment of HIV-1 infection in treatment-experienced adults
Intended Population	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The antiviral efficacy and safety data reviewed in this NDA support the recommendation that Vitekta® (elvitegravir, EVG), and HIV-1 integrase inhibitor, be approved as a choice for treatment of antiretroviral treatment experienced adults when co-administered with a ritonavir-boosted protease inhibitor and other antiretroviral agents.

1.2 Risk Benefit Assessment

Benefits

The recommendation to approve EVG co-administered with a ritonavir boosted protease inhibitor in treatment experienced adults is based on the results of a single Phase 3 and a supportive Phase 2 study which demonstrate comparable antiviral activity to an optimized background regimen or a comparator integrase inhibitor. Ritonavir (r, RTV) is an active anti-HIV protease inhibitor and a potent inhibitor of CYP3A4. Low doses of RTV are co-administered with protease inhibitors to increase exposures. Similarly RTV increases EVG's C_{max} and helps maintain EVG's plasma half-life thereby increasing EVG's intracellular half-life and potentiating its antiviral activity.

In the Phase 3 study, non-inferiority was demonstrated between EVG in combination with protease inhibitors boosted with ritonavir (EVG/r) and other antiretroviral agents-containing regimens and a comparator integrase inhibitor raltegravir (RAL) in combination with other antiretroviral agents. Both regimens resulted in -2.2 log₁₀ reduction from baseline in HIV-1 RNA, an increase of ~200 CD4 cells/mm³, 52% of subjects having HIV-1 RNA <50 copies/mL after 96 weeks of treatment, and similar rates of virologic failure.

In a separate study, elvitegravir exposure was generally comparable between adolescents (12-17 years of age) and adults. EVG appeared generally well tolerated in adolescents and no new patterns of adverse events were identified. Nine adolescents received 48 weeks of EVG plus a ritonavir-boosted protease inhibitor and other antiretroviral agents, and 2/9 achieved HIV-1 RNA <50 copies/mL at the end of the study. This poor outcome may be due to non-adherence as there were times when sparse pharmacokinetic sampling failed to detect elvitegravir drug levels.

(b) (4)

In summary, EVG co-administered with a RTV-boosted protease inhibitor plus other antiretroviral agents represents another choice in the treatment armamentarium available to treatment-experienced patients.

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Risks

The following safety-related issues were identified in the review of the data from the pivotal Phase 3 and supportive Phase studies:

The most common adverse events at least possibly related to EVG include: diarrhea, nausea, vomiting, abdominal distention, fatigue, back pain, headache, dizziness, dysgeusia, rash (dermatitis, drug eruption, eczema, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash popular, rash pruritic, and urticaria). The majority of these events were mild to moderate in severity. Only diarrhea occurred more often among EVG treated subjects compared to comparator regimens.

There were no clinically relevant changes in renal or hepatic function, other clinical chemistries or hematologic parameters among subjects treated with EVG.

There were no differences in the safety outcomes of adolescents compared to adults observed.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

Recommendations for Postmarket Requirements and Commitments have not been finalized at the time this review was completed.

2 Introduction and Regulatory Background

2.1 Product Information

Vitekta® is an anti-HIV integrase inhibitor that inhibits the integration of human immunodeficiency virus DNA into host chromosomal DNA. EVG was in-licensed by Gilead from Japan Tobacco Company.

EVG is primarily and rapidly metabolized by CYP3A4 thus limiting its exposures and subsequent antiviral activity. The Applicant proposed co-administration of EVG with ritonavir, which is a potent inhibitor of CYP3A that leads to increased bioavailability of EVG. RTV has antiviral activity on its own and when used at lower than therapeutic doses as a pharmacologic enhancer, must be co-administered with another protease inhibitor in order to protect against the emergence of protease associated resistance mutations.

2.2 Currently Available Treatments for Proposed Indications

There are currently 26 individual drugs, and three fixed-dose combinations of multiple drugs, approved for the treatment of HIV-1 infection. Based on the mechanism of action on the life cycle of the human immunodeficiency virus, the drugs are classified into 6 HIV-1 drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors, CCR5 antagonists, and integrase inhibitors. Table 1 summarizes the individually approved anti-retroviral drugs.

Table 1: Approved Antiretroviral Drugs

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT)	Retrovir®
	Didanosine (ddI)	Videx®/Videx EC®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Delavirdine	Rescriptor®
	Nevirapine	Viramune®
	Efavirenz (EFV)	Sustiva®
	Etravirine	Intelence®
	Rilpivirine	Edurant®
PI	Indinavir	Crixivan®
	Ritonavir	Norvir®
	Saquinavir, hard gel	Invirase®
	Saquinavir, soft gel	Fortavase®
	Nelfinavir	Viracept®
	Amprenavir	Agenerase®
	Fosamprenavir	Lexiva®
	Atazanavir (ATV)	Reyataz®
	Lopinavir/ritonavir (LPV/r)	Kaletra®
	Tipranavir (TPV)	Aptivus®
	Darunavir (DRV)	Prezista®
Fusion/Entry Inhibitor	Enfuvirtide (ENF)	Fuzeon®
CCR5 receptor antagonist	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir	Isentress®

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The three single tablet fixed-dose combinations approved for treatment of HIV-1 infection, Atripla® (efavirenz/emtricitabine/ tenofovir) approved on 12 July 2006, Complera™ (emtricitabine/rilpivirine/tenofovir) approved on 10 August 2011, and Stribild® (elvitegravir/tenofovir/emtricitabine/cobicistat approved in August 2012.

2.3 Availability of Proposed Active Ingredient in the United States

The drug substance/product is readily available in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

Raltegravir (RAL, Isentress®) is currently the only approved integrase inhibitor in the US. RAL is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment naïve and experienced patients ^{(b) (4)} years of age.

RAL may cause severe, potentially life-threatening, and fatal skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

The most common RAL-related adverse events include headache, insomnia, nausea, and fatigue. Also, thrombocytopenia, elevated fasting serum glucose, increased amylase, lipase, creatine kinase, AST, ALT, alkaline phosphatase, and bilirubin levels (due to metabolism by UGT1A1) have been reported in patients treated with RAL.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This section summarizes those notable events which had a direct bearing related to this NDA.

EVG was initially in-licensed by Gilead from Japan Tobacco Company. The IND for elvitegravir (#72,177) was submitted in April 2005. The IND opening study was determined safe to proceed. Shortly thereafter, a protocol was submitted to evaluate elvitegravir boosted with ritonavir.

In May 2006, elvitegravir was granted Fast Track status based on its potential to treat a serious and life-threatening illness, and its distinct mechanism of action.

In late 2006, the sponsor requested an EOP2 meeting based on 16-week data from an ongoing Phase 2 study of EVG in HIV-1 treatment-experienced adult patients. The meeting was cancelled based on the Division's responses to the sponsor's questions. Written comments stated that DAVP did not agree that it would be safe to initiate Phase 3 studies of EVG in HIV-1 treatment-experienced adults due to concerns about the relatively high rate of virologic failure in the EVG arms in the Phase 2 study, and the lack of complete resistance information on these failure subjects.

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DAVP requested that Week 24 virologic activity data, as well as longer term virologic failure data be submitted and reviewed to ensure that it would be appropriate to administer EVG to a larger population in a longer duration study. In addition, DAVP recommend that the Applicant conduct an additional Phase 2 study in which EVG would be co-administered with a boosted PI as a component of the OBT to provide evidence of a more acceptable virologic failure rate.

Also, DAVP requested a more detailed assessment of safety including narratives of SAEs, and reconciliation of the total number of patients and their outcomes with Grade 3 or 4 hematuria and CK increases.

In May 2007, the Applicant requested a second EOP2 meeting. The Applicant's position was based on the results of analyses of 24-week data from Study GS-US-183-0105 showing that subjects receiving 2 or more active drugs in their background regimen had an acceptable virologic failure rate, initiation of Phase 3 studies was warranted.

Again the Division did not agree that initiation of Phase 3 studies was appropriate due to concerns about the level of anti-HIV activity in patients who received EVG in the ongoing Phase 2 study, and that the potential dose range for EVG has not been evaluated in this population. DAVP again recommended that the Applicant conduct an additional Phase 2 study of EVG that includes additional doses (e.g., 150 qd, 150 bid, and 300 qd) with comprehensive assessments of pharmacokinetics/pharmacodynamics.

DAVP raised concern with the design of the proposed Phase 3 study because it was based on assumptions and modeling. The Phase 2 study contained limited data on EVG in combination with a boosted protease inhibitor; the data did not demonstrate a contribution of EVG, the data are inconsistent and the durability of the response is questionable.

The Applicant acknowledged that the data were limited but stated that adding a protease inhibitor to EVG would not increase the durability of the response. DAVP suggested conducting a Phase 3 study simultaneously with another Phase 2 study of various doses of EVG in combination with a boosted PI that included an early evaluation of viral suppression, an evaluation of exposure-response and intensive pharmacokinetic/pharmacodynamic testing. The Applicant stated they were not interested in conducting any additional Phase 2 studies and would like to proceed with a Phase 3 study (b) (4)

In August 2007 the Applicant submitted protocols for two identically designed Phase 3 studies to be conducted in treatment-experienced adults (Studies **GS-US-183-0144** and **GS-US-183-0145**); one to be conducted primarily in the US and the other in Australia, North America and the European Union. Both studies were to be double-blind, multicenter, randomized, and active-controlled. Approximately 780 patients who meet the inclusion/exclusion criteria would have been randomized 1:1:1 to one of three arms:

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Arm 1: Optimized Background (OB) + EVG 150 mg QD
Arm 2: OB + EVG 300 mg QD
Arm 3: OB + Raltegravir 400 mg BID

The proposed primary endpoint was proportion of subjects achieving and maintaining HIV RNA <400 copies/mL through Week 24; this was later revised to a more acceptable endpoint of <50 copies/mL through Week 48.

In April 2008, the Applicant submitted revised protocols. The revised study design was:

Arm 1: EVG QD + a RTV-boosted protease inhibitor + other background agents
Arm 2: Raltegravir 400 mg BID + background agents

The dose of EVG would be 150 mg QD or 85 mg QD in subjects taking atazanavir/r or lopinavir/r.

DAVP commented that the population proposed for the studies was treatment experienced subjects who can construct a BR with a fully active ritonavir-boosted PI; this may present a challenge to enrollment as many highly treatment experienced patients no longer have a fully susceptible PI available. DAVP suggested that the PI would not have to be fully susceptible, but the Applicant chose to not include this allowance due to a possibility of inducing additional PI resistance. Further, the Applicant chose a non-inferiority margin of 10% based on arms of previously conducted studies in which T-20 was not included. The Applicant was advised that inclusion of T-20 in the EVG studies may substantially reduce or erase any expected margins, and lead to difficulty in interpreting the results, especially if there are no apparent differences between treatment arms.

The studies were subsequently commenced as designed. In late 2008, the Applicant amended the studies to combine the two studies into one (GS-US-183-0145).

Pre-NDA communications occurred and there was general agreement on the content and format of the NDA submission.

2.6 Other Relevant Background Information

Elvitegravir is approved as a component of Stribild® (a fixed dose combination containing EVG, cobicistat (COBI), tenofovir dipivoxil fumarate (TDF) and emtricitabine (FTC)) approved only for use in treatment naïve patients (NDA 203100). Cobicistat is a mechanism-based cytochrome P450 3A (CYP3A) inhibitor that enhances or “boosts” the exposure of CYP3A substrates, including EVG.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was reviewable. All bookmarks and hyperlinks functioned normally. All required components were included.

3.2 Compliance with Good Clinical Practices

In general, the clinical studies were conducted in accordance with the Good Clinical Practice guidelines. The trial protocols and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). Written informed consent was obtained from all subjects prior to any trial-related procedures. Inspections of three selected clinical sites by DSI (LaMarca, Gathe, and Jefferson) were conducted. The data in support of the clinical efficacy and safety at all three sites were considered reliable and considered acceptable in support of the application.

Of note, subjects enrolled at Dr. F. Marquez's site (Site 4390; 3 EVG and 7 RAL) of Study 0145 were excluded from the ITT analysis sets (but included in the safety analysis set) due to failure to comply with the signed investigator agreement. Important protocol deviations at this site included the following: (1) subjects were given the study drug without other active antiretroviral drugs; and (2) subjects who met protocol-defined inclusion and exclusion criteria could not be verified by the source documentation.

3.3 Financial Disclosures

Twenty-nine investigators or sub-investigators that participated in Studies GS-US-183-0105, 130 and/or 145 reported significant payments >\$25,000.

Studies 105 and 145 were randomized studies with an objective endpoint of HIV-1 RNA <50 copies/mL. Study 0130 is an ongoing non-comparative study in which all subjects are receiving open-label EVG. All data from these studies were reviewed by a Clinical Research Organization as well as centrally by the Applicant. As such, the Applicant feels that the payments made to these investigators have minimal potential for introducing bias.

- Twenty-four principal or sub-investigators in Study 145 contributed 96 of 728 (13%) subjects. The majority of sites enrolled 1-5 subjects; four sites (b) (6) enrolled (b) (6) subjects into the study.
- Ten principal or sub-investigators in Study 105 contributed 39 of 278 (14%) subjects. Two sites (b) (6) enrolled (b) (6) subjects.

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- Fifteen principal or sub-investigators in Study 130 contributed 59 of 192 (31%) subjects; all subjects rolled into this trial from prior trials in which subjects were receiving an EVG-containing regimen.

Reviewer Comment: This reviewer agrees that since efficacy and safety were reviewed independent of the investigators, and that most investigators enrolled only small numbers of subjects, these financial payments were unlikely to have biased interpretation of study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Elvitegravir drug substance is a white to yellowish white powder with very low aqueous solubility. The chemical (CAS) name for EVG is 6-(3-Chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

An original formulation (reference) contained 125 mg of EVG. A second formulation (Formulation 2) was developed as the intended for marketing formulation. This formulation showed ~10% lower bioavailability compared to the reference formulation. As such, the dose of Formulation 2 was increased to 150 mg to achieve comparable exposures to the 125 mg dose of the reference formulation. Also, subjects receiving atazanavir or lopinavir boosted with ritonavir would receive a lower 85 mg QD dose of EVG due to elevated EVG exposures.

The Vitekta® tablet is an immediate-release tablet developed in two strengths, 85 mg and 150 mg. The 85 mg tablets are green, pentagon-shaped, film-coated and debossed with “GSI” on one side and “85” on the other side. The 150 mg tablets are green, triangle-shaped, film-coated and debossed with “GSI” on one side and “150” on the other side.

Vitekta tablets are packaged in 60 ml, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and is capped with a white, continuous thread, child-resistant (b) (4) screw cap fitted with an induction sealed, aluminum-faced liner. The bottle label states that the tablets are to be dispensed in original container.

The shelf life for Vitekta® tablets in the approved container is 48 months when stored at 25 °C (excursions permitted 15 – 30 °C). The drug product stability profile also supports a labeled storage recommendation of “Store below 30 °C”. Elvitegravir tablets are not light sensitive.

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4.2 Clinical Microbiology

Please refer to the Virology Review by Dr. Rhee for additional details.

EVG is an HIV-1 integrase strand transfer inhibitor (INSTI), which prevents the integration of HIV-1 DNA made by reverse transcription of the viral genomic RNA into the host cell chromosome. Integrated viral DNA (provirus) is required for productive HIV-1 infection. Using recombinant HIV-1 integrase, EVG was shown to inhibit the DNA strand transfer reaction with an IC₅₀ value of 8.8 nM.

The antiviral activity of EVG was shown against laboratory isolates of HIV-1, T- and M-tropic viruses, with EC₅₀ values ranging from 0.1 to 0.7 nM. In addition, EVG had antiviral activity against multiple clinical isolates of HIV including clades A, B, C, D, E, F, G, and O isolates (EC₅₀ values ranged from 0.1 to 1.3 nM) and a single HIV-2 clinical isolate (EC₅₀ value of 0.53 nM).

EVG-resistant isolates of HIV-1 have been isolated during serial passage of HIV-1_{IIIB} in the presence of increasing concentrations of EVG. Genotypic analysis of the IN-coding region in passaged virus showed emergence of an E92Q substitution, followed by S147G, H51Y, and E157Q substitutions. These substitutions persisted until the end of the selection. These mutant viruses showed reduced susceptibility to EVG (9- to 449-fold). In other selection experiments, D10E, S17N, T66I/K, F121Y, Q148R, S153Y, D232N, and R263K substitutions were selected and viruses harboring these substitutions showed reduced susceptibility to EVG (5- to 109-fold).

Additional integrase mutations including H51Y, F121Y, S147G, S153Y, E157Q, and R263K were also selected by EVG and further decreased susceptibility to EVG when added to either the T66I or E92Q mutations.

In a pooled resistance analysis reviewed as part of NDA 203100 (Stribild®), HIV-1 variants harboring EVG-treatment emergent amino acid substitutions in the HIV-1 IN protein were detected in failure isolates from 20 of the 24 evaluated subjects. These failure isolates had reductions in susceptibility to EVG ranging from 1 to >198-fold that of wild-type HIV-1. IN substitutions previously identified in clinical trials or in cell culture as conferring reduced susceptibility to EVG were detected in 11 subjects' isolates (46% of evaluated E/C/F/T-treatment failures). These substitutions included T66I, E92Q, Q148R, and N155H (EVG resistance-associated substitutions) and H51Y, I68I/V, G140C, S153A, E157Q, and V165I IN substitutions. Isolates harboring these substitutions had reduced susceptibility to EVG (6- to >198-fold compared to wild-type HIV-1). The remaining 9 subjects' failure isolates harbored one or more treatment emergent IN substitutions that have not been identified as associated with EVG resistance and had ≤2.1-fold reduced susceptibility to EVG.

In *in vitro* combination assays, EVG exhibited additive interactions with zidovudine, tenofovir, efavirenz, indinavir, nelfinavir, and tenofovir/lamivudine and synergistic interactions with

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lamivudine and zidovudine/lamivudine. EVG has no anti-reverse transcriptase or protease activity. EVG and raltegravir are cross-resistant.

4.3 Preclinical Pharmacology/Toxicology

EVG has undergone an extensive battery of nonclinical assessments, which were fully evaluated as part of the Stribild application. Following is a summary of the salient findings:

- Single dose and repeat dose nonclinical studies in rats and dogs with EVG demonstrated no adverse target-organ toxicity. Treatment-related effects included changes in cecum weights, dilation of the cecum, and the presence of lipid vacuoles in the lamina propria of the upper small intestines of rats and dogs were observed.
 - The NOAEL in rats is 2000 mg/kg/day (4x (males) and 14x (females) human exposure at 1600 mg/day).
 - The NOAEL in dogs is 100 mg/kg/day (3x human exposure at 1600 mg/day).
 - Focal retinal atrophy was noted in rats at all doses studied, but not in controls.
 - There was no adverse central nervous system, gastrointestinal, renal or behavioral effects observed at doses up to 2000 mg/kg in rats.
 - EVG did not change blood pressure, heart rate, ECG, respiratory rate or oxygen saturation at doses up to 100 mg/kg in dogs.
 - EVG reduced the amplitude of the hERG tail current and the amplitude of acetylcholine- and BaCl₂-induced contractions in isolated guinea pig ileum.
 - EVG was not phototoxic and did not induce convulsions when combined with an NSAID (studies to assess potential quinolone-related toxicities).
 - Treatment-related changes in cecum weights, dilation of the cecum, and the presence of lipid vacuoles in the lamina propria of the upper small intestines of rats and dogs were observed.

Elvitegravir was negative for mutagenic potential in a bacterial reverse mutation test, equivocal in a chromosomal aberration test in Chinese hamster lung (CHL) cells, and negative in 2 rat micronucleus assays.

Long-term 2-year carcinogenicity studies in mice and rats with EVG showed no carcinogenic potential at exposures 14- to 20-fold greater than the exposure observed in humans at the therapeutic dose.

Elvitegravir did not have any effects on rat fertility, embryo-fetal viability or development in rats or rabbits, or on perinatal or postnatal development in rats. Elvitegravir was well tolerated in juvenile rats up to 2000 mg/kg/day. Given the extent of the available nonclinical data, EVG is considered to have low potential for toxicity in the pediatric population 0 to < 18 years of age.

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Special Toxicology Studies: EVG was not phototoxic or immunotoxic and was negative for delayed-type hypersensitivity. It is neither a skin irritant nor a strong eye irritant.

4.4 Clinical Pharmacology

In preclinical testing:

- Bioavailability was 34.1% in rats and 29.6% in dogs.
- Following single oral doses, C_{max} ranged between 0.25 and 1 hour in rats and dogs, respectively. Half-life was 2.3 hours in rats and 5.2 hours in dogs.
- The main route of metabolism of EVG is via glucuronic acid conjugation.
- EVG is highly protein bound (99.4%).
- CYP3A4 is the main CYP isoform involved in oxidative metabolism of EVG.
- In single dose studies in humans, EVG showed near-proportional increases in plasma concentrations up to the 400 mg dose and non-proportionality at the 800 mg dose (relative to the 100 mg dose).
- In humans, bioavailability is increased 2.5 to 3.5-fold in the presence of food.

4.4.1 Mechanism of Action

During HIV-1 infection, HIV IN removes 2 terminal nucleotides from the 3'-end of viral deoxyribonucleic acid (DNA) (3'-processing) and then ligates the processed viral DNA ends into the host cell DNA (strand transfer reaction); EVG inhibits this process.

4.4.2 Pharmacodynamics

In vitro, EVG showed no detectable inhibition of human hepatic microsomal CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 activity and weak inhibition of CYP3A. At clinically relevant concentrations, EVG is a weak inducer of CYP3A activity. Elvitegravir is a potent inhibitor of human organic anion transporting polypeptide 1B3 (OATP1B3), and a weak inhibitor of human Pgp and organic anion transporting polypeptide 1B1 (OATP1B1).

In an exploratory PK/PD substudy conducted as part of the Pivotal Phase 3 study, analyses indicated that across the various quantiles of EVG exposure, virologic response spanned the observed PVF-based efficacy for all 3 quantile-based analyses (ie, for quartiles, quintiles, or octiles of EVG C_{trough} for both the 85-mg and 150-mg doses. Modestly lower response rates were observed in the lowest quartile (51% for the 150 mg and 58% for the 85 mg) compared to 74% and 69%, respectively, in the highest quartile.

EVG should be administered with food.

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4.4.3 Pharmacokinetics

Absorption: Absorption of EVG is unaffected by local gastrointestinal pH. It is, however, subject to chelating in the GI tract by high concentrations of di- and tri-valent cations (e.g. high-strength antacids). Peak concentrations are observed ~ 3 to 4 hours following oral dosing.

Distribution: EVG is highly protein bound (98% to 99% with preferential binding to albumin over AAG) and predominantly distributed to plasma relative to the cellular components of the blood. The distribution of EVG into peripheral compartments (e.g., cerebrospinal fluid or genital tract secretions) has not been evaluated in humans.

Metabolism: The biotransformation of EVG is primarily via CYP-mediated aromatic and aliphatic hydroxylation and/or primary or secondary glucuronidation. Two primary metabolites are observed following unboosted administration: (1) M1 (GS-9202), produced by CYP3A4, and whose formation is almost completely inhibited when administered with RTV or COBI, and (2) M4 (GS-9200), produced by uridine diphosphate glucuronosyltransferase (UGT) 1A1/3, whose plasma exposure (AUC_{tau}) is very low and not affected by boosting. Potent UGT1A1 inhibition can result in increased EVG exposure.

Elimination: Following administration of boosted [14C]EVG, 94.8% of the radioactive dose was recovered in feces, consistent with hepatobiliary excretion; 6.7% was recovered in urine, primarily as glucuronide metabolites, with no unchanged EVG observed. In plasma, EVG was the predominant species, representing ~ 93% of circulating radioactivity. All observed metabolites, including several minor metabolites, constitute < 10% relative systemic exposure (AUC_{tau}) to parent drug in humans.

Drug-Drug Interactions: A number of drug-drug interaction studies have been conducted with EVG. These studies found no interaction between EVG and tipranavir/r, darunavir/r, fosamprenavir/r, emtricitabine, tenofovir, zidovudine, stavudine, abacavir, or didanosine. Higher EVG exposures were observed in interaction studies with atazanavir/r and lopinavir/r, and a lower dose of EVG is recommended when co-administered with these boosted PIs.

Ritonavir (RTV) is an active anti-HIV protease inhibitor and a potent inhibitor of CYP3A4. Low doses of RTV are co-administered with protease inhibitors to increase their exposures. Similarly RTV increases EVG's C_{max} and helps maintain EVG's plasma half-life thereby increasing EVG's intracellular half-life and potentiating its antiviral activity.

Drug-Disease Interaction (Hepatic Impairment): A hepatic impairment study demonstrated comparable steady-state plasma exposure of EVG in subjects with mild and moderate hepatic impairment (CPT Class A and B) compared to matched healthy controls, and no dose adjustment of EVG is required. EVG has not been studied in patients with severe hepatic impairment (CPT Class C).

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Drug-Disease Interaction (Renal Impairment): The PK of boosted EVG were evaluated in non-HIV-1 infected subjects with severe renal impairment (eGFR using the Cockcroft-Gault equation $[eGFR_{CG}] \leq 30$ mL/min) and a matching cohort of subjects with normal renal function ($eGFR \geq 90$ mL/min). EVG exposure on Day 7 among subjects with normal renal function was substantially higher than that observed in clinical studies with EVG. No differences in EVG plasma protein binding were observed between the 2 groups. The differences in exposures between subjects with severe renal impairment and those with normal renal function are not considered clinically relevant. Accordingly, no dose adjustment of EVG is required for patients with renal impairment.

Effect on QTc: Results from the Thorough QTc Study (GS-US-183-0128) indicated a lack of an effect of ritonavir-boosted EVG on the QT/QTc interval.

Effect of Higher Doses: In open-label Study 130 (reviewed in more detail below), 40 subjects received EVG/r 300/100 mg for a median of 39.9 weeks. EVG exposures were only modestly greater (~17% higher C_{tau}) relative to EVG/r 150/100 mg. In comparison to historical data, EVG C_{max} and AUC_{tau} were modestly increased by 33% and 31%, respectively. These data suggest that a 2-fold increase in EVG dose resulted in a markedly less than proportional increase in its exposures, consistent with its solubility-limited absorption profile. The modest increases in EVG exposures are considered to be safe and not clinically meaningful or relevant.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant submitted the final study reports for one Phase 1, one Phase 2 and one Phase 3 study to support this NDA. In addition, longer duration data was included in the NDA from subjects who received open-label EVG (see Table 2).

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Table 2 Supportive and pivotal studies

Study Number	Design	Population	Study treatments	Subjects
Phase 1				
GS-US-183-0101	Double-blind, randomized, placebo controlled	HIV-1 infected treatment naïve and experienced adults	EVG 200 mg BID, 400 mg BID, 800 mg BID, 800 mg QD or 50 mg + 100 mg of ritonavir (r) QD for 10 days.	N=40 30 EVG 10 Pbo
GS-US-183-0152	Open label	Treatment experienced adolescents	EVG 85 or 150 mg QD in combination with a RTV-boosted protease inhibitor	N=25
Phase 2				
GS-US-183-0105 (Supportive)	Randomized, partially blinded comparative trial	HIV-1 infected, antiretroviral treatment-experienced adults	CPI/r EVG 20, 50 or 125 mg plus 100 mg ritonavir (r) QD for 48 weeks	N=278 63 CPI/r 71 EVG/r 20/100 mg 71 EVG/r 50/100 mg 73 EVG/r 125/100 mg.
Phase 3				
GS-US-183-0145 (Pivotal)	Multicenter, randomized, double-blind, double-dummy,	HIV-1 infected, antiretroviral treatment-experienced adults	EVG 85 or 150 mg once daily + RAL Pbo twice daily + BR or RAL 400 mg twice daily + EVG Pbo once daily + BR for up to 96 weeks BR contained a ritonavir boosted PI	N=728 361 EVG 363 RAL
GS-US-183-0130 (Supportive)	Open-label, multicenter, rollover	Subjects who completed a prior EVG/r study without experiencing treatment-limiting toxicity	EVG 85 or 150 mg QD	N=192

5.2 Review Strategy

Section 5.3 provides a summary of the design and results of completed Phase 1 and Phase 2 trials, and the pivotal Phase 3 trial is reviewed in Section 6.1. Comprehensive safety data are reviewed in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

Phase 1

Study **GS-US-183-0101** (Study 101) was a double-blind, randomized, placebo controlled study of the safety, pharmacokinetics, and antiviral activity of EVG in subjects infected with HIV-1.

A total of 40 treatment naïve and experienced HIV-1 infected adults 18-60 years of age who were not receiving antiretroviral therapy with HIV-1 RNA $\geq 10,000$ to $\leq 300,000$ c/mL and a screening CD4 cell count of ≥ 200 cells/mm³ were enrolled. Eight subjects (6 EVG and 2 placebo) received EVG 200 mg BID, 400 mg BID, 800 mg BID, 800 mg QD or 50 mg + 100 mg of ritonavir QD for 10 days.

- 2/30 subjects achieved HIV-1 RNA <50 copies/mL; both were in the EVG 800 mg BID group.
- The mean maximum reduction in HIV RNA (log₁₀ c/mL) at day 11 was -1.48 log (200 mg BID), -1.94 (400 mg BID), -0.98 (800 mg QD), -1.91 (800 mg BID) and -1.99 (50 mg + 100 mg/ritonavir).
- EVG did not exhibit dose-proportional increases in pharmacokinetics with ascending doses and demonstrated dose-dependent autoinduction of metabolism. Co-administration of a 50 mg dose of EVG + 100 mg of ritonavir once-daily resulted in net inhibition of CYP3A-mediated metabolism and high systemic exposures, in particular trough concentrations. The estimated inhibitory quotient of EVG was 5.9, 6.7, and 18.8 ng/mL at the 400 mg BID, 800 mg BID, and 50 mg and 100 mg + ritonavir QD dose levels, respectively. EVG trough concentrations at these doses exceeded the protein binding-adjusted in vitro IC₉₅ of 44.9 ng/mL (100 nM) for the entire dosing interval.
- The most common adverse events were headache, diarrhea, nausea and fatigue.

Reviewer comment: These data demonstrated that EVG had anti-HIV activity, the pharmacokinetics supported twice-daily dosing alone or once-daily when co-administered with ritonavir, and that EVG was generally well tolerated, and supported continued development.

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Phase 2

Study **GS-US-183-0105** (Study 105) compared ritonavir-boosted EVG (EVG/r) versus a comparator ritonavir-boosted protease inhibitor (CPI/r) in combination with a background of antiretroviral therapy in HIV-1-infected treatment-experienced adults.

The primary objective was to assess non-inferiority of EVG/r relative to CPI/r, both in combination with a background antiretroviral regimen as determined by the time-weighted average change in log₁₀ HIV-1 RNA levels from baseline at Week 16 post-treatment (DAVG₁₆). This endpoint was later revised to DAVG₂₄ as it was determined that DAVG₁₆ was not clinically relevant. The main secondary objective was evaluation of the safety and tolerability of EVG/r.

The study was multicenter (78 sites in the US and 3 in Puerto Rico) and was conducted between 21 February 2006 and 13 July 2007.

• Investigational Plan

This was a partially blinded, four-arm, multi-center study. Prior to randomization, the components of the CPI were selected by the investigator without input from the Applicant and based on each subject's antiretroviral drug history and results of a viral resistance profile. The genotype/phenotype were analyzed using the PhenoSense GTTM assay provided by Monogram Biosciences.

The initial CPI portion of the regimen was composed of at least two marketed agents not including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. The remainder of the CPI could be composed of one or two protease inhibitors (in addition to RTV as a boosting agent) if deemed appropriate by the investigator. Darunavir boosted with ritonavir (DRV/r) could be used if the patient was assigned to the CPI treatment group, however, it could not be used in combination with other protease inhibitors. A maximum of 50% of subjects were to use T-20 (a fusion inhibitor) as part of their background antiretroviral regimen.

A total of 278 patients were enrolled and randomized (1:1:1:1) to the following four arms:

Arm 1: CPI/r + OBT

Arm 2: EVG 20 mg QD + RTV 100 mg QD + OBT

Arm 3: EVG 50 mg QD + RTV 100 mg QD + OBT

Arm 4: EVG 125 mg QD + RTV 100 mg QD + OBT

The formulation of EVG used was an older reference formulation. Treatment duration was for 48 weeks. Subjects who completed this 48-week study were offered open-label EVG/r in a rollover protocol (Study **GS-US-183-0130**).

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In October 2006, the Independent Data Monitoring Committee (IDMC) reviewed data from the initial 8 weeks of the study and recommended the following changes, which were implemented in a protocol amendment:

- Lower than predicted pharmacokinetic exposure in subjects receiving EVG/r 20/100 mg led to higher rates of virologic rebound. Subjects in this group were unblinded and switched to open-label EVG/r 125/100 mg, in combination with their optimized background therapy. The EVG/r 50/100 and 125/100 mg groups remained blinded.
- The use of one of two ritonavir-boosted protease inhibitors (DRV/r or tipranavir/r) with unboosted EVG was permitted in both of the ongoing blinded EVG/r groups (50/100 and 125/100 mg), based on data confirming the lack of interactions between EVG and these agents. Subjects receiving EVG with either darunavir or tipranavir, had their ritonavir dose adjusted to 100 or 200 mg twice daily, respectively, reflecting the recommended doses of ritonavir to be used with these two protease inhibitors. Subjects who switched from EVG/r 20/100 mg to open-label EVG/r 125/100 mg were also allowed to receive either DRV or TPV.
- **Disposition of Study Subjects**

Two-hundred ninety-seven subjects were enrolled, 278 were treated, and 211 (76%) completed the study. A total of 179 subjects (64%) discontinued their original randomized study drug assignment; the most common reason was lack of efficacy.

Table 3 Disposition of study subjects, Study 105

	CPI/r	EVG/r 20 mg	EVG/r 50 mg	EVG/r 125 mg
Randomized	73	75	75	74
Never dosed	10	4	4	1
Switched to open-label EVG 125 mg	30	60	15	17
Safety, tolerability or efficacy reasons	4	6	11	8
Investigator's discretion	3	2	5	4
Withdrew consent	3	2	1	1
Lost to follow-up	1	1		3

Subjects who switched from CPI/r to EVG or to open-label EVG/r 125/100 mg did so primarily due to lack of efficacy.

- 30 subjects in the CPI/r group experienced virologic failure were re-randomized to double-blind EVG/r and/or were switched to open-label EVG/r 125/100 mg.
- 60 subjects randomized to the EVG/r 20/100 mg group were switched to open-label EVG/r 125/100 mg when the 20/100 mg treatment group was discontinued and the other 11 subjects discontinued the study.
- 15 and 17 subjects, respectively, originally randomized to EVG/r 50/100 or 125/100 mg switched to open-label EVG/r 125/100 mg to manage virologic failure.

• Demographic and Disease Characteristics

Enrolled subjects were to be HIV-1 infected with HIV-1 RNA $\geq 1,000$ copies/mL at screening and documented presence of at least one of the protease gene mutations as defined by the International AIDS Society- (IAS-) USA 2005 Guidelines. The protease gene mutation(s) must have been documented in a historical genotype report(s) or in the screening procedures for this study. Subjects were to have been on a stable antiretroviral regimen for at least 30 days before the screening visit and were to have remained on that regimen until the baseline visit.

The Demographic and Disease characteristics of the ITT analysis set (randomized subjects who received at least one dose of study medication) are shown in Table 3. There were no clinically relevant differences between treatment groups.

Table 4 Demographic and disease characteristics, Study 105

	CPI/r N=63	EVG/r 20 mg N=71	EVG/r 50 mg N=71	EVG/r 125 mg N=73
Age (years) Mean $\pm$ SD	46 $\pm$ 7	45 $\pm$ 7	45 $\pm$ 7	44 $\pm$ 7
Male	54 (86%)	70 (99%)	63 (89%)	62 (85%)
Race				
-White	54 (86%)	48 (68%)	47 (66%)	54 (74%)
-Black	6 (10%)	21 (30%)	22 (31%)	14 (19%)
-Other	3 (5%)	2 (3%)	2 (3%)	5 (7%)
HIV RNA (log ₁₀ c/mL Mean $\pm$ SD	4.54 $\pm$ 0.80	4.66 $\pm$ 0.79	4.47 $\pm$ 1.07	4.71 $\pm$ 0.81
CD4 cell count (cells/ μ L)	158 $\pm$ 150	180 $\pm$ 196	243 $\pm$ 223	157 $\pm$ 158
Number of PI- associated mutations Mean $\pm$ SD	10.2 $\pm$ 4.15	9.7 $\pm$ 3.80	9.2 $\pm$ 4.28	9.8 $\pm$ 4.35
GSS for NRTI Mean $\pm$ SD	0.76 $\pm$ 0.911	0.80 $\pm$ 0.950	0.84 $\pm$ 0.942	0.95 $\pm$ 1.092
PSS for NRTI				

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Mean $\pm$ SD	1.05 $\pm$ 0.991	1.01 $\pm$ 0.860	0.88 $\pm$ 0.900	1.07 $\pm$ 0.998
PSS for PI				
Mean $\pm$ SD	2.17 $\pm$ 2.733	2.51 $\pm$ 2.952	2.60 $\pm$ 2.866	2.42 $\pm$ 2.906
T-20 experienced	20 (32%)	28 (39%)	26 (37%)	23 (32%)

- Outcome Assessments**

The primary efficacy endpoint was the time-weighted average change from baseline through Week 24 in HIV-1 RNA (DAVG₂₄).

Other efficacy endpoints included DAVG by T-20 use, DAVG by number of active drugs in background, proportion of subjects with HIV-1 RNA <400 and <50 copies/mL, mean change from baseline in CD4 cells, and virologic failure/resistance.

Safety was evaluated by assessment of adverse events, clinical laboratory tests, vital signs, electrocardiograms, physical examinations, and retinal examinations. An intensive pharmacokinetic substudy was performed at selected sites in a subset of subjects receiving EVG/r. A blood sample was also collected at all visits starting at Week 2 from all subjects receiving EVG/r. The pharmacokinetics of EVG, its metabolites GS-9200 (M4) and GS-9202 (M1), and ritonavir were evaluated (where possible) in the EVG/r treatment groups.

Changes in study drug treatment regimens recommended by the IDMC confound the interpretation of results in evaluating the non-inferiority of EVG/r versus CPI/r after Week 16.

Before Week 16, only four subjects receiving EVG/r 50/100 or 125/100 mg added DRV or TPV, so the efficacy data up to Week 16 were the least confounded.

The EVG/r 20/100 mg treatment group demonstrated lower than predicted EVG exposures and a higher rate of virologic rebound. In this group, the mean change from baseline in HIV-1 RNA was $-1.54 \log_{10}$ copies/mL at Week 2 and $-1.07 \log_{10}$ copies/mL at Week 8. No additional efficacy analyses for this dose were performed because this treatment group was discontinued prematurely.

Assessment of the primary efficacy endpoint, DAVG₂₄ for the two higher dose groups, is presented in Table 5.

Table 5 DAVG₂₄ at Week 24, Study 105

	CPI/r N=63	EVG/r 50/100 mg N=71	EVG/r 125/100 mg N=73
Mean $\pm$ SD	-1.19 $\pm$ 1.17	-1.44 $\pm$ 1.07	-1.66 $\pm$ 1.20
Median	-1.00	-1.34	-1.57
P-value vs CPI/r		0.29	0.021

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Difference (95% CI)		-0.19 (-0.54 to 0.17)	-0.42 (-0.77 to -0.06)
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Subjects with no or few active drugs in their background regimens responded poorly in all treatment arms. Specifically, in the 125/100 mg arm, subjects with no other active drugs in their regimen had a -0.7 log reduction compared to -1.7 log for subjects with ≥ 1 active drug, -1.6 log for those with at least 2 active drugs and no T-20 (fusion inhibitor), and -2.9 log for those with 2 active agents plus T-20. Similarly, patients in the CPI/RTV arm who added T-20 experienced a -1.8 log reduction.

Protease inhibitors were not initially allowed to be administered as part of the background therapy. First use of T-20 represented the only additional potent, fully active drug given from study inception with EVG/r. Results for DAVG at Weeks 16, 24, and 48 are presented below for the CPI/r and EVG/r 50/100 mg and 125/100 mg groups based on use of T-20.

Table 6 DAVG₂₄ by T-20 Use, Study 105

Mean $\pm$ SD	CPI/r N=63	EVG/r 50/100 mg N=71	EVG/r 125/100 mg N=73
DAVG ₁₆	-1.63 $\pm$ 1.15	-2.01 $\pm$ 0.85	-2.80 $\pm$ 0.90
DAVG ₂₄	-1.68 $\pm$ 1.06	-1.95 $\pm$ 0.91	-2.85 $\pm$ 0.82
DAVG ₄₈	-1.75 $\pm$ 1.07	-1.84 $\pm$ 0.88	-2.77 $\pm$ 0.83

Subjects in the two EVG/r groups who did not receive T-20 had a mean -1.3 log₁₀ reduction in HIV-1 RNA from baseline at all time points.

The number and proportion of ITT subjects who achieved HIV-1 RNA <400 copies/mL and <50 copies/mL are presented in Tables 7 and 8. The addition of T-20 or adding DRV or TPV to the regimen increased response rates, but the numbers of subjects is less than one-third of each treatment group.

Table 7 Number and proportion of subjects with HIV RNA <400 c/mL, Study 105

	CPI/r N=63	EVG/r 50/100 mg N=71	EVG/r 125/100 mg N=73
Week 16	21 (33%)	29 (41%)	32 (44%)
Week 24	26 (41%)	30 (42%)	34 (47%)
Week 48	25 (40%)	34 (48%)	39 (53%)

Table 8 Number and proportion of subjects with HIV RNA <50 c/mL, Study 105

	CPI/r N=63	EVG/r 50/100 mg N=71	EVG/r 125/100 mg N=73
Week 16	19 (30%)	27 (38%)	29 (40%)
Week 24	12 (19%)	19 (27%)	19 (26%)
Week 48	10 (16%)	14 (20%)	20 (27%)

At Week 48, the mean increase in CD4 cell counts were +68 cells/μL in the CPI/r arm, +49 cells/μL in the 50/100 mg arm, and +83 cells/μL in the 125/100 mg arm.

Virologic failure was defined as either suboptimal response (HIV RNA <1 log₁₀ reduction from baseline and >400 c/mL by week 12 confirmed by week 16) or virologic rebound (rebound in HIV RNA to <1 log₁₀ reduction from baseline and HIV RNA >400 copies/mL at or any time after week 16). Virologic failure occurred in 50% of CPI/r, 69% of 20/100 mg, 46% of 50/100 mg, and 41% of 125/100 mg recipients by week 16, respectively. Some patients receiving EVG had evidence of virologic rebound beginning as early as week 4.

Post-baseline integrase genotypes were obtained for 144 subjects randomized to one of the EVG/r containing regimens; 136/144 (94%) developed one or more mutations in the integrase gene that have been associated with integrase inhibitor resistance while on treatment. The most common mutation observed was E92Q (66, 46%), followed by Q148R/K/H (58, 40%), S147G (29, 20%), E138K/A/D (27, 19%), T661/A/K/V (21, 15%), Q95K/R (8, 6%), H51Y (6, 4%), and E157Q/K (5, 3%). Phenotypic analysis demonstrated a mean reduction in susceptibility to EVG of >88-fold (median 62-fold, range 1 to >301). Both the mean and median fold changes in susceptibility to EVG in the post-baseline samples showed evidence of dose dependence with mean fold changes of 54-, > 85-, and > 143-fold in the 20-, 50- and 125-mg groups, respectively.

Reviewer comment: In this population of moderately experienced subjects, EVG/r 50/100 and 125/100 mg both met the criteria for non-inferiority compared to CPI/r, and EVG/r 125/100 mg was superior to CPI/r. Mean values for decrease from baseline of HIV-1 RNA demonstrated a rapid initial decline in all EVG/r treatment groups. Maintaining virologic suppression was dependent on having another potent, fully active drug (i.e., T-20 or DRV or TPV) as a component of the background regimen. At the EOP2 meeting, DAVP raised questions about the apparent low rate of efficacy across treatment arms and recommended that the Applicant conduct an additional Phase 2 study to evaluate other doses of EVG; the Applicant chose not to conduct such a study (see Section 2.5 above), and pushed on into Phase 3 development. Since there were no significant safety issues identified, it was not possible for DAVP to halt development, and the Applicant was advised that it could conduct Phase 3 studies at their own risk of not being able to demonstrate non-inferiority of EVG/r compared to other therapies.

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Phase 3

The results from a single Phase 3 study were submitted to support approval of this NDA: Study **GS-US-183-0145** (Study 145). This was a multicenter, randomized, double-blind, double-dummy study of the safety and efficacy of EVG boosted with ritonavir (EVG/RTV) versus raltegravir (RAL) each administered with a background regimen (BR) in HIV-1 infected, antiretroviral treatment-experienced subjects. Subjects were to be antiretroviral treatment-experienced adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL who had documented resistance from 2 or more different classes of antiretroviral agents or at least 6 months experience before screening with at least one antiretroviral agent and were fully sensitive to a selected PI.

Subjects were randomized 1:1 to one of the following treatment groups and treated in the blinded phase for 96 or more weeks:

- Group 1: EVG 150 mg (or 85 mg) once daily + RAL Pbo twice daily + BR
- Group 2: RAL 400 mg twice daily + EVG Pbo once daily + BR

Due to known PK interactions, subjects who were receiving atazanavir (ATV) or lopinavir (LPV) as part of their BR were to receive a reduced EVG dose of 85 mg once daily if randomized to Group 1.

The BR was constructed by the investigator based on viral resistance testing and was to be composed of a fully active RTV-boosted PI and a second active agent. The ritonavir used to pharmacologically boost EVG was from the ritonavir-boosted PI that was required to be in the regimen. The fully active PI was defined by phenotypic resistance analysis. For phenotypic susceptibility, fully active was defined as being below the lower clinical or biological cutoff. The following RTV-boosted PIs were allowed to be prescribed by the investigator as part of the BR: ATV, DRV, fosamprenavir (FPV), LPV, or TPV. Subjects took their RTV dose based on the dosing schedule indicated in the prescribing information for the PI and no additional RTV was required to be taken with EVG.

Randomization was stratified by screening HIV-1 RNA level ($\leq 100,000$ c/mL or $> 100,000$ copies/mL) and the class of the second agent (NRTI vs other classes).

During Week 2, a PK substudy was conducted at selected sites. Additionally, a trough PK sample (at Weeks 2, 12, 16, 24, and 48) and a post-dose sample (at Weeks 8, 20, 32, and 40) were collected for all subjects.

All subjects who remained on blinded study drug until their Unblinding Visit were given the option to participate in an extension phase of the study, during which EVG would be provided for an additional 144 weeks or until commercial approval was received in the applicable country (whichever occurred first) in Study 130. At Week 96, subjects originally randomized to RAL

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who elected to continue in the open-label extension phase would be switched to EVG. After Week 144, subjects were given the option to participate in another open-label extension phase of the study if commercial approval had not yet been obtained in the applicable country.

At the time this study was initiated, RAL was only indicated for use in treatment experienced subjects. Also, as noted under Section 2.5 above, the Applicant initially enrolled subjects in two identically designed studies that were later combined into a single study.

To be eligible, subjects were to be antiretroviral treatment-experienced HIV-1 infected adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL and documented resistance, as defined by current IAS-USA definitions, or at least 6 months experience prior to screening with 2 or more different classes of antiretroviral agents. Thus, subjects may have had resistance to 1 class and at least 6 months experience prior to screening with a second class of antiretroviral agents, or resistance to 2 classes of antiretroviral agents, or at least 6 months experience with the 2 classes of antiretroviral agents. Subjects may also have had resistance or at least 6 months experience prior to screening with 3 or more classes of antiretroviral agents

In addition, subjects were to have been on a stable antiretroviral regimen for at least 30 days prior to screening and up until the baseline visit and be eligible to receive one of the fully active RTV-boosted-PIs, based on the results of screening phenotype analysis provided by (b) (4), and an allowed second agent

Reviewer Comment: As described above, the Applicant originally initiated two identically designed studies and during their conduct combined the two into a single study. Of note, subjects received between 100 mg and 400 mg per day of ritonavir depending on the protease inhibitor they were receiving.

Study GS-US-183-0130 (Study 130) is an ongoing rollover, open-label, multicenter, multiple-dose, single-arm extension study designed to assess the safety of EVG/r, in combination with other ARV agents, in treatment-experienced HIV-1 infected adults and adolescents. Subjects were eligible for this study if they had completed a prior EVG/r treatment study without experiencing any dose-limiting toxicity; eligible subjects may or may not have received EVG in their prior study.

Subjects were enrolled in this extension study regardless of their baseline HIV-1 RNA level. Non-virologically suppressed subjects entering the study had, for the most part, failed prior ARV regimens and had limited treatment options available; these subjects were allowed in the current extension study even if they had been exposed to EVG in their prior study.

Genotyping was not performed at baseline, so subjects who met eligibility requirements were enrolled at the discretion of the investigator. The components of each subject's background ARV regimen were selected by the investigator without input from the Applicant. Background ARV

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regimens consisted of at least 2 agents, but were not to include the NNRTIs efavirenz, nevirapine, or delavirdine, or the PIs saquinavir, nelfinavir, or indinavir.

Subjects who were receiving an RTV-boosted PI (PI/r) as part of their ARV regimen took the RTV dose and followed the dosing schedule indicated in the prescribing information for the PI. No additional RTV was administered. Subjects whose ARV regimen did not include RTV took RTV 100 mg once daily with their EVG dose. Subjects who were taking lopinavir/r (LPV/r) or atazanavir/r (ATV/r) as part of their ARV regimen received EVG 85 mg once daily due to an established drug-drug interaction with these agents; all other subjects received EVG 150 mg once daily.

Review of Efficacy

Efficacy Summary

6.1 Indication

The Applicant's proposed indication for treatment experienced subjects was:

Vitekta, coadministered with a ritonavir-boosted protease inhibitor and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults.

6.1.1 Methods

The primary efficacy review is based on the results from the Phase 3 Study 145 and supportive Phase 2 Study 105 (reviewed above). It was not possible to pool the efficacy results from the two studies because they had different designs, enrolled different populations, and used different endpoints. What follows is an in-depth review of Study 145.

6.1.2 Demographics

Approximately 63% of subjects were randomized at sites located in the United States, and the others were enrolled at sites in North and South America, Europe, Australia, and Puerto Rico.

Between Studies 144 and 145, 1663 subjects were screened. Of these 724 were enrolled, 712 were randomized and received at least one dose of study medication, and 428 completed 96 weeks of treatment.

Overall demographic and baseline characteristics were similar between treatment groups. Combined demographic data for the ITT population showed that subjects ranged from 19 to 78 years, with a median age of 44 years, 83% were male, 64% were white, and 32% were Black or

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African American. At baseline, approximately 45% subjects in both groups had CD4 cell counts ≤ 200 cells/ μ L and approximately 26% of study subjects had HIV-1 RNA $>100,000$ c/mL (see Table 9).

Table 9 Demographic and disease characteristics, Study 145

	EVG N=361	RAL N=363
Age (Years)		
-Mean (SD)	44 (9.0)	45 (9.2)
-Median (range)	45 (20, 78)	45 (19, 74)
Sex		
-Male	292 (83%)	284 (81%)
-Female	59 (17%)	67 (19%)
Race		
-White	211 (60%)	226 (64%)
-Black/AA	125 (36%)	113 (32%)
-Asian	9 (3%)	5 (1%)
-American Indian/Alaska native	2 ($<1\%$)	3 (1%)
-Native Hawaiian/Pacific Islander	1 ($<1\%$)	0
-Other	3 (1%)	4 (1%)
Ethnicity		
-Hispanic or Latino	79 (22.5%)	73 (21%)
-Not Hispanic or Latino	271 (77%)	277 (79%)
-Not Reported	1 ($<1\%$)	1 ($<1\%$)
Baseline HIV-1 RNA ($\log_{10}$ c/mL)		
-Mean (SD)	4.26 (0.971)	4.27 (0.994)
-Median (range)	4.35 (1.69, 6.63)	4.42 (1.69, 6.10)
Baseline HIV-1 RNA $\leq 100,000$ c/mL	261 (74%)	261 (74%)
Baseline HIV-1 RNA $>100,000$ c/mL	90 (26%)	90 (26%)
Baseline CD4 (cells/ mm^3)		
-Mean (SD)	259.3 (204.4)	264.0 (207.92)
-Median (range)	227.0 (2.0, 1374)	215.0 (1.0, 1497)
HIV Status		
-Asymptomatic	170 (48%)	168 (48%)
-Symptomatic HIV Infections	51 (14.5%)	54 (15%)
-AIDS	126 (36%)	125 (36%)
-Unknown	4 (1%)	4 (1%)
Chronic HBV Infection	17 (5%)	12 (3%)
Chronic HCV Infection	44 (13%)	54 (15.5%)
Baseline Genotypic Sensitivity Score		
-0	4 (1%)	1 ($<1\%$)
-1	50 (14%)	53 (15%)
-2	284 (81%)	291 (83%)
-3	12 (3%)	6 (2%)
Baseline Phenotypic Sensitivity Score		
-1	5 (1%)	4 (1%)

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-1.5	23 (7%)	28 (8%)
-2	306 (87%)	306 (87%)
-2.5	2 (<1%)	1 (<1%)
-3	14 (4%)	10 (3%)
-3.5	0	1 (<1%)
Type of PI in Background Regimen		
-Atazanavir	61 (17%)	51 (14.5%)
-Darunavir	202 (57.5%)	207 (59%)
-Fosamprenavir	14 (4%)	19 (5%)
-Kaletra	68 (19%)	68 (19%)
-Tipranavir	6 (2%)	7 (2%)
Type of NRTI in Background Regimen		
-Abacavir	5 (1%)	12 (3%)
-Combivir	6 (2%)	5 (1%)
-Didanosine	1 (<1%)	5 (1%)
-Emtricitabine	2 (<1%)	2 (<1%)
-Epzicom	4 (1%)	8 (2%)
-Lamivudine	11 (3%)	13 (4%)
-Tenofovir DF	163 (46%)	171 (48%)
-Truvada	91 (26%)	67 (19%)
-Zidovudine	3 (<1%)	3 (2%)

Reviewer comment: There were no clinically relevant differences between treatment groups. The majority of subjects had a Genotypic Sensitivity Score (GSS) of ≥ 2 . The GSS is a tool to predict virological treatment outcome and a score of 2 or 3 means that a background regimen of two or three fully active drugs can be constructed. Similarly, subjects with higher Phenotypic Sensitivity Scores (PSS), e.g., ≥ 2 are expected to respond better than those with lower scores. Of note is the relatively low enrollment of females.

6.1.3 Subject Disposition

The disposition of subjects at Week 96 is shown in the following table. The reasons for early discontinuation were generally matched between treatment groups except there were more discontinuations because of withdrawal of consent in the EVG group compared with the RAL; it is unknown if these subjects discontinued due to adverse events, lack of efficacy or some other reason(s).

Table 10 Disposition of study subjects through Week 96, Study 145

	EVG	RAL
Subjects discontinued between Week 48 and Week 96	146 (41%)	150 (41%)
Reason for Study Discontinuation		
Lost to follow-up	30 (8%)	31 (8.5%)
Subject non-compliance	38 (10.5%)	34 (9%)
Withdrew consent	30 (8%)	17 (5%)

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Lack of efficacy	17 (5%)	21 (6%)
Protocol violation	11 (7.5%)	14 (9%)
Adverse event	11 (3%)	15 (4%)
Sponsor/Investigator's decision	5 (1%)	8 (2%)
Death	1 (<1%)	9 (2.5%)
Pregnancy	3 (<1%)	1 (<1%)

A total of 533 subjects had an important protocol deviation. The most common protocol deviation was departure from required dosing requirement; subject missed ≥ 2 consecutive days of dosing, 125 subjects in each treatment group.

Subjects enrolled at Site 4390 (Dr. F. Marquez; 3 EVG and 7 RAL) were excluded from the ITT analysis sets (but included in the safety analysis set) due to failure to comply with the signed investigator agreement. Important protocol deviations at this site included: (1) subjects were given the study drug without other active antiretroviral drugs; and (2) subjects who met protocol-defined inclusion and exclusion criteria could not be verified by the source documentation. All 10 subjects at Site 4390 prematurely discontinued study drug; 9 subjects because of protocol deviations and 1 subject (in the EVG group) withdrew consent. In the efficacy analysis all 10 would be considered as missing=failure.

Reviewer Comment: Inclusion of subjects from Site 4390 in the efficacy analysis would not have changed the overall conclusions; these subjects are included in safety analysis. It was not possible to corroborate the disposition of subjects who reportedly discontinued due to other reasons, sponsor or investigator's decision, protocol violation, or withdrawal of consent because these data were not collected. Specifically, in subjects who discontinued study drug, the reason for study drug discontinuation was determined solely by the investigator.

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint was the percentage of subjects who achieved and maintained confirmed HIV-1 RNA <50 copies/mL through Week 48. This endpoint is universally accepted as a measure of efficacy in trials of HIV-1 therapies as well as in routine clinical practice. The analysis of the primary efficacy endpoint was again conducted using the Week 96 dataset. For the primary efficacy endpoint, non-inferiority of EVG treatment relative to RAL treatment (in addition to the BR) was assessed. The Applicant's would claim non-inferiority if the lower bound of the 2-sided 95% CI of the stratum-weighted difference (EVG – RAL) in the response rate was -10%.

The FDA analysis is based on the snapshot methodology which evaluates the proportion of subjects with HIV-1 RNA <50 c/mL at a single time point within the Week 48 visit window (day 309-364).

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Table 11 FDA's analysis of subjects with <50 copies/mL at Weeks 48 and 96¹

	EVG N=351	RAL N=351	
Week 48			
Snapshot	211 (60%)	205 (58%)	Difference and 95% CI EVG-RAL -1.7% (-5.6%, 9.0%)
Week 96			
Snapshot	184 (52%)	188 (54%)	Difference and 95% CI EVG-RAL -1.1% (-8.5%, 6.2%)

1. The number of subjects in each group reflects the removal of 3 from the EVG group and 7 from the RAL group that were enrolled at site 4390 (see Sections 3.2 and 6.1.3 above)

Reviewer Comment: The efficacy analysis demonstrated the non-inferiority of EVG compared to RAL based on the pre-specified non-inferiority margin of the lower bound of the 95% confidence interval of less than 10%.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary outcome measures included assessments at Week 96 of:

- The percentages of subjects with virologic failure and resistance (see below).
- The mean (SD) decreases from baseline in HIV-1 RNA: -2.26 (1.078) log₁₀ copies/mL in the EVG group and -2.31 (1.068) log₁₀ copies/mL in the RAL group.
- The mean (SD) increase from baseline in CD4 cell counts: +205 (191.5) cells/mm³ in the EVG group and +198 (162.2) cells/mm³ in the RAL group.

• Virologic Failure and Resistance

The following virologic failure criteria were used:

- Suboptimal virologic response: HIV-1 RNA $\geq$ 50 copies/mL and $<$ 1 log₁₀ reduction from baseline at the Week 8 visit, confirmed at the Week 12 visit.
- Virologic rebound: After achieving HIV-1 RNA $<$ 50 copies/mL at any visit, a rebound in HIV-1 RNA to $\geq$ 400 copies/mL, which was subsequently confirmed at the following scheduled or unscheduled visit; or confirmed $>$ 1 log₁₀ increase in HIV-1 RNA from their nadir.

A total of 237 subjects experienced virologic failure through Week 96.

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Table 12 Virologic failure rates at Week 96

	EVG N=351	RAL N=351	
Week 48			
Snapshot	115 (33%)	110 (31%)	Fail rate and 95% CI EVG-RAL 1.4% (-5.5%, 8.3%)
Week 96			
Snapshot	128 (36%)	109 (31%)	Fail rate and 95% CI EVG-RAL 5.4% (-1.6%, 12.4%)

If virologic rebound was confirmed, the HIV-1 genotype and phenotype (RT and protease) were to be analyzed, and if commercially available, integrase resistance data were also provided.

Seven percent of subjects in both treatment groups developed resistance. Genotypic data from 66 subjects who were eligible for EVG resistance testing in the Phase 3 GS-US-183-0145 trial and 24 subjects were found to have primary EVG resistance-associated substitutions (1.6 - >158.1 fold change in EVG susceptibility): T66A/I: 8, E92G/Q: 7, T97A: 5, Q146R: 1, S147G: 4, Q148R: 4, and N155H: 5; all are previously identified primary EVG resistance-associated substitutions.

6.1.6 Subpopulations

Response rates by various baseline demographic and disease parameters are shown in Table 13.

Table 13 HIV-1 RNA Outcomes, <50 copies/mL (Snapshot analysis) by disease and demographic characteristics

N/n (%)	EVG	RAL
Baseline HIV-1 RNA $\leq$ 100,000 copies/mL	171/261 (65.5)	168/261 (64)
Baseline HIV-1 RNA >100,000 copies/mL	39/90 (43)	34/90 (38)
CD4 $\leq$ 200 cells/mm ³	72/151 (48)	71/153 (46)
CD4 >200 cells/mm ³	132/189 (70)	128/188 (68)
Second class of agent: NRTI	163/280 (58)	156/278 (56)
Second class of agent: Other	47/71 (66)	46/73 (63)
Baseline PI (FPV, DRV or TPV)	137/222 (62)	137/232 (59)
Baseline PI (LPV or ATV)	73/129 (57)	65/119 (55)
Age $\leq$ 45 years	117/204 (57)	100/182 (55)
Baseline GSS $\leq$ 1	41/54 (76)	37/54 (69)
Baseline GSS >1	169/296 (49)	165/297 (51)
Age >45 years	93/147 (63)	102/169 (60)
Male	182/292 (55)	160/284 (54)
Female	28/59 (39)	42/67 (52)
White	140/211 (66)	134/226 (59)
Non-White	70/140 (50)	68/125 (54)

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US and Puerto Rico	122/231 (53)	123/228 (54)
Non-US Countries	88/120 (73)	79/123 (64)

A difference in outcome was noted between males and females in the EVG group with males having much higher response rates. One hypothesis was that more females discontinued the study and in the analyses would be considered failures. Fifty-four percent of females discontinued EVG compared to 78% of males. As such, the response difference cannot be explained by discontinuations. Another possibility was differences in the pharmacokinetics of EVG between males and females; however, no differences were observed.

GSS scores >1 are usually associated with higher responses. In this study, 76% percent of EVG and 69% of RAL subjects with a GSS of ≤ 1 had HIV-1 RNA <50 copies/mL at week 96, and among subjects with a GSS >1, 57% and 56% had HIV-1 RNA <50 copies/mL in the EVG and RAL groups, respectively. It is also interesting to note that almost all subjects (>92%) had PSS=1.5 or 2, regardless of their GSS scores. Among 107 subjects with PSS ≤ 1 , 8(7%) had PSS=1, 32 (30%) had PSS=1.5, and 66 (62%) had PSS=2. Among 593 subjects with PSS>1, 1 (0.2%) had PSS=1, 19 (3.2%) had PSS=1.5, and 546 (92%) had PSS=2, 2 (.3%) had PSS=2.5, and 25 (4%) had GSS>3. Almost all subjects had PSS=1.5 and 2. The other two ends, PSS ≤ 1 and PSS>2 have limited data. As noted above, this trial had a very high rate of discontinuation and, among 25 subjects with PSS>3, only 7 achieved virologic success at week 96.

Reviewer comment: The overall results support the conclusion that EVG-containing regimens were non-inferior to the RAL-containing regimens. Subgroup analyses suggest that EVG conveyed less benefit for females; however, the reason(s) for this difference is unknown.

6.1.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

A total of 192 subjects were enrolled into Study 130 and received EVG. Of the 192 enrolled subjects, 184 (96%) adults rolled over from the Phase 2 Study 105 (154 who previously received EVG and 30 who had not), and 8 (4%) adolescents rolled over from the Phase 1B Study 152. No subjects were enrolled from Study 145. Subjects were primarily enrolled from sites on mainland US (93%) and 7% were enrolled from sites in Puerto Rico.

Enrolled subjects were predominantly male (90%) and white (72%), with a mean age of 45 years (range 15 to 65 years), with baseline HIV-1 RNA <50 copies/mL in 85 subjects (44.5%), 50 to <400 copies/mL in 40 subjects (21%), and ≥ 400 copies/mL in 66 subjects (35%), and a mean baseline CD4 cell count of 282 cells/mm³.

As noted above in Section 4.4.3, a total of 40 subjects participated in and completed a substudy in which they received a higher dose of EVG (300 mg) for a median duration of 39.9 weeks, before returning to the main study to receive EVG 150 mg.

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At the time of the data cutoff date for the Week 192 analysis, a total of 113 subjects (59%) were still participating in the study, and 79 (41%) had prematurely discontinued from the study: 22 for lack of efficacy, 17 for Investigator's Discretion, 15 withdrew consent, nine due to adverse events, seven died, six were lost to-follow-up, two had protocol violations (one took a prohibited medication and one was incarcerated), and 1 became pregnant. One subject was excluded from the efficacy analysis because he had no post baseline HIV-1 RNA or CD4 cell count data.

Overall 47.5% of subjects achieved HIV-1 RNA <50 copies/mL at Week 192: 68% of those who entered the study with HIV-1 RNA <50 copies/mL and 31% of subjects who entered with HIV-1 RNA >50 copies/mL.

Forty-nine subjects had virologic failure and underwent resistance testing: 37/49 with prior IN resistance mutations had a new mutation at the time of failure, and 12 had no prior IN resistance mutation but had a new mutation at failure. The most common resistance mutation was the E92Q/A, which is a known IN mutation.

There were no differences in the efficacy outcomes between subjects who received EVG 300 mg and those who received 85 or 150 mg in Study 130.

Reviewer comment: Some subjects did and some did not receive EVG during their initial regimen, the high attrition rates, and the lack of a comparator arm preclude reaching definitive conclusions about the contribution of EVG to efficacy.

7 Review of Safety

The most common treatment-emergent related adverse events observed in adults included: diarrhea, nausea, vomiting, abdominal distention, fatigue, headache, dizziness, dysgeusia, and rash (dermatitis, drug eruption, eczema, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash popular, rash pruritic, and urticaria). The majority of events were mild to moderate in severity. and only diarrhea occurred more often among EVG treated subjects.

There were no differences in the safety outcomes of adolescents compared to adults observed.

There were no clinically relevant changes in renal or hepatic function, other clinical chemistries or hematologic parameters among subjects treated with EVG.

Reviewer comment: The assignment of attribution of adverse events to EVG is confounded as all subjects received multiple other antiretroviral agents that contributed to the toxicity profile. For example, some subjects received as much as 400 mg of ritonavir per day, and ritonavir causes gastrointestinal adverse events, darunavir is associated with gastrointestinal events, skin reactions and may cause hepatotoxicity, and tenofovir causes a Fanconi-like syndrome with proximal renal tubulopathy.

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7.1 Methods

As discussed previously, the primary Phase 3 Study 145 was a randomized, double-blind, double-dummy study with a 1:1 randomization scheme. Adverse event data from this study were reviewed using Empirica Study. In addition, selected safety data from the Phase 2 study (Study 105) and the rollover Study 130 was reviewed manually.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The principal source of safety data for EVG that contributes to this summary of safety is the analysis of 96-week data from Phase 3 Study 145. Supportive safety information is provided from Phase 1 Study 101 and Phase 2 Studies 105 and 130. Safety data specific to adolescents is reviewed in Section 7.6.3, below.

Additional safety data was excerpted from the clinical review of Stribild in which EVG is a component of this fixed dose combination containing, cobicistat (a non-virologically active pharmacologic enhancer) 150 mg, tenofovir dipivoxil and emtricitabine.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using the MedRA adverse event dictionary (Version 14.0) and the Division of AIDS Table for Grading the Severity of Adult Adverse Events and Laboratory Abnormalities of the National Institutes of Health. Both systems are well established and acceptable as means for defining adverse clinical and laboratory events.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

It was not possible to pool safety data as the Phase 2 and Phase 3 studies were conducted using different designs in different populations.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The dose and formulation selected for marketing are the EVG 85mg and 150 mg tablets. This formulation was used during the Phase 3 study, and as such is appropriate to assess the safety of the proposed dose and formulation intended for marketing.

A total of 629 HIV-1 infected subjects received from 10 days to 192 weeks of EVG. Of these, 361 subjects received the final formulation proposed for marketing for up to 96 weeks in the Phase 3 Study 145: 85 mg or 150 mg QD (depending on concomitant PI use). The safety database also includes long-term exposure data on 192 subjects (184 from prior EVG studies

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who received EVG and 30 from prior studies that had not received EVG) who received EVG for an additional 192 weeks in the long-term treatment Study 130.

7.2.2 Explorations for Dose Response

The exposure-safety analyses for EVG evaluated whether there was a potential relationship between predicted EVG AUC_{tau} and C_{tau} and the most common adverse events observed during the Phase 3 study. For all EVG analyses, no relationship was observed between predicted AUC_{tau} or C_{tau} and adverse events.

7.2.3 Special Animal and/or In Vitro Testing

Comprehensive programs of non-clinical studies with EVG were conducted, and full data from these studies were provided in this NDA submission. Please refer to Section 4.3 above and the Pharmacology-Toxicology Review by Dr. Verma for additional details.

7.2.4 Routine Clinical Testing

Routine clinical testing for adverse clinical and laboratory events was comprehensive. Adverse events, serious and non-serious, were collected beginning after the informed consent form was signed through the Safety follow-up assessment. Adverse events were recorded regardless of the suspected cause of the event. Study visits occurred at Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 (end of longest duration of dosing) and at FU Weeks 4, 12 and 24. Unscheduled visits were conducted as needed to assess progression and/or resolution of events.

Safety evaluations included clinical laboratory assessments, clinical evaluation of vital signs, physical examinations, ECGs, and the subjective reporting of adverse events. For each adverse event, the following information was collected: description, classification of “serious” or “not serious,” date of first occurrence and date of resolution (if applicable), severity, causal relationship (possible, probably or definite), action taken, outcome, and concomitant or other treatment given. Similar requirements were in place for laboratory abnormalities as adverse events. Events were graded using the Applicant’s Grading Scale for Severity of Adverse Events and Laboratory Abnormalities as Grade 1 (mild), 2 (moderate), 3 (severe) and 4 (life-threatening).

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see Sections 4.4.2 and 4.4.3 above for a discussion of the PD profile of EVG. Please see section 7.7 below for a discussion of drug-drug interactions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Raltegravir (RAL) is the only other approved integrase inhibitor. The most common RAL-related adverse events include headache and insomnia. Also, thrombocytopenia, elevated fasting serum

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glucose, amylase, lipase, creatine kinase, AST, ALT, alkaline phosphatase, and bilirubin (due to metabolism by UGT1a1) have been reported related to RAL.

RAL has been reported to cause severe, potentially life-threatening, and fatal skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Hypersensitivity reactions have also been reported that were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including hepatic failure.

7.3 Major Safety Results

7.3.1 Deaths

The safety database contains information on 27 subjects who died during participation in an EVG study. There were no patterns to the causes of death that could be attributed to EVG.

Three subjects died in Study 105 due to large B-cell lymphoma on Day 159, *Pneumocystis jiroveci* pneumonia on Day 149, and cardiorespiratory failure on Day 221.

Comment: All three subjects were highly treatment experienced and achieved minimal antiviral benefit from treatment with an EVG-containing regimen. The cases of B-cell lymphoma and Pneumocystis were likely due to continued progression of HIV to AIDS and unlikely related to treatment with EVG. It is not possible to assess the relationship to EVG in the subject who died to cardiorespiratory failure as he was found dead at home and no autopsy was conducted.

In Study 145, 13 subjects (2%) died during the study; 3 subjects in the EVG group and 10 in the RAL group. Causes and timing of death are presented in Table 14.

Table 14 Deaths in Study 145

Subject	Treatment Group	Cause of Death	Applicant's Assessment of Relatedness to Study Drug	Day of Last Study Drug	Study Day of Death
0566-3310*	EVG	Cardiac failure due to ischemic cardiomyopathy	No	Day 831	Day 831
0595-4154	EVG	Hepatic failure due to HCV	No	Day 187	Day 244
1555-4095*	EVG	Peritonitis due to intestinal perforation	No	Day 263	Day 284
0359-3353*	RAL	Choking by foreign body	No	Day 226	Day 226
0637-3051*	RAL	Acute heroin	No	Day 288	Day 306

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		intoxication			
0744-3151	RAL	Hodgkins lymphoma and sepsis	No	Day 676	Day 725
1543-3294	RAL	Cardiomegaly, mitral valve prolapse	No	Day 279	Day 312
1925-3341*	RAL	Trauma due to auto accident	No	Day 1	Day 5
2140-3229*	RAL	Severe autoimmune anemia	Yes	Day 37	Day 45
2493-3396*	RAL	Possible acute coronary event	Yes	Day 139	Day 147
2493-3472*	RAL	Cardiac arrest	Yes	Day 43	Day 44
3718-4100*	RAL	Non-Hodgkins lymphoma	No	Day 485	Day 485
4024-4043*	RAL	Biliary sepsis related to small cell/neuroendocrine tumor	No	Day 1023	Day 1040

* Treatment-emergent: death event occurred after day 1 of dosing to ≤ 30 days after stopping study medication

Reviewer comment: It is not possible to confirm or deny the relatedness of death in subjects 2140-3229, 2493-3396, and 2493-3472 because there is a lack of information. For subject 2493-3396 relatedness is impossible to determine as the subject was found dead at home and no autopsy was performed. For subject 2140-3229, the investigator stated there was a possible relationship between study drug and anemia, but the consulting hematologist concluded there was no relationship. For subject 2493-3472, the cause of death was listed as cardiac arrest secondary to status epilepticus; however, no tests (EEG, MRI or LP) were performed to document the subject actually had status epilepticus. At the time of death, the subject was receiving RAL, RTV, darunavir and abacavir/lamivudine; none of these agents are known to cause seizures or status epilepticus.

Eleven subjects died during the open-label extension Study 130. Causes of death included: subdural hematoma following recreational drug overdose, PCP resulting in respiratory failure, presumed autoerotic asphyxiation, perforated ulcer, colorectal carcinoma, sepsis, occlusive coronary arterial sclerosis with dilated cardiomyopathy, killed by strangulation, PML, Hodgkins lymphoma, and advanced HIV disease. None of the deaths were considered related to study drug.

Reviewer comment: Narratives were reviewed and no pattern or events were identified that would suggest EVG poses an increased risk to subjects treated for longer than 96 weeks duration.

7.3.2 Nonfatal Serious Adverse Events

Overall, nonfatal SAEs occurred in 29% (176/599; 104 during randomized treatment and 72 during open-label treatment) of subjects treated with EVG compared to 22% (94/421) in subjects in comparator regimens in Studies 105 and 145. There were eight SAEs for which a relationship to EVG could not be ruled out:

- One event of hypersensitivity in a 51 year old Caucasian male in the EVG/RTV 20/100 mg arm of Study 105. The subject's symptoms included rash over his torso and extremities, fever, chills, and severe aches in his hands, elbows, and shoulders. All medications were stopped. EVG and abacavir/lamivudine were restarted the following day. The arthralgia and rash progressed. All medications were again discontinued the following day. The subject was seen in the study clinic with additional complaints of dizziness and swelling of the hands and feet. Physical examination revealed scattered large erythematous, well-demarcated annular lesions, some with central clearing. Laboratory evaluations included elevated liver function tests (ALT, AST, and GGT elevated to approximately twice the upper limit of the normal ranges) and a negative blood parasite examination. The subject was rechallenged with EVG and developed a rash about 3 hours after administration. He did not complain of systemic symptoms such as fever or arthralgias. EVG was discontinued. The hypersensitivity reaction was considered resolved in 10 days. The study investigator assessed the event as definitely related to EVG.
- One event of syncope was reported in the EVG/RTV 50/100 mg arm of Study 105. This was a 46-year-old Caucasian male who experienced a single episode of syncope approximately 3.5 months after starting study drug; the subject recovered without sequelae.
- One event of new onset diabetes mellitus and renal failure in a 44 year old African American male in Study 145. The subject was receiving EGV/RTV, FPV, and TVD. On study day 506 the subject presented with a serum glucose level of 854 mg/dL and complaints of polydipsia/polyuria. He was admitted with a diagnosis of hyperosmolar non-ketotic hyperglycemia and renal failure; study drugs were interrupted. He recovered and the investigator assessed these events as related to study medication; study drugs were restarted unchanged. On study day 583 he was hospitalized with acute renal failure and possible rhabdomyolysis; metformin/glipizide and gemfibrozil were discontinued and study drugs were interrupted. Upon recovery, study drugs and metformin/glipizide were restarted and renal function continued to improve.
- One event of transaminitis in a 34 year old Caucasian male on EVG/RTV, DRV and Truvada in Study 145. On study day 282 the subject experienced increased transaminases with GGT of 189 U/L (normal range 10-61), ALT 339 U/L (6-43), and AST 117 U/L (11-36). This event was considered related to study drug. On day 285, GGT was 197 U/L, ALT 352 U/L, and AST 113 U/L. The subject discontinued only study drug, last dose was on day 309. On day 337, HIV-1 RNA was < 50 copies/mL and CD4 count was 291 cells/mL, GGT 124 U/L, ALT 179 U/L, and AST 71 U/L. On study day 392 the subject again had an episode of transaminitis (off EVG): GGT 124 U/L, ALT 284 U/L, and AST 99 U/L. On day 410, the

subject began treatment with atazanavir, tenofovir DF, emtricitabine, and ritonavir. Transaminases and GGT declined progressively, and returned to within normal limits.

- One event of cholestatic hepatitis in a 39 year old Caucasian male on EVG/RTV, DRV, and etravirine in Study 145. On day 263 the subject presented with jaundice, dark urine, pruritis and nausea. ALT was 120 U/L, AST 258 U/L, GGT 92 U/L, Total bilirubin 134 mg/dL, and ALP was 179 U/L. On day 270, study treatment as well as all background antiretrovirals and celecoxib therapy were interrupted. On day 271, allopurinol was interrupted. On day 273, itch was resolved, ALT was 107 U/L, AST 230 U/L, GGT 92 U/L, total bilirubin 113 mg/dL, ALP 174 U/L, and albumin 33 g/L. A liver ultrasound showed hepatosplenomegaly, normal direction of blood flow to the portal system, thickening of the gallbladder wall, gallstones in the gallbladder, no stones in the common bile duct or hepatic ducts, and no biliary tract dilation. The investigator assessed the potential causative agents were, in descending order, DRV, etravirine, and EVG.
- One event of necrotizing retinitis in a 23 year old African American male in Study 130 being treated with EVG/RTV, TDF/FTC and darunavir. The subject presented complaining of progressive vision loss, floaters and blurred vision over the prior three weeks. The subject admitted to poor adherence to antivirals. He refused a diagnostic workup. Two days later he was admitted to hospital for progressive outer retinal necrosis and treated with intravenous ganciclovir and an intravitreal injection of foscarnet. Aqueous humor testing was negative for Varicella, CMV and herpes viruses. The next day he was found to have increased creatinine that was most likely due to medications, such as tenofovir, ganciclovir and Cozaar; FTC/TDF were discontinued and his BUN and creatinine improved. The retinal lesions also improved. The investigator attributed the retinal necrosis to EVG and his acute on chronic renal insufficiency to TDF/FTC.
- One event of increased CK with pancreatitis in a 38 year old Hispanic male in Study 130. The subject was receiving EVG/RTV, darunavir and FTC/TDF. He complained of abdominal pain, nausea, fever, chills and vomiting. His CK was 1934 U/L and lipase was 538 U/L; he was diagnosed with pancreatitis and all study medications were discontinued. His CK went down to 538 U/L and he recovered from pancreatitis. EVG/RTV, FTC/TDF and darunavir were restarted and he continued to improve. The investigator attributed the elevated CK levels to the subject's ARV regimen.
- One event of acute decompensation of dilated cardiomyopathy in a 41 year old African American in Study 130. This subject was found to have dilated cardiomyopathy on TEE with an ejection fraction of 25%. He became short of breath and had acute decompensation with hypoperfusion of the kidneys. He also had an IVC thrombus which was treated with a filter. He was also receiving CHOP and Rituxan as treatment for Castleman's syndrome. The investigator initially assessed these events as related to RTV because it is known to increase exposure to doxorubicin and that EVG is likely to increase exposure to doxorubicin, but changed the assessment to not related. The subject recovered.

There were a few SAE events of renal insufficiency/renal failure reported which appeared related to co-administration of tenofovir, which is known to cause proximal renal tubulopathy. Otherwise, SAEs were reported in single subjects and many reflected progression of the subject's

underlying HIV disease or were completely unrelated to study treatment (admission to hospital for elective surgery, trauma secondary to MVAs or assaults, overdoses, pneumonia, exacerbation of other underlying illnesses, and various carcinomas/lymphomas).

7.3.3 Dropouts and/or Discontinuations

In Studies 105, 130, and 145, 4.5% (27/599) of subjects receiving an EVG-containing regimen discontinued treatment due to adverse events, compared to 4% (17/421) of subjects treated with a non-EVG containing regimen.

Six subjects discontinued an EVG-containing regimen in Study 105 due to:

- Anxiety in a subject on EVG, RTV, Epzicom and TDF on day 6; treated with Xanax.
- Worsening seizures on day 5 in a subject on EVG, RTV and Truvada; subject had a history of seizures
- Substance abuse exacerbation in a subject on EVG, RTV, ddI and Truvada; subject admitted to inpatient treatment facility
- B-cell lymphoma in a subject on EVG, RTV, Truvada and enfuvirtide (also SAE and death)
- Hypersensitivity in a subject on EVG, ATV, RTV and Epzicom. On ~day 14 subject had rash and stopped all medications, on day 15 restarted but on day 16 stopped due to increased rash and arthralgias; rash and arthralgias resolved. The subject was rechallenged with EVG and developed a rash approximately 3 hours after administration.
- Cerebellar syndrome in a subject on EVG, RTV, TDF, LAM and enfuvirtide. During month 6 this subject had left sided clumsiness and gait imbalance; MRI showed hypodense cerebellar lesion and assessed as possible PML.

Two subjects discontinued from the CPI/r group due to:

- Diarrhea, nausea and oral hypoesthesia on day 1 in a subject on ATV, RTV and Truvada
- Pneumococcal sepsis in a subject on DRV, RTV, TDF, LAM and enfuvirtide. During month 4 subject complained of back pain, fever and myalgias and decreased oxygen saturation; blood cultures grew out *Streptococcus pneumoniae*.

Ten subjects discontinued study drug due to an AE. None of the AEs leading to discontinuation of study drug were considered by the investigator to be related to study drug.

Eleven subjects (3%) in the EVG group discontinued from Study 145 due to adverse events compared to 15 (4%) of subjects in the RAL group. Adverse events leading to discontinuation and considered related to study drug(s) by the investigator are further described in the following table.

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Table 15 Discontinuations due to adverse events, Study 145

ID Number	Events	SAE	Description
EVG			
0688-4077	Grade 2 abdominal pain, vomiting, increased waist girth	N	38 year old white female on atazanavir, RTV, and tenofovir discontinued on day 3.
0744-3470	Hemolytic anemia	Y	45 year old white male with history of HBV and HCV on atazanavir, RTV, abacavir, lamivudine. Day 30 received multiple blood transfusions for hemolytic anemia. Subject recovered and was subsequently diagnosed with lung cancer (day 45). Discontinued study medications on day 81.
1925-3259	Transaminitis	N	34 year old white male on darunavir, RTV, tenofovir, and FTC. Subject discontinued around day 240 for GGT 189, ALT 339 and AST 117. On day 198 the subject was diagnosed with unrelated Bowen's disease.
2493-3065	Grade 3 nausea, vomiting, headache	N	50 year old Black female on fosamprenavir, RTV and tenofovir/emtricitabine and discontinued on day 8.
3672-4022	Fatigue	N	49 year old white female on darunavir, RTV and tenofovir discontinued on day 18 for Grade 2 fatigue; also had nausea and myalgia considered not related.
4099-4121	Cholestatic hepatitis	Y	34 year old white male with history of HCV on darunavir, etravavir, ETV and RTV. On day 263 the subject presented with jaundice, dark urine and pruritis. ALT 120, AST 358, GGT 92, total bilirubin 1.34. Abdominal ultrasound showed hepatosplenomegaly and gall stones.
RAL			
0310-3047	Abdominal cramping	N	54 year old white male on darunavir, lamivudine, tenofovir, and RTV discontinued day 7.
0433-3102	Maculo-papular facial rash	N	41 year old Black female initially on darunavir, tenofovir, RTV, switched to fosamprenavir, RTV, tenofovir. Events started day 43; treated with benzoyl peroxide with clindamycin (topical), hydrocortisone IM, fexofenadine, and diphenhydramine hydrochloride. Last dose of study drugs were day 80; event resolved by day 162.
0661-3173	Hepatic enzyme increased	N	57 year old white female on etravavir and lopinavir/ritonavir discontinued day 29 for

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			elevated enzymes.
1021-4031	Increased GGT	N	45 year old white male on darunavir, lamivudine, RTV, and tenofovir. Subject had history of high GGT; discontinued day 127 for worsening GGT increase.
1536-3031	Acute hepatitis, nephritis, serum sickness, rash	N	47 year old Black male on darunavir, RTV and tenofovir. Events started day 25 and subject discontinued on day 57.
1603-3363	Elevated triglycerides	N	54 year old Black male on darunavir, TRV and tenofovir/emtricitabine. Subject discontinued on day 96.
1950-3252	Lipohypertrophy	N	52 year old Black female on darunavir, RTV and tenofovir. Event started day 491; subject discontinued on day 531.
3991-4023	Vasculitic rash	N	60 year old white male on darunavir, RTV and tenofovir. Rash started on day 9, study medications were discontinued on day 10 and rash resolved day 18.
5007-3451	Hepatitis	Y	46 year old Black female on darunavir, tenofovir and RTV. Approximately day 30 subject complained of nausea, vomiting and fever; ALT 191, AST 218, total bilirubin 0.6. Repeat labs showed total bilirubin 4.6 (direct 3.4), ALT 210 and AST 201. The subject developed a generalized rash. Study medications were discontinued Week 8; rash resolved and LFTs returned to normal.

Narratives for events considered not-related to study medications or procedures were reviewed. In the RAL group, not related events included: renal cell carcinoma, exacerbation of chronic hepatitis C, lung cancer, increased lipids, hepatitis (acute hepatitis B) and substance abuse (prescription narcotics and alprazolam). Not related events in the EVG group included: acute renal failure, large B cell lymphoma, lung cancer (2), and rectal hemorrhage.

Comment: There was no pattern to the events leading to discontinuations.

7.3.4 Significant Adverse Events

Significant, defined as treatment emergent Grade 2 or higher, adverse events were reported for similar proportions of subjects who received EVG and those in comparator groups: 55% (329/599) and 52% (219/421), respectively. There were no patterns to these events that would suggest a specific EVG effect.

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Comparable proportions of subjects, 21% in the EVG and 19% in the CPI/r group of Study 105 experienced Grade 3 and 4 treatment emergent adverse events. The events were similar in both groups, there were no patterns to the events, and individual events occurred in no more than two subjects.

In Study 145, 68% of subjects in both treatment groups experienced a treatment-emergent AE of at least moderate severity (Grade 2-4). Only diarrhea was reported with greater frequency among subjects treated in the EVG group. Table 16 summarizes events reported in at least 2% of subjects.

Table 16 Significant treatment-emergent adverse events reported $\geq 3\%$ of subjects through Week 96

N(%)	EVG (n=354) ¹	RAL (n=358) ¹
Diarrhea	47 (13)	28 (8)
Nausea	14 (4)	10 (3)
Abdominal pain	11 (3)	10 (3)
Vomiting	11 (3)	9 (3)
Fatigue	10 (3)	9 (3)
Oedema peripheral	10 (3)	4 (1)
Bronchitis	17 (5)	21 (6)
Upper respiratory tract infection	19 (5)	18 (5)
Pneumonia	15 (4)	8 (2)
Urinary tract infection	14 (4)	18 (5)
Back pain	21 (6)	15 (4)
Pain in extremity	14 (4)	15 (4)
Arthralgia	18 (5)	9 (2.5)
Headache	13 (4)	7 (2)
Depression	21 (6)	20 (6)
Insomnia	9 (3)	9 (3)
Anxiety	9 (3)	6 (2)
Cough	8 (2)	11 (3)

1. Excludes 10 subjects from site 4390; 3 EVG and 7 RAL subjects.

The majority of events summarized in Table 3 were of moderate (Grade 2) severity in both treatment groups. Grade 3 or 4 AE were reported by 24% of EVG (86 subjects) and 24% of RAL (85 subjects) treated subjects.

In Study 130 significant adverse events reported for 73 subjects. Events reported in more than one subject included anemia, neutropenia, myocardial infarction, cardiac failure congestive, congestive cardiomyopathy, pyrexia, pneumonia, cellulitis, HIV wasting syndrome, esophageal candidiasis, *Pneumocystis jiroveci* pneumonia, ALT increased, back pain, muscle spasms,

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Hodgkin's disease, peripheral neuropathy, depression, mental status changes, acute renal failure, and hypotension.

Four of these subjects (2%) experienced Grade 3 events that were considered by the investigator to be related to study drug (acute pancreatitis, hepatitis B, and peripheral neuropathy [2 subjects]).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Across the EVG safety database, the most common treatment-emergent adverse events related to EVG included: diarrhea, nausea, vomiting, abdominal distention, fatigue, back pain, headache, dizziness, dysguesia, rash (dermatitis, drug eruption, eczema, pruritus, pruritus generalized, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash popular, rash pruritic, and urticaria), bronchitis, sinusitis, nasopharyngitis, and upper respiratory tract infection/symptoms

Treatment-emergent adverse events with $\geq 10\%$ incidence in any treatment group included: diarrhea, constipation, nausea, vomiting, fatigue, pyrexia, injection site reaction, upper respiratory tract infections, sinusitis, headache, cough, and pharyngolaryngeal pain.

There were no differences in the adverse event profile between subjects who received EVG 300 mg and those who received 85 or 150 mg in Study 130.

Any adverse events reported by at least 5% of subjects in each treatment group of Study 145 are shown in Table 17, and those considered treatment-related are shown in Table 18. Only diarrhea occurred more frequently among subjects treated with an EVG-containing regimen.

Table 17 All grade treatment-emergent adverse events through Week 96

N(%)	EVG (n=354)	RAL (n=358)
Any adverse event	319 (90)	319 (89)
Diarrhea	119 (34)	78 (21)
Upper respiratory tract infection	67 (19)	56 (16)
Headache	47 (13)	37 (10)
Nausea	44 (12)	41 (12)
Back pain	39 (11)	35 (10)
Fatigue	37 (10.5)	26 (7)
Cough	37 (10.5)	47 (13)
Bronchitis	36 (10)	36 (10)
Nasopharyngitis	33 (9)	30 (8)
Sinusitis	29 (8)	28 (8)

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Depression	29 (8)	29 (9)
Arthralgia	28 (8)	26 (7)
Rash	26 (7)	27 (7.5)
Urinary tract infection	26 (7)	56 (16)
Pain in extremity	25 (7)	25 (7)
Abdominal pain	23 (6.5)	20 (6)
Insomnia	23 (6.5)	21 (6)
Vomiting	20 (6)	29 (8)
Pneumonia	18 (5)	9 (2.5)
Folliculitis	18 (5)	7 (2)
Pyrexia	15 (4)	20 (6)
Hypertension	14 (4)	23 (6)

Table 18 All grades related treatment-emergent adverse events through Week 96

N(%)	EVG (n=354)	RAL (n=358)
Diarrhea	25 (7)	19 (5)
Nausea	14 (4)	9 (2.5)
Vomiting	4 (1)	5 (1)
Abdominal distention	2 (<1)	4 (1)
Fatigue	7 (2)	4 (1)
Headache	10 (3)	9 (2.5)
Dizziness	2 (<1)	5 (1)
Dysgeusia	2 (<1)	4 (1)
Rash	3 (<1)	5 (1)

7.4.2 Laboratory Findings

There were no pre-clinical signals for laboratory toxicities. Across the studies included in the safety database, no clinically relevant pattern of treatment-related adverse laboratory abnormalities in hematologic or clinical chemistry values were attributable to EVG.

The number of subjects with treatment-emergent marked (Grade 3 and 4) laboratory abnormalities through Week 48 in Study 105 was low; typically 1-2 subjects with any individual abnormality.

In Study 130, 59 subjects (31%) had a maximum Grade 3 laboratory abnormality, and 20 subjects (10.5%) had a maximum Grade 4 abnormality. Grade 3 or 4 laboratory abnormalities were most frequently reported for creatine kinase (15 subjects), GGT (15 subjects), serum amylase (14 subjects), fasting triglycerides (12 subjects), and urine glucose (10 subjects). Most of the Grade 3 or 4 laboratory abnormalities were not accompanied by clinical adverse events and many were due to underlying comorbidities (eg, glycosuria in subjects with diabetes, GGT

elevation in subjects with chronic Hepatitis C). One subject with Grade 3 GGT elevation also had an adverse event of Hepatitis B, Grade 3 AST elevation, and Grade 4 ALT elevation reported on the same date. The safety data from the substudy, during which subjects received a higher dose of EVG (300 mg/day) for a median duration of 39.9 weeks, did not differ when compared with the main study, during which subjects received EVG 150 or 85 mg/day.

More detailed review of laboratory abnormalities in Study 145 are presented below.

- **Renal-Related Abnormalities**

Some nucleos(t)ide analogues, such as tenofovir, as well as the cobicistat component of Stribild are associated with a constellation of renal AEs (e.g. renal failure, Fanconi's syndrome, hypophosphatemia, and increased blood creatinine). In the Stribild NDA, there was a disproportionate number of renal adverse events leading to study drug discontinuation (including proximal tubulopathies) in the Stribild group combined with a higher frequency of graded serum creatinine and urine protein abnormalities; these toxicities were ascribed to cobicistat, which also produced an asymptomatic increase in creatinine related to inhibition of secretion of creatinine at level of tubule, and tenofovir which causes a Fanconi-like syndrome.

In Study 145, there were no clinically relevant differences in renal abnormalities between treatment groups. The majority of clinical renal events occurred in five or less subjects per group. Further, there were no events of Fanconi's syndrome in any study subject.

Creatinine: There was no difference in the number of subjects with creatinine increases between treatment groups, or the median change from baseline in serum creatinine levels at Week 96: +0.10 mg/dL in both groups. Treatment-emergent serum creatinine abnormalities were reported for 32 subjects in the EVG group and 36 subjects in the RAL group; the majority of which were considered mild to moderate in severity. Grade 3 or 4 serum creatinine abnormalities were reported for 2 subjects in each group; all were considered marked laboratory abnormalities, and none were accompanied by concomitant clinical events.

eGFR_{CG}: There was no difference in the number of subjects or median change from baseline at Week 96 in the EVG or RAL groups: -10.8 mL/min and -11.7 mL/min, respectively.

Proteinuria: Treatment-emergent proteinuria was reported for similar numbers of subjects in the two groups (~50%). One event of Grade 3 proteinuria was reported in a single subject in the EVG group. The majority of these subjects were receiving concomitant tenofovir.

Phosphate: Treatment-emergent hypophosphatemia was reported for 41 EVG subjects and 31 RAL subjects. Most events were Grade 1 or Grade 2 in severity; Grade 3 hypophosphatemia was reported for 2 subjects in the EVG group.

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Table 19 Renal-related laboratory abnormalities

N (%)	EVG	RAL
↑ Serum creatinine		
-Grade 1-4	32/349 (9)	36/353 (10)
-Grade 3-4	2 (<1)	2 (<1)
Proteinuria		
-Grade 1-4	170/348 (49)	176/353 (50)
-Grade 3-4	1 (<1)	0
Hypophosphatemia		
-Grade 1-4	41/349 (12)	31/353 (9)
-Grade 3-4	2 (<1)	0

Narratives for 14 subjects (5 EVG, 9 RAL) with a constellation of increased creatinine, decreased GFR, proteinuria and/or hypophosphatemia were reviewed. The five cases among EVG recipients are discussed below.

- Subject 0730-3435 was a 44 year old Black male treated with EVG, FPV/r, and Truvada. At baseline his creatinine was 1.20 mg/dL and eGFR was 98.78 mL/min. At Week 20 he was diagnosed with a urinary tract infection and treated with Bactrim (Cr 2.48 mg/dL; eGFR 50.48 mL/min). At Week 72 he was diagnosed with Grade 3 diabetes mellitus and placed on insulin and metformin (Cr 2.67 mg/dL; eGFR 49.76 mL/min; serum glucose 854). At Week 84 he was diagnosed with acute renal failure (Cr 7.22 mg/dL; BUN 112). He was hospitalized, all study medications were discontinued and his renal function returned to baseline levels.

Reviewer comment: The etiology for this subject's renal impairment is unknown, and may have been attributable to UTI, antibiotic use, or diabetes. It was unlikely due to tenofovir as he remained on tenofovir throughout the course of events.

- Subject 1534-3297 was a 49 year old Black female treated with EVG, DRV/r, and tenofovir. At baseline her creatinine was 0.76 mg/dL and eGFR was 104.74 mL/min. Between Weeks 2-48 her creatinine fluctuated between 0.84 and 1.10 mg/dL and eGFR between 70.41 and 94 mL/min. At Week 56 her creatinine increased to 1.33 mg/dL, eGFR decreased to 56.32 mL/min, with trace proteinuria. No changes to study medications were made and her creatinine continued to range from 0.95 to 1.26 mg/dL and her eGFR from 82.51 to 54.29 mL/min.

Reviewer comment: The etiology for this subject's renal impairment is unknown. She received tenofovir during the entire course of events, so the etiology was unlikely tenofovir-associated proximal tubulopathy.

- Subject 0559-4070 was a 44 year old White male treated with EVG, etravavirine and DRV/r. At baseline he had a serum phosphate level of 2.2 (Grade 1) which decreased to 1.2 (Grade 3

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at Week 16. He received treatment with phosphorous and his level increased to 1.5. Throughout the course of events his creatinine and eGFR remained normal, and there were no changes made to his study medications. This subject was also diagnosed with chronic alcohol abuse.

Reviewer comment: Hypophosphatemia was present at baseline and is likely attributable to his chronic alcohol abuse.

- Subject 1960-3197 was a 65 year old Black male treated with EVG, DRV/r, and Truvada. At baseline his serum phosphate level was normal and at Week 4 it was 1.7 (Grade 1); creatinine and eGFR were normal with trace proteinuria. At Week 12 his phosphate level was normal at 2.8 and continued to fluctuate between 1.7 and 2.3 for the remainder of the study. There were no changes made to his study medications.

Reviewer comment: The etiology for this subject's hypophosphatemia is unknown.

- Subject 0765-3431 was a 47 year old Black male treated with EVG, DRV/r, and Truvada. This subject had a history of hypertension. At baseline his serum creatinine was 0.95 mg/dL and eGFR was 134.36 mL/min. Between Weeks 2-40, his creatinine ranged from 1.08 to 1.24 mg/dL, eGFR from 114.46 to 100.06, with trace to 1+ proteinuria. At Week 40 he was noted to have 2+ proteinuria, creatinine 1.24 mg/dL and eGFR 100.06 mL/min (Grade 2); Truvada was discontinued and he was started on ABC/3TC.

Reviewer comment: The etiology for this subject's renal impairment was likely due to hypertension, but tenfovir-associated proximal tubulopathy can not be ruled out.

Reviewer comment: In summary, the preclinical data, data reviewed in the Stribild® NDA and in this NDA do not indicate that EVG causes renal toxicity on its own or potentiates renal toxicity due to other co-administered medications.

- **Other Clinical Laboratory Parameters**

In general, it does not appear that EVG has a negative impact on any laboratory parameters.

Glucose: There were no clinically relevant changes from baseline through Week 96 in fasting glucose levels.

Lipids: Similar numbers of subjects in each treatment group had treatment-emergent abnormalities reported for fasting total cholesterol levels >300 mg/dL (5%) or fasting triglycerides (5%).

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Amylase/Lipase: Six percent of subjects in both treatment groups had serum amylase levels >2 X ULN and twice as many subjects treated with EVG experienced lipase elevations: 14% versus 7%. However, only 1 subject in the EVG group had a clinical event of acute pancreatitis.

AST/ALT: Subjects in the EVG group had lower percentages of Grade 3 or 4 liver enzyme and other liver-related abnormalities reported (EVG versus RAL: ALT >5 X ULN 2% versus 5%; AST >5 X ULN 2% versus 6%; GGT 3% versus 7%; and bilirubin >2.5 X ULN 6% versus 9%).

There were 13 subjects (EVG 6, RAL 7) who had ALT or AST values >3 X ULN with total bilirubin values >2 X ULN. Enzymatic elevations were transient and subjects generally recovered after study drug discontinuation with no sequelae, and none of these events met the definition of Hy's law.

In most cases subjects had alternative reasons for liver enzyme elevations. For example, in the EVG group, four subjects were on atazanavir (ATV), one of which had AST elevation and normal ALT following an acute myocardial infarction, one was on darunavir (DRV) and had chronic HCV infection, and two others were co-infected with chronic Hepatitis C. Both ATV and DRV are known (and labeled) to cause transaminitis and elevated bilirubin levels. There was case of cholestatic hepatitis (reported as an SAE and described in Section 7.3.2) that was considered related to EVG/r, DRV, etravirine and co-infection with HCV.

Among subjects in the RAL group, again most had alternative explanations for transaminitis: acute and chronic Hepatitis B infection, metastases, on ATV or DRV, and/or alcohol use.

Creatine Kinase: A recent report suggested that RAL is associated with CK elevations. In Study 145, the frequency of CK elevations ≥ 10 X ULN were similar in both treatment groups: 4% RAL versus 6% EVG.

- **Hematologic Parameters**

No clinically relevant changes from baseline through Week 96 were observed among various hematologic parameters between the two treatment groups in Study 145.

Table 20 Hematologic abnormalities, 96 week analysis

N (%)	EVG	RAL
Hemoglobin		
-Grade 1-4	25/349 (7)	11/352 (3)
-Grade 3-4	1 (<1)	4 (1)
Neutrophils		
-Grade 1-4	60/349 (17)	54/352 (15)
-Grade 3-4	11 (3)	11 (3)
Platelets		
-Grade 1-4	26/348 (7)	32/352 (9)
-Grade 3-4	1 (<1)	2 (<1)

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- **Urinalysis**

Six percent of EVG-treated and 7% of RAL-treated subjects had Grade 3 hematuria, and no subject had Grade 4 hematuria. Grade 3 glycosuria was also comparable between treatment groups: 4% and 3% in the EVG and RAL group, respectively.

7.4.3 Vital Signs

No clinically relevant pattern of changes in vital signs was observed between subjects who received EVG in combination with ritonavir and other antiretroviral agents and those who received comparator regimens.

7.4.4 Electrocardiograms (ECGs)

There were no clinically relevant changes in ECGs observed among subjects treated with EVG. Results from the Thorough QTc Study (GS-US-183-0128) indicated a lack of an effect of ritonavir-boosted EVG on the QT/QTc interval.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were required or conducted.

7.4.6 Immunogenicity

EVG is not immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no apparent dose dependency for any adverse events. Adverse events considered possibly, probably or definitely related to EVG (see Section 7.4.1) occurred at all dose levels.

7.5.2 Time Dependency for Adverse Events

Adverse events occurred at all times during treatment. There was no pattern of adverse events that suggested that certain events occurred earlier or later during treatment.

7.5.3 Drug-Demographic Interactions

There were no differences in adverse clinical events or laboratory abnormalities between demographic subgroups.

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7.5.4 Drug-Disease Interactions

No drug-disease interactions were identified.

7.5.5 Drug-Drug Interactions

Please refer to the Clinical Pharmacology Review by Dr. for a detailed discussion of the drug-drug interaction studies, and to Section 4.4.2 for a discussion of the PD and PK properties of EVG.

There are no relevant interactions between EVG and protease inhibitors boosted with RTV (tipranavir, darunavir, fosamprenavir), or the nucleos(t)ide analogues emtricitabine, tenofovir, zidovudine, stavudine, abacavir, or didanosine. Higher EVG exposures were observed in interaction studies with RTV-boosted atazanavir and lopinavir; the lower 85 mg dose of EVG is recommended when co-administered with these boosted PIs.

EVG exposures decrease when co-administered with moderate-to-strong CYP3A inducers. Because EVG may lose therapeutic activity, the following agents are not recommended for co-administration with EVG/RTV : rifampin, rifabutin, rifapentine, St. John's wort, systemic dexamethasone, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin.

By inhibiting CYP3A, RTV substantially increases systemic exposure of CYP3A substrates [e.g. alfozsin, ergot derivatives, cisapride, HMG CoA reductase inhibitors (particularly lovastatin & simvastatin), phosphodiesterase-5 inhibitors, sedative hypnotics (particularly midazolam and triazolam)].

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Preclinical testing demonstrated that EVG is not carcinogenic (see Section 4.1). The overall incidence of neoplasm in the Phase 3 trial was similar in the EVG/r group (4%) compared to the RAL group (4%); none were considered related to study medication.

7.6.2 Human Reproduction and Pregnancy Data

No adequate and well-controlled studies of EVG have been conducted in pregnant women. Animal studies did not indicate direct or indirect harmful effects of EVG with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. Elvitegravir should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

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No pregnancies were reported in Study 105. In Study 130, one pregnancy was reported that resulted in a spontaneous abortion. Seven pregnancies were reported in Study 145 (4 EVG, 3 RAL).

- Two subjects (1 in each treatment group) were determined to be pregnant prior to study drug administration; 1 spontaneous abortion and 1 induced abortion.
- Two in the EVG group delivered healthy babies.
- One in the RAL group had a spontaneous abortion.
- Two pregnancies (one in each group) were ongoing at the time of NDA submission.

Reviewer comment: EVG will be labeled as Pregnancy Category B. From the very limited number of cases, there does not appear to be an increased risk of adverse outcomes among women who become pregnant while taking EVG.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant proposed a pediatric investigational plan for EVG as follows:

- EVG tablets (dose strengths 85-mg and 150-mg) being developed for adults have been administered to treatment-experienced HIV-1 adolescent subjects ages 12 to 18 years of age (Study GS-US-183-0152).

-  (b) (4)

As stated, the Applicant has completed one study in treatment experienced adolescents (12 to 17 year of age) using the proposed to be marketed EVG tablet formulation.

Study **GS-US-183-0152** was a Phase 1 open-label, multicenter study with a 10-day pharmacokinetic evaluation phase to determine the pharmacokinetic parameters and appropriate dose(s) of EVG in HIV-1 infected antiretroviral treatment-experienced adolescent subjects, ages 12 to < 18 years of age. Subjects who completed the 10-day PK evaluation phase and had baseline HIV-1 RNA >1000 copies/mL were eligible to enroll in an optional treatment phase.

Eligible subjects were assigned to treatment groups as follows:

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Group 1: EVG 150 mg plus RTV-boosted darunavir, fosamprenavir, or tipranavir (n=11)
Group 2: EVG 85 mg plus RTV-boosted lopinavir (LPV) or atazanavir (ATV) (n=14)

- **Demographic and Disease Characteristics**

Of the 25 enrolled subjects, 13 (52%) were male, 7 (28%) were White, and 18 (72%) were African-American. The median age was 16 years (range 12 to 17 years: 80% 15 to < 18 years: 48% Tanner Stage 5). Approximately one-half (14/25, 56%) of subjects were asymptomatic at baseline. Twelve subjects had baseline HIV-1 RNA <400 copies/mL and 13 had HIV-1 RNA levels >1000 c/mL.

Thirteen of 14 subjects in the 85 mg and 10/11 in the 150 mg groups completed the PK evaluation phase. One subject in each treatment group discontinued study medications on Day 1 due to nausea, vomiting, dizziness and chills.

- **Efficacy Assessment**

Responses at the end of the 10-day PK evaluation phase are shown in Table 21.

Table 21 Antiviral outcomes at Day 10, Study 152

	Baseline HIV-1 RNA <400 c/mL (N=12)	Baseline HIV-1 RNA >1000 c/mL (N=13)
Mean (SD) Change from Baseline in HIV-1 RNA (log10 copies/mL)	-0.09 (0.212)	-1.87 (0.403)
Mean (SD) Change from Baseline in CD4 cell count (cells/ μ L)	65 (199.8)	40 (92)
Proportion with HIV-1 RNA <400 copies/mL	10 (83%)	8 (61.5%)
Proportion with HIV-1 RNA <50 copies/mL	9 (75%)	0 (0%)

Eleven (3 in the 85 mg and 8 in the 150 mg group) subjects with HIV RNA >1000 copies/mL at screening who completed the 10-day PK study were eligible for enrollment in the optional treatment phase, and 9/11 enrolled in it. Of these, all nine completed treatment through 48 weeks. Four of the nine (44%) achieved HIV RNA <400 copies/mL and 2 (22%, 1 85 mg and 1 150 mg) subjects achieved HIV RNA <50 copies/mL at Week 48.

Baseline protease and reverse transcriptase genotypic and phenotypic data were available at screening for 12 subjects with HIV-1 RNA >1000 c/mL; 9 of the 12 subjects had major reverse transcriptase (RT) and protease (PR) resistance mutations and 7 subjects had phenotypic resistance to at least 1 drug.

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- **Virologic Failure and Resistance Assessment**

Four subjects who had protocol-defined virologic failure had post-baseline resistance analyses conducted. At baseline none had primary IN resistance mutations (T66I/A/K, E92Q, Y143R/H/C, Q148H/K/R, and N155H/S) and three had secondary IN mutations (V72I, L74L/M, and S119R/G). The fourth subject did not have any IN resistance mutations at baseline and developed a secondary IN mutation (V72V/I) while on treatment. All four subjects had HIV-1 that was and remained phenotypically susceptible to EVG, and no primary PI resistance mutations emerged in these subjects.

- **Pharmacokinetic Assessment**

Analysis of pharmacokinetic data indicated that a once-daily adult dose of EVG 85-mg or 150-mg added to a regimen that includes an RTV-boosted PI resulted in EVG exposures comparable with those in HIV-1 infected adults. Preliminary evaluation shows no correlation between response and age, exposure or baseline viral load (see Clinical Pharmacology and Pharmacometrics reviews).

- **Safety Assessment**

No deaths were reported. One SAE occurred following the 10-day PK evaluation phase in a 17 year old male treated with EVG 150 mg due to Grade 3 pneumonia on Day 23. Two subjects (one in each treatment group) discontinued on Day 1 due to vomiting, chills, dizziness and pyrexia.

During the 10-day PK evaluation phase of the study, treatment-emergent AEs were reported in 10/14 subjects (71%) in the EVG 85 mg group and in 8/11 subjects (73%) in the EVG 150 mg group. Overall, nausea (6/25, 24%), abdominal pain (2/25, 14%), and dizziness (3/25, 12%) were the most frequently reported adverse reactions.

During the optional 48 week treatment phase, all nine subjects reported at least one treatment-emergent adverse event. The most frequently reported events were nausea, diarrhea, vomiting, and headache.

Reviewer Comment: Elvitegravir exposure was comparable between adolescents and adults. EVG appeared generally well tolerated in adolescents and no new patterns of adverse events were identified. Only 9 adolescent subjects received EVG for more than 10 days and 2 of these achieved a successful outcome. It appears that the lack of correlation between exposures and HIV-1 RNA levels may be due to lack of adherence. There were no relevant differences in safety outcomes in adolescents when compared to adults.

Since HIV-1 infection is a serious and life-threatening illness, DAVP is willing to accept some uncertainty about the general efficacy of EVG. As such, it is reasonable to include

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the available pharmacokinetic, safety and efficacy data from the 12-17 year olds in the EVG label. (b) (4)

No assessment of the impact of EVG on growth and development was conducted.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are limited clinical experience is available at doses higher than the therapeutic doses of EVG. No severe adverse reactions were reported at higher (300 mg/day) or supratherapeutic doses. Two subjects in the EVG group of Study 0145 received 150 mg instead of 85 mg, for 3 and 29 days, respectively, without any signs or symptoms.

No safety issues concerning the abuse or misuse of EVG are anticipated from the available data as EVG does not produce any euphoric effects. No specific studies have been conducted to evaluate the effects of subjects being withdrawn from EVG.

8 Postmarket Experience

There is no Postmarket Experience with EVG tablets alone as they are not currently marketed anywhere in the world. EVG is a component of the fixed dose combination Stribild®. Stribild was approved in the US on 27 August 2012. A Periodic Adverse Drug Experience Report (PADER) covering the period 27 August 2012 to 26 November 2012 was reviewed. A total of 15 adverse experience reports describing 22 events were included in the PADER.

15-Day Alert reports

- Diverticulitis of the sigmoid colon in a 48 year old Caucasian male
- Suicide attempt/depression in a 36 year old Caucasian male. This patient had a history of major depression and attempted suicide by licing his right hand.
- Suicidal ideation in a 26 year old Caucasian male who broke up with his partner and presented with suicidal ideation.

Non-serious listed events

- Diarrhea
- Discolored feces
- Lip disorder (nerve contraction)
- Nausea and vomiting
- Weight gain with increased appetite
- Dysgeusia (metallic after taste)
- Syncope with orthostatic hypotension
- Rash

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- Urticaria
- Flushing, ataxia, hypotension, and possible interaction with tamsulosin
- Hot flashes
- Hypotension

In summary, no events attributable to the EVG component of Stribild® were identified from the data presented in this report.

9 Appendices

9.1 Labeling Recommendations

1. Indications and Usage

The Applicant's initial proposed Indication was:

1.1 In Treatment-Experienced Patients

Vitekta, coadministered with a ritonavir-boosted protease inhibitor and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced patients >18 years of age. (b) (4)

The description of the adult clinical trial is redundant. The proposed revised Indication, if accepted, would read:

1.1 In Treatment-Experienced Patients

Vitekta, coadministered with a ritonavir-boosted protease inhibitor and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults. (b) (4)

Other Proposed Labeling Revisions

6.1 Adverse Reactions from Clinical Trials Experience

- Table 2 will be revised to display related treatment-emergent adverse reactions.
- A statement describing the most common adverse reactions observed in the adolescent study will be added.

8.4 Pediatrics

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- This section will be revised to state that safety and efficacy have not been established in pediatric patients [REDACTED] (b) (4) and clinical data from the adolescent study will be included.

12.3 Pharmacokinetics in Pediatric Patients

- This section will be revised to include pharmacokinetic data from the adolescent study.

14.1 Treatment-Experienced Adult Patients

- Geographic distribution data will be added to the description of the clinical trial.
- Table 10 will be revised to delete the [REDACTED] (b) (4) data as they are unnecessary.

Additional changes to these and other sections of the label may be forthcoming.

9.2 Advisory Committee Meeting

No AC was required for this application.

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/s/

RUSSELL D FLEISCHER
03/22/2013

LINDA L LEWIS
03/22/2013

I concur with the Clinical Reviewer's assessment of this application.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 209093

Applicant: Gilead Sciences

Stamp Date: 06/27/2012

Drug Name: Elvitegravir

NDA/BLA Type: 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: GS-US-183-101 Study Title: A Double-blind, Randomized, Placebo-controlled Phase ½ Study of the Safety, Pharmacokinetics, and Antiviral Activity of GS-9137 Following Oral Administration in Subjects Infected with HIV-1 Sample Size: 40 Arms: Cohort 1, 400 mg of GS-9137 twice-daily; Cohort 2, 800 mg of GS-9137 twice-daily; Cohort 3, 800 mg of GS-9137 once-daily; Cohort 4, 200 mg of GS-9137 twice-daily; Cohort 5, 50 mg of GS-9137 + 100 mg of ritonavir, each once-daily Location in submission: 5.3.3.2	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? <u>Pivotal Study #1: GS-US-183-0145</u> <u>Indication:</u> Treatment of HIV-1 in treatment experienced adults. <u>Supportive Study #2: GS-US-183-0105</u> <u>Indication:</u> Treatment of HIV-1 in treatment experienced adults.	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			Study 0128
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			~360 patients at the proposed doses for marketing up to 96 weeks
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			EVG does not cause significant rash compared to the other

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					approved integrase inhibitor
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	No special studies or data were requested
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __ YES __

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If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Russell Fleischer, PA-C, MPH	08/13-2012
Reviewing Medical Officer	Date
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL D FLEISCHER
08/21/2012

LINDA L LEWIS
08/21/2012