CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212887Orig1s000
212888Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information, NDA 212887

Category	Application Information
Application type	NDA
Application number(s)	212887
Priority or standard	Priority
Submit dates	7/28/2020
Received dates	7/28/2020
PDUFA goal date	1/28/2021
Division/office	Division of Antivirals (DAV)
Review completion date	1/19/2021
Established name	Cabotegravir Tablets
(Proposed) trade name	VOCABRIA
Pharmacologic class	Cabotegravir: integrase strand transfer inhibitor [INSTI]
Code name	Cabotegravir: CAB, GSK1265744
Applicant	ViiV Healthcare
Dose form/formulation(s)	Tablet
Dosing regimen	30 mg of cabotegravir taken orally once daily for approximately 1 month in combination with one 25 mg tablet of EDURANT (rilpivirine) orally once daily prior to the initiation of CABENUVA to assess tolerability of cabotegravir and rilpivirine
Applicant proposed indication(s)/population(s)	(b) (4) [redacted] cabotegravir or rilpivirine for use as: - Oral lead-in to assess the tolerability of cabotegravir prior to administration of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions - Oral therapy for patients who will miss planned injection dosing with CABENUVA injectable suspensions
Proposed SNOMED indication	(b) (4) [redacted]
Regulatory action	Approval
Approved indication(s)/ population(s) (if applicable)	VOCABRIA, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), is indicated in combination with EDURANT, oral rilpivirine, for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as: - Oral lead-in to assess the tolerability of cabotegravir prior to administration of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions - Oral therapy for patients who will miss planned injection dosing with CABENUVA injectable suspensions

Category	Application Information
Approved SNOMED indication	40780007: Human immunodeficiency virus I infection (disorder)

Table 2. Administrative Application Information, NDA 212888

Category	Application Information
Application type	NDA
Application number(s)	212888
Priority or standard	Priority
Submit dates	7/28/2020
Received dates	7/28/2020
PDUFA goal date	1/28/2021
Division/office	Division of Antivirals (DAV)
Review completion date	1/19/2021
Established name	Cabotegravir extended-release injectable suspension; Rilpivirine extended-release injectable suspension
(Proposed) trade name	CABENUVA
Pharmacologic class	Cabotegravir: integrase strand transfer inhibitor [INSTI] Rilpivirine: nonnucleoside reverse transcriptase inhibitor [NNRTI]
Code name	Cabotegravir: CAB, GSK1265744 Rilpivirine: RPV, TMC278, GSK1329758
Applicant	ViiV Healthcare
Dose form/formulation(s)	Injectable suspension
Dosing regimen	Initiate injections of CABENUVA (3 mL) on the final day of oral lead-in and continue with injections of CABENUVA (2 mL) every month thereafter
Applicant proposed indication(s)/population(s)	(b) (4)
Proposed SNOMED indication	(b) (4)
Regulatory action	Approval
Approved indication(s)/ population(s) (if applicable)	CABENUVA, a two-drug copackaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 nonnucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.
Approved SNOMED indication	40780007: Human immunodeficiency virus I infection (disorder)

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Glossary

3TC	lamivudine
ABC	abacavir
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATLAS	Antiretroviral Therapy as Long-Acting Suppression
BMI	body mass index
CAB	cabotegravir
CAR	current antiretroviral regimen
CRL	Complete Response letter
DAV	Division of Antivirals
DILI	drug-induced liver injury
DTG	dolutegravir
FDA	Food and Drug Administration
FLAIR	First Long-Acting Injectable Regimen
HIV-1	human immunodeficiency virus type 1
HPTN	HIV-1 prevention trial number
HSR	hypersensitivity reaction
IM	intramuscular
INSTI	integrase strand transfer inhibitor
ISR	injection site reaction
LA	long-acting
NDA	new drug application
NNRTI	nonnucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
OLI	oral lead-in
OND	Office of New Drugs
PK	pharmacokinetics
Q4W	every 4 weeks
Q8W	every 8 weeks
RAS	resistance-associated substitution
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
SAE	serious adverse event
SUR	safety update report
ULN	upper limit of normal

I. Executive Summary

1. Summary of Regulatory Action

ViiV Healthcare (the Applicant) submitted new drug applications (NDAs) for VOCABRIA, an oral formulation of cabotegravir (CAB), and CABENUVA, an extended-release, injectable, two-drug copackaged product containing CAB and rilpivirine (RPV). CAB is a new integrase strand transfer inhibitor (INSTI) and RPV is a previously approved nonnucleoside reverse transcriptase inhibitor (NNRTI).

The intended indication for VOCABRIA is use in combination with oral RPV for short-term treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable regimen, with no history of treatment failure and with no known or suspected resistance to either CAB or RPV. It is intended for use as 1) an oral lead-in (OLI) to assess the tolerability of CAB prior to administration of CABENUVA and 2) as an oral therapy (up to 2 consecutive months) for patients who will miss planned dosing with CABENUVA injectable suspensions.

The intended indication for CABENUVA is a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral (ARV) regimen (CAR) in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable regimen, with no history of treatment failure and no known or suspected resistance to either CAB or RPV. CABENUVA is administered by a healthcare provider every 4 weeks.

These NDAs were reviewed by a multidisciplinary review team. None of the disciplines (clinical, virology, clinical pharmacology, pharmacology/toxicology statistics and regulatory) identified any issues that preclude approval for VOCABRIA and CABENUVA. I, the signatory authority, agree that the benefit/risk assessment favors approval for VOCABRIA and CABENUVA. The original submission for NDA 212888 (CABENUVA) received a Complete Response letter on December 19, 2019, because of deficiencies observed at the GLAXO OPERATIONS UK LIMITED manufacturing facility. NDA 212877 (VOCABRIA) also received a Complete Response because its approval was contingent on that of CABENUVA. Specifically, (b) (4) . Furthermore, the Drug Master File for RPV was found inadequate to support approval for NDA 212888. The Applicant has adequately addressed the deficiencies in the December 19, 2019, Complete Response letter.

ViiV submitted two adequate and well-controlled phase 3 trials that provided substantial evidence of efficacy for the indications approved. The reviewers did not identify any significant issues relevant to the benefit of CAB+RPV. The two-drug CAB+RPV regimen was noninferior to controls (subjects remain on their current three-drug ARV regimen). Higher virologic failure rates were seen in females, subjects with body mass index (BMI) $\geq$30 kg/m^2, and females with BMI $\geq$30 kg/m^2 than in their counterparts. Further post hoc exploratory analyses did not reveal a singular explanation for the higher virologic failure rates. These post hoc exploratory analyses were limited by sample size, and further analyses from ongoing trials are needed to assess these findings.

Oral CAB and extended-release injectable suspension forms of CAB and RPV are safe for the intended use. Aside from local and systemic injection site reactions (ISRs), no new or unexpected safety findings were noted. The adverse event (AE) profile was consistent with previous trials with RPV and INSTIs. Prior to CAB and RPV injections, oral CAB and RPV were used as a 4-week OLI to adequately assess the tolerability of CAB and RPV. Discontinuations during the OLI phase were infrequent. We concur that the identified risks can be mitigated through labeling and further evaluated during routine pharmacovigilance.

The "long-acting" (LA) properties of CABENUVA have potential advantages and disadvantages. The extended-release injectable formulations eliminate the need for adherence to oral daily medications and can be administered every 4 weeks. However, because residual concentrations of CAB and RPV can remain for prolonged periods (12 months or longer), careful selection of patients who agree to the required monthly injection dosing schedule is imperative. Nonadherence to the monthly injections or missed injections can lead to loss of virologic response and development of resistance to CAB, RPV, or the INSTI and NNRTI drug classes.

For detailed information supporting the basis for the benefit-risk assessment please refer to the December 19, 2019, review. This review summarizes the safety update report (SUR) for the NDA resubmissions of VOCABRIA (NDA 212887) and CABENUVA (NDA 212888). The Applicant proposes no safety- or efficacy-related labeling changes to the proposed labeling in the NDA resubmissions and retains 48-week trial data for trials 201584 (FLAIR) and 201585 (ATLAS).

Please also refer to the Product Quality Review which recommended an approval action for NDAs 212887 and 212888.

2. Benefit-Risk Assessment

Table 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Human immunodeficiency virus type 1 (HIV-1) is a transmissible virus that attacks CD4+ cells and thereby weakens the immune system. Without effective treatment, HIV-1 infection leads to progressive destruction of the immune system, acquired immunodeficiency syndrome (AIDS)-defining illnesses, and premature death in almost all cases. • In the United States, 1.2 million people were living with HIV at the end of 2018, and 37,968 people were newly diagnosed with HIV in 2018 (Centers for Disease Control and Prevention 2019). • The goals of HIV treatment are to durably suppress HIV RNA, preserve and restore the immune system, reduce HIV-associated morbidity, and ultimately improve long-term survival.	HIV-1 continues to be a significant public health concern, both globally and domestically. Without effective treatment, HIV-1 leads to progressive destruction of the immune system and therefore is a serious, life-threatening condition. With effective management, however, HIV-1 is a controllable chronic condition. Effective viral load suppression can also provide the additional public health benefit of decreased HIV-1 transmission.
Current Treatment Options	• The current antiretroviral (ARV) treatment armamentarium is robust. Excluding fixed-dose combination products and different formulations, 29 individual ARV drugs and 2 drugs (cobicistat and ritonavir), which inhibit metabolic enzymes and enhance the exposure of ARVs, are approved and available for the treatment of HIV-1. (A complete list is provided in the December 19, 2019, review, Section 12). • The current recommended standard of care for most people with HIV is a three-drug regimen, typically an integrase strand transfer inhibitor (INSTI) plus two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) (Department of Health and Human Services) • In clinical practice, patients may choose to switch from an initially effective three-drug ARV regimen for a variety of reasons, including adverse event (AE), drug–drug or drug−food interactions, or a desire for a simpler regimen with fewer pills. In this situation, current guidelines recommend switching to an alternative regimen that maintains viral suppression without jeopardizing future treatment options.	Optimal management of HIV-1 is complex and must consider patients' individual needs. The expansion of the HIV treatment armamentarium with another ARV that is efficacious, well-tolerated, with relatively few clinically relevant drug−drug interactions benefits virologically suppressed patients who want to switch from their current ARV regimen to another. A two-drug extended-release injectable regimen, administered monthly by a healthcare professional would be expected to be beneficial for some patients. The monthly two-drug injectable regimen would reduce the complexity of ARV treatment, decrease the risk of adverse reactions of the third drug in a regimen, and provide an option to address pill-fatigue associated nonadherence with daily medication. One would anticipate more effective treatment of HIV-1 in some patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of CAB+RPV (cabotegravir and rilpivirine) in the virologically suppressed (HIV-1 RNA <50 copies/mL) population was established in two randomized phase 3 trials: – FLAIR and ATLAS were trials with similar designs that compared CAB+RPV extended-release injectable versus a three-drug regimen (with INSTI, protease inhibitor, or nonnucleoside reverse transcriptase inhibitor (NNRTI) as the third agent). – Together, the trials enrolled 1,182 subjects, with 591 each in the CAB+RPV treatment group and the pooled control group. • Both trials included the primary endpoint HIV RNA ≥50 copies/mL at Week 48 to measure the effectiveness of sustaining virologic suppression from baseline. A key secondary endpoint included threshold for virologic response with HIV-1 RNA <50 copies/mL. This endpoint is well-established as a clinically meaningful endpoint and correlates with clinical benefits. • In the stratified pooled analysis of FLAIR and ATLAS, the Week 48 adjusted treatment difference and 95% confidence interval was 0.2 (-1.4, 1.7). The result met the threshold for noninferiority to the three-drug comparator group. The results from the individual trials were consistent with the pooled analysis result. • Higher virologic failure rates were seen for the CAB+RPV treatment group versus the control group among the following subgroups compared to their counterparts: female subjects, subjects with body mass index (BMI) ≥30 kg/m^2, and female subjects with BMI ≥30 kg/m^2. • The presence of pre-existing NNRTI resistance-associated substitutions (RAS) could potentially reduce the virologic response to RPV and contribute to virologic failure on the CAB+RPV regimen. However, the limited data from the FLAIR trial did not suggest the presence of reverse transcriptase (RT) K103N NNRTI RAS at screening is associated with virologic failure.	The submitted clinical trial data demonstrated a meaningful benefit of CAB+RPV in treating virologically suppressed, HIV-1–infected patients. The efficacy of CAB+RPV, a two-drug extended-release injectable regimen is noninferior to the comparator three-drug regimens. The review did not identity significant issues with trial design or conduct. Limited data are available on the durability of a two-drug regimen to maintain virologic suppression beyond 48 weeks. Other uncertainties as described below are from exploratory analyses and cannot be addressed with the current data, primarily due to limited sample size. Therefore, additional evaluation for differences in outcome among these subgroups is warranted. • Although the presence of RT K103N resistance-substitution is generally a concern for patients initiating an NNRTI-based regimen, the limited data from the FLAIR trial did not suggest the presence of the RT K103N NNRTI RAS at screening was associated with virologic failure to CAB+RPV. Additional data are needed to further assess the presence of the K103N substitution on the effectiveness of CAB+RPV regimen before recommending an indication for this subpopulation. • Virologic failure rates were higher for the CAB+RPV treatment group versus the control treatment group among females, baseline BMI ≥30 kg/m^2, and females with baseline BMI ≥30 kg/m^2 compared to their counterparts. Our review further focused on the subgroup of females with baseline BMI ≥30 kg/m^2. Drug exposure or baseline virologic characteristics did not explain this finding. Despite these current results, limitation of use is not recommended at this time. We view the results from our analyses as hypothesis-generating because the outcomes were based on a post hoc, exploratory subgroup analysis;

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		did not apply multiplicity adjustment; and had limited sample size. Additional evaluation for differences in outcome among these subgroups is warranted. Further assessment with more data from other independent trial(s) is necessary to confirm the observed higher virologic failure rate in the CAB+RPV treatment arm in females with baseline BMI ≥30 kg/m^2 and to explore the possible explanations for the higher virologic failure rate.
Risk and Risk Management	• The safety data from the FLAIR and ATLAS trials exceeded the 300 to 500 subjects recommended for safety evaluations in the U.S. Food and Drug Administration (FDA) HIV Treatment Guidance (November 2015). The safety data are also supplemented by extensive experience with RPV, marketed either as individual drugs or as part of other fixed-dose combination products. Data from the phase 2 trials (LATTE and LATTE-2), and safety reports from ongoing trials (ATLAS-2M, HPTN083 and HPTN084), also provided supportive safety data/information for CAB. • The 4-week oral lead-in was adequate to assess the tolerability of CAB and RPV prior to initiating extended-release CAB and RPV injections. Few subjects discontinued oral therapy prior to receiving CAB and RPV injections. • The most common adverse drug reactions during treatment with CAB+RPV extended-release were injection site reactions (ISRs). Additionally, systemic reactions such as pyrexia, musculoskeletal pains, and sciatica were associated with injections. • Other common adverse reactions include pyrexia, fatigue, headache, nausea, musculoskeletal pain, sleep disorders, dizziness, and rash. • The most serious AEs (or potential events), including depressive disorders, hypersensitivity reaction (HSRs), and hepatotoxicity, are adequately labeled under WARNINGS and PRECAUTIONS. These events are associated with other INSTIs. NNRTIs, including RPV, are also labeled for similar events. Neuropsychiatric events, including suicide-related events, have been described with RPV use and as a potential class-associated safety concern with INSTI use. While serious or severe HSRs were not observed during the phase 3 clinical	Overall, the safety data are adequate to assess the safety of CAB+RPV for the proposed indication, dosage regimen, duration, and patient populations. The safety profile of CAB+RPV has been well characterized, and none of the identified safety issues would preclude approval of CAB+RPV. Except for injection-related events, the overall safety profile of CAB+RPV was generally similar to the anticipated profile for an INSTI and the known profile of RPV. The Safety Update Report for the new drug application (NDA) resubmissions did not identify any new or unexpected findings. An oral lead-in to assess the tolerability of CAB+RPV prior to initiating dosing with the extended-release injections may not be needed in the future. Review of the data from future trials will help determine if CAB+RPV extended-release can be administered without an oral lead-in. Although FLAIR and ATLAS trials were not designed to show a benefit on the basis of any specific safety outcome, the descriptive safety analyses showed that the two-drug regimen lacked the additional safety concerns associated with a third drug (e.g., NRTIs). While the risk of development of resistance or cross-resistance among virologic failures is shared across ARVs, the prolonged window for risk of resistance development during the residual concentration of CAB and RPV is unique. To address this concern, the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	trials, cases such as drug reaction with eosinophilia and systemic symptoms have been observed with RPV. Additionally, HSRs have been described with other INSTIs and thus considered a potential safety concern with CAB. • Weight increase is an emerging important safety issue with INSTI use. Weight increase was observed among subjects treated with CAB+RPV as well as among those treated with abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) in FLAIR. Additional long-term follow-up data are anticipated to further assess cardiovascular and/or metabolic risks associated with weight gain. • Emergence of resistance to both CAB and RPV occurred frequently among virologic failures in the CAB+RPV treatment group; the incidence of emergent resistance was also higher than in the control group. • The combination of HIV subtype A1 and presence of the baseline IN L74I polymorphism were associated with virologic failure. The IN L74I polymorphism alone was only associated with virologic failure in subjects with subtype A1. Subtype A1 is prevalent in Russia. However, no detectable phenotypic resistance to CAB was conferred by the IN L74I substitution at baseline. • The CAB and RPV resistance substitutions selected during exposure to CAB+RPV confer cross-resistance to other INSTIs and NNRTIs, respectively. Thus, future treatment options with other INSTIs and NNRTIs may be compromised for CAB+RPV virologic failures. • The concentrations of CAB and RPV can be detected at least 52 weeks after the last injections. An extended-release formulation may help with adherence or compliance by eliminating pill burden or pill fatigue for some patients. On the other hand, the prolonged exposures cause concern for the development of resistance to CAB+RPV and cross-resistance to the INSTI and NNRTI classes in patients who do not comply with monthly injections or fail to initiate an alternative, effective regimen after discontinuing CAB+RPV.	DOSAGE AND ADMINISTRATION section clearly outlines the importance of selecting the right patient population prior to initiating CAB+RPV and counseling patients on the importance of adherence/compliance to the scheduled monthly visits for CAB+RPV administration. The DOSAGE AND ADMINISTRATION section also instructs to initiate a suppressive regimen within 30 days.

Conclusions Regarding Benefit-Risk

Infection with HIV-1 continues to be a significant public health concern both domestically and internationally. Although the HIV treatment armamentarium is robust, additional effective ARV treatment options that provide greater flexibility in meeting patients' individual needs and facilitating their tolerance for and adherence to lifelong HIV-1 treatment are needed. The extended-release injectable formulations of CAB and RPV offer patients the advantage of once-monthly dosing and eliminate the need for daily oral medication. However, the prolonged residual exposure is an important consideration for the appropriate selection of patients who can adhere to monthly in-office injections.

The submitted evidence clearly demonstrates CAB+RPV is effective as a two-drug complete regimen for patients who are virologically suppressed and plan to replace their current regimen with CAB+RPV. We can also conclude that CAB+RPV is noninferior to a three-drug regimen, with the caveat that uncertainty remains about the durability of these benefits beyond 48 weeks of treatment. While higher virologic failure rates were seen in some subgroups (females, subjects with BMI $\geq$30 kg/m^2, and females with BMI $\geq$30 kg/m^2), these results are from exploratory subgroup analyses with limited sample size. More data are needed to assess the higher virologic failure rates in these subgroups. Also, the efficacy of CAB+RPV is unknown among patients who have a baseline K103N substitution, acquired INSTI or NNRTI resistance, or with history of treatment failure.

The safety evaluation for CAB+RPV was adequate, and the demonstrated safety profile of CAB+RPV in the virologically suppressed HIV-1 population is acceptable for the indicated dose and population. With the exception of local and systemic ISRs, the overall safety profile of CAB+RPV was consistent with prior trials with RPV and INSTIs. No new or unexpected safety concerns were identified. Other safety findings, specifically those identified with prior experience with RPV or the INSTI class, can be adequately addressed in labeling and by routine pharmacovigilance. The CAB and RPV oral lead-in (OLI) dosing was safe, and few subjects discontinued prior to the injection phase. Data from future trials will provide additional data regarding the need for an OLI prior to CAB and RPV injections.

With all factors considered, the benefits of an all-injectable two-drug regimen clearly outweigh the risks. CAB+RPV is the first all-injectable two-drug regimen to be approved as a complete regimen for HIV-1–infected, virologically suppressed adults to replace their current ARV regimen. The availability of CAB+RPV will offer patients and providers another safe and effective option to manage this complex chronic disease.

II. Interdisciplinary Assessment

3. Introduction

Refer to the review completed on December 19, 2019.

4. Patient Experience Data

Refer to the review completed on December 19, 2019.

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Refer to the review completed on December 19, 2019.

5.1. Nonclinical Assessment of Potential Effectiveness: CAB

Refer to the review completed on December 19, 2019.

5.2. Nonclinical Assessment of Potential Effectiveness: RPV

Refer to the review completed on December 19, 2019.

6. Evidence of Benefit (Assessment of Efficacy)

6.1. Assessment of Dose and Potential Effectiveness: CAB

Refer to the review completed on December 19, 2019.

The new drug application (NDA) resubmissions contain no new benefit information.

6.2. Assessment of Dose and Potential Effectiveness: RPV

Refer to the review completed on December 19, 2019.

6.3. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

Refer to the review completed on December 19, 2019.

6.4. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

Refer to the review completed on December 19, 2019.

6.5. Review Issues Relevant to the Evaluation of Benefit

Refer to the review completed on December 19, 2019.

7. Risk And Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Refer to the review completed on December 19, 2019.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The potential safety concerns for cabotegravir (CAB) were initially based on the clinical experiences with approved integrase strand transfer inhibitor (INSTI) products. Serious adverse reactions associated with INSTIs include hypersensitivity reactions (HSRs), hepatotoxicity, depressive disorders (including suicidal ideation, attempt, behavior, or completion), anxiety, and weight gain.

Oral rilpivirine (RPV) is an approved product, and the potential risks and safety concerns are based on previously reviewed clinical trial data and postmarketing reports for EDURANT or RPV-containing products. RPV is associated with serious adverse drug reactions such as HSRs, depressive disorders, and hepatotoxicity. These risks are generally consistent with the nonnucleoside reverse transcriptase inhibitor (NNRTI) drug class.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Severe skin and HSRs have been reported during the postmarketing experience with RPV-containing regimens, including cases of drug reaction with eosinophilia and systemic symptoms.

7.4. FDA Approach to the Safety Review

Refer to the review completed on December 19, 2019, for the complete safety review of the original NDAs.

This review summarizes the Complete Response letter (CRL) safety update report (SUR) for the NDA resubmissions of VOCABRIA (NDA 212887) and CABENUVA (NDA 212888). Ultimately, this review assesses whether safety events occurring in the update period warrant new or additional labeling. The Applicant proposes no safety- or efficacy-related labeling changes to the proposed labeling in the NDA resubmissions and retains 48-week trial data for trials 201584 (FLAIR) and 201585 (ATLAS).

The review of the CRL SUR does not entail independent data analyses because the NDA resubmissions do not contain datasets. In addition, the Applicant is not updating labeling with longer-term (i.e., greater than 48 weeks) clinical trial data. The Applicant and the Agency agreed that the NDA resubmissions would contain a CRL SUR of the four key trials (201584, 201585, 207966, and 200056) that would include extent of exposure, deaths, serious adverse events (SAEs), adverse events (AEs) leading to withdrawal, discontinuation due to liver events, pregnancy exposures (where available), and common AEs (reported by ≥5%) during the safety update period. In addition, the CRL SUR contains additional safety information from five trials of CAB (trial 201767) or CAB+RPV (trials 209035, 209493, 208580, and 204843) that was not included in the original NDA submissions.

The update period for the CRL SUR included the time between the 60-day SUR in the original NDAs through the data cutoff dates of the NDA resubmissions. For the original NDA submissions, the Applicant submitted a 60-day SUR on June 27, 2019, which included a summary of new deaths, SAEs, AEs leading to withdrawal, discontinuations due to liver events, and pregnancy exposures from trials 201584, 201585, LAI116482, and 200056. The 60-day SUR included data received up to and including the submission date of the original NDA submissions (April 29, 2019).

Predefined Safety Analysis Plan and Definitions

AEs were defined as "any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product." Adverse events of special interest (AESI) were determined for CAB and RPV based on preclinical and clinical experience, along with information for the INSTI and NNRTI drug classes.

SAEs were defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization (except for elective treatment of a pre-existing condition that did not worsen at baseline)
- Results in disability/incapacity
- Is a congenital anomaly/birth defect

- Other situations, including medical/scientific judgement or events that require invasive treatment (e.g., convulsions) that do not result in hospitalization
- Is associated with liver injury and impaired liver function defined as either of the following:
  - Alanine aminotransferase (ALT) ≥3× upper limit of normal (ULN) and total bilirubin ≥2× ULN (>35% direct)
  - ALT ≥3× ULN and international normalized ratio >1.5

Data Used for Clinical Safety Assessment

This review focuses on the updated safety information from the four key trials. The key trials included the two pivotal randomized, controlled, phase 3 trials (201584 [FLAIR] and 201585 [ATLAS]), which were supplemented by data from one randomized, controlled, phase 3b trial (207966 [ATLAS-2M]) and one randomized, controlled, phase 2b trial (200056 [LATTE-2]). In addition, the CRL SUR includes SAEs and pregnancy exposures from five supporting trials. Table 4 summarizes the updated safety information included in the CRL SUR.

Table 4. Updated Safety Information Included in the CRL SUR

Trial	Phase	Updated Safety Information
Key trials		
201584 (FLAIR) NCT02938520	3	SAEs including any fatal cases AEs leading to withdrawal
201585 (ATLAS) NCT02951052	3	Discontinuation due to liver events Pregnancy exposures to CAB+RPV including outcomes (where available)
207966 (ATLAS-2M) NCT03299049	3b	Most common adverse events (reported by ≥5%)
200056 (LATTE-2) NCT02120352	2b	Exposure tables
Supporting trials		
209035 (POLAR) NCT03639311	2b	SAEs Pregnancy exposures
209493 (CUSTOMIZE) NCT04001803	Implementation sciences	
201767 (Tissue PK; CAB only) NCT02478463	1	
208580[1] (MOCHA) NCT03497676	2 (pediatrics)	
204843[1] (ACTG 5359) NCT03635788	3b	

Source: Adapted from the Applicant's CRL SUR (Table 1, page 8; Table 2, page 9)
[1] Sponsored by the National Institute of Allergy and Infectious Diseases
Abbreviations: AE, adverse event; CAB, cabotegravir; CRL, Complete Response letter; PK, pharmacokinetics; RPV, rilpivirine; SAE, serious adverse event; SUR, safety update report

The four key trials are briefly summarized below.

Trial 201584 (FLAIR)

This is a phase 3, randomized, open-label, active-controlled, noninferiority trial conducted in human immunodeficiency virus type 1 (HIV-1)–infected, antiretroviral (ARV) therapy-naïve adult subjects. All subjects enrolled were first entered into the 20-week induction phase where

abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) was administered. Subjects who had HIV-1 RNA <50 copies/mL 4 weeks before the end of the 20-week induction phase were randomized (1:1) to either stay on their current ARV regimen (CAR) or receive oral CAB+RPV once daily for a minimum of 4 weeks (oral lead-in [OLI]) followed by CAB+RPV injections every 4 weeks (Q4W) thereafter. Subjects in the CAR arm had the opportunity to switch to CAB+RPV at the end of Week 100.

Trial 201585 (ATLAS)

This is a phase 3, randomized, open-label, active-controlled, noninferiority switch trial conducted in HIV-1–infected, virologically suppressed adult subjects. All subjects were on a stable regimen for at least 6 months prior to enrollment and had documented evidence of at least two plasma HIV-1 RNA <50 copies/mL within the prior 12 months. At the randomization visit, subjects were randomized (1:1) to either stay on their original CAR or switch to a once daily regimen of oral CAB+RPV for a minimum of 4 weeks (OLI) followed by CAB+RPV injections Q4W thereafter. Subjects in the CAR arm would have the opportunity of switching to CAB+RPV regimen at the end of Week 52.

Trial 207966 (ATLAS-2M)

This is a phase 3, randomized, open-label, parallel-group, noninferiority trial in HIV-1–infected, virologically suppressed adult subjects. Eligible participants entered the trial as either newly recruited participants receiving oral standard of care ARV therapy or were enrolled directly from trial 201585 (ATLAS), during which they received CAB+RPV (Q4W). Participants were then randomized (1:1) to receive CAB+RPV injections every 8 weeks (Q8W) or Q4W.

Trial 200056 (LATTE-2)

This is a phase 2b, randomized, open-label trial evaluating the CAB+RPV regimen for maintenance of virologic suppression after an induction period with a once daily regimen of oral CAB 30 mg plus two nucleoside reverse transcriptase inhibitor (NRTIs) in treatment-naïve adults. Subjects with viral suppression (plasma HIV-1 RNA <50 copies/mL) were then randomized (2:2:1) to CAB+RPV (Q8W), CAB+RPV (Q4W), or continued oral regimen.

The supporting trials are briefly summarized below.

Trial 209035 (POLAR)

This is a phase 2b, open-label, multicenter rollover trial designed to assess the antiviral activity and safety of CAB+RPV administered every 2 months in adult HIV-1–infected participants from trial LAI116482 (LATTE).

Trial 209493 (CUSTOMIZE)

This is a qualitative hybrid phase 3 implementation trial to identify and evaluate strategies for successful implementation of CAB+RPV (Q4W). This is a single arm, open-label interventional design. The primary objective is to evaluate acceptability, appropriateness, and feasibility of

delivering CAB+RPV injections through assessments of staff and subjects using qualitative and quantitative measures across a range of clinic types.

Trial 201767 (Tissue PK)

This was a phase 1, multicompartmental pharmacokinetic study of oral and injectable CAB in healthy adult subjects. Subjects received CAB 30 mg tablet once daily oral dose for 28 days followed by a washout period of 14 to 42 days. After the washout, subjects received a single intramuscular (IM) dose of CAB 600 mg.

Trial 208580 (MOCHA)

This is a phase 1/2, multicenter, open-label, noncomparative study to confirm the dose and to evaluate the safety, tolerability, acceptability, and pharmacokinetics of oral CAB and CAB+RPV (Q8W or Q4W) injections in virologically suppressed, HIV-1–infected children and adolescents aged 12 to <18 years.

Trial 204843 (ACTG 5359)

This is a phase 3, prospective, randomized, open-label trial comparing the safety, efficacy, and tolerability of CAB+RPV (Q4W) versus standard of care in previously nonadherent, HIV-1–infected individuals.

Data Cutoff Dates

The CRL SUR includes cumulative data from the time of data cutoffs used for the NDA submissions through January 31, 2020, inclusive of data reported in the 60-day SUR (data cutoff date: April 30, 2019). Table 5 displays the data cutoff points for the four key trials in the CRL SUR compared to the original NDAs (212887 and 212888).

Table 5. Data Cutoff Dates for the Key Trials

Trial	Phase	CSR Submitted in Original NDAs	Date of Last Reporting Effort (LSLV)	Last Milestone/ CSR Completed	Global Safety Database Search Dates
201584 FLAIR	3	Week 48	12-Sep-2019	Week 96	12-Sep-2019 to 31-Jan-2020
201585 ATLAS	3	Week 48	16-Apr-2019	Week 96	16-Apr-2019 to 31-Jan-2020
207966 ATLAS-2M	3b	N/A	6-Jun-2019	Week 48	6-Jun-2019 to 31-Jan-2020
200056 LATTE-2	2b	Week 160	21-Jan-2020	Week 256	21-Jan-2020 to 31-Jan-2020

Source: Adapted from the Applicant's CRL SUR (Table 1, page 8)
Abbreviations: CRL, Complete Response letter; CSR, clinical study report; LSLV, last subject last visit; N/A, not applicable; NDA, new drug application; SUR, safety update report

Table 6 displays the data cutoff points for the additional data (SAEs and pregnancy exposures) from the five supporting trials of CAB or CAB+RPV that were also included in the CRL SUR.

Table 6. Data Cutoff Dates for the Supporting Trials

Trial	Phase	First Subject First Visit	Global Safety Database Search Dates
209035 POLAR	2b	20-Aug-2018	20-Aug-2018 to 31-Jan-2020
209493 CUSTOMIZE	Implementation sciences	28-Jul-2019	28-Jul-2019 to 31-Jan-2020
201767 Tissue PK (CAB only)	1	27-Feb-2017	27-Feb-2017 to 31-Jan-2020
208580[1] MOCHA	2 (pediatrics)	3-Apr-2019	3-Apr-2019 to 31-Jan-2020
204843[1] ACTG 5359	3b	6-May-2019	6-May-2019 to 31-Jan-2020

Source: Adapted from the Applicant's CRL SUR (Table 2, page 9)
[1] Sponsored by National Institute of Allergy and Infectious Diseases
Abbreviations: CAB, cabotegravir; CRL, Complete Response letter; PK, pharmacokinetic; SUR, safety update report

Overall Extent of Exposure for the Key Trials

Trial 201584 (FLAIR)

In trial 201584, 282 subjects received oral CAB+RPV for a median duration of 37 days in the OLI period during the Maintenance Phase. During the Maintenance + Extension Phase at the Week 96 analysis, 278 subjects in the CAB+RPV Q4W group had a median of 27 injection visits per subject, and 246 subjects had ≥100 weeks of exposure to CAB+RPV. At Week 100, subjects who switched from CAR to CAB+RPV during the Extension Phase had the option for a CAB+RPV OLI for 4 weeks; 121 subjects received CAB+RPV OLI for a median of 37 days. The 228 subjects in the Extension Switch from CAR to CAB+RPV (Q4W) had a median of 4 injection visits per subject, and 118 subjects had ≥4 weeks of exposure to CAB+RPV.

Trial 201585 (ATLAS)

In trial 201585, 308 subjects received oral CAB+RPV for a median of 36 days in the OLI and had a median of 13 injection visits per subject during the Maintenance + Extension Phase at the Week 96 analysis. Upon completion of the Week 52 visit, subjects had the option to continue in the Extension Phase (all CAR subjects switched to CAB+RPV), transition to trial 207966 (ATLAS-2M), or leave the trial. The 174 subjects who transitioned from the CAR arm in the Extension Phase had a CAB+RPV OLI for a median duration of 36 days; subsequently subjects had a median of a single injection visit each (range: 0 to 17 injection visits). The 168 subjects in the Extension Switch to CAB+RPV group were exposed to CAB+RPV for ≥8 weeks. After the Maintenance Phase, 253 subjects in the CAB+RPV group and 251 subjects from the CAR group transitioned to trial 207966 (ATLAS-2M). At Week 96, 51 subjects remained ongoing in the Extension Phase (23 subjects in the CAB+RPV group and 28 subjects in the Extension Switch to CAB+RPV group).

Trial 207966 (ATLAS-2M)

In trial 207966, approximately half of the subjects were enrolled from trial 201585 (ATLAS) and the other half were receiving standard of care at the time of enrollment. During the Maintenance Phase at Week 48, 516 subjects in the Q8W group received CAB+RPV injections, with a median of 8 injection visits per subject. The 517 subjects in the Q4W group received CAB+RPV injections, with a median of 16 injections per subject. Subjects who transitioned from standard of care (Q8W, n=328; Q4W, n=327) had an OLI, and their exposure to oral CAB+RPV was for a

median duration of 39 days for both treatment groups. During the Maintenance Phase, 443 subjects (85%) in the Q8W group and 480 subjects (92%) in the Q4W group had ≥52 weeks of exposure to CAB+RPV.

Trial 200056 (LATTE-2)

In trial 200056, all subjects received 20 weeks of oral CAB in the Induction Period. At the start of the Maintenance Phase, eligible subjects were randomized to either Q8W, Q4W, or an oral CAB-based regimen. Subjects randomized to Q8W or Q4W injections continued to receive their Maintenance Period IM dosing regimen in the Extension Period. At Week 256, 230 subjects were originally randomized to either Q4W or Q8W CAB+RPV in the Maintenance Phase of the trial and continued to receive the same treatment during the Extension Phase of the trial (ongoing during the period of the CRL SUR). During the Maintenance and Extension Phases of the trial, 115 subjects in the randomized Q4W arm had a median of 69 injection visits per subject, and 115 subjects in the randomized Q8W group had a median of 37 injection visits per subject. In the Extension Switch, subjects who had successfully completed 96 weeks of oral CAB treatment were then able to continue to the Extension Phase by switching to an optimized IM dosing regimen of their choice. In the optimized Q4W group, 9 of 10 (90%) subjects received ≥40 CAB injections, and the median injection visits per subject was 44. In the optimized Q8W group, 32 of 34 (94%) subjects received ≥20 CAB injections and the median injection visits per subject was 23.

7.5. Adequacy of the Clinical Safety Database

Refer to the integrated review completed on December 19, 2019.

The Applicant's CRL SUR for the NDA resubmissions is adequate.

7.6. Safety Findings and Safety Concerns Based on Review of the CRL SUR

The safety evaluation for CAB+RPV is adequate, and the safety profile of CAB+RPV in the virologically suppressed HIV-1–infected population remains acceptable for the indicated doses and population studied. No clear pattern with respect to the reported death or SAEs suggests a specific safety concern. Incidence of drug discontinuation due to AEs were low without a clear pattern of association with any specific events. Our safety assessments, based on the data reviewed, are summarized in the following subsections.

7.6.1. Overall Adverse Event Summary

Overall, there are no new or unexpected safety concerns for CAB+RPV based on one new death, nonfatal SAEs, AEs leading to treatment discontinuation, pregnancy exposures, or common AEs. AEs that occurred during the safety update period were either consistent with proposed labeling or unlikely to be related to CAB+RPV. Except for injection-related events, the overall safety profile of CAB+RPV is generally similar to the anticipated profile for an INSTI and the known profile of RPV.

7.6.2. Deaths

Since the original NDA submissions and the 60-day SUR, a single death was reported in the CRL SUR and is summarized below. The death does not represent a new safety concern and does not change the overall safety profile of CAB+RPV.

A 64-year-old male subject received CAB+RPV (Q4W) for a total of almost 3 years after first receiving CAB+RPV (Q4W) in trial 201585 (ATLAS). Almost 2 years after the subject's first dose of CAB+RPV (Q4W) in trial 207966 (ATLAS-2M), the subject was found dead at home by a self-inflicted gunshot wound; the reported cause of death was suicide. The subject had a longstanding history of depression and anxiety, and he was compliant with his psychiatric follow-ups and medications. At his last trial visit, the subject reported feelings of depression and anxiety, which he attributed to social stressors, and was isolating himself from family and friends. Furthermore, the subject denied suicidal ideation or intent, and there were no electronic Columbia-suicide severity rating scale alerts or possible suicidality-related adverse events throughout the subject's trial participation. The investigator considered that there was no reasonable possibility that the suicide was related to CAB+RPV; in addition, the Applicant does not consider the fatal event to be related to CAB+RPV because of the subject's underlying risk factors and the long latency period before the event.

After reviewing the provided case narrative, the clinical team could not rule out the possibility that the event was treatment-related; however, the event is considered unlikely to be related to CAB+RPV because of the subject's risk factors and the long time-to-onset before the event. Neuropsychiatric events, including suicide-related events, have been described with RPV use and as a potential class-associated safety concern with INSTI use; in addition, the proposed labeling includes depressive disorders (e.g., depression, major depression, suicidal ideation or attempt) under WARNINGS AND PRECAUTIONS.

7.6.3. Serious Adverse Events

The narratives of all the SAEs that were provided in the CRL SUR were reviewed and revealed no new safety concerns and do not change the overall safety profile of CAB+RPV. Overall, the SAEs were either unlikely to be related to CAB+RPV or consistent with the proposed labeling. Therefore, no labeling changes are warranted. SAEs are briefly summarized by individual trial below.

7.6.3.1. Trial 201584 (FLAIR)

Week 96 Safety Analysis (Through September 12, 2019)

The SAEs reported through Week 96 were generally consistent with those reported through Week 48. Hepatitis A was the most frequently reported SAE during the Maintenance Phase through Week 96 for CAB+RPV; all other SAEs were reported in one subject in either treatment group. No fatal SAEs or new drug-related SAEs were reported. Table 7 shows the total number of SAEs (any event) and the SAEs that were reported in at least two subjects in any treatment group.

Table 7. Summary of Serious Adverse Events, Trial 201584

	Maintenance Phase					
	Week 48[1]		Week 96[2]		Maintenance + Ext. Phase[2,3]	Ext. Phase[3,4]
Adverse Event	CAB+RPV N=283	CAR N=283	CAB+RPV N=283	CAR N=283	CAB+RPV N=283	Ext. Switch[5] N=232
Any event	18 (6)	12 (4)	24 (8)	22 (8)	31 (11)	5 (2)
AE preferred term						
Hepatitis A	3 (1)	1 (<1)	4 (1)	1 (<1)	4 (1)	0
Anal abscess	0	1 (<1)	0	2 (<1)	0	0
Anogenital warts	1 (<1)	1 (<1)	2 (<1)	1 (<1)	2 (<1)	0
Pyrexia	1 (<1)	0	1 (<1)	0	2 (<1)	0

Source: Adapted from the Applicant's CRL SUR (Table 8, Page 25)
All values are expressed as n (%).
[1] Presented in original NDA
[2] Cumulative data = Original NDA + Safety Update
[3] Week 96 analysis; Extension Phase includes data beyond Week 96
[4] Included in the Safety Update
[5] In the Extension Switch, subjects transitioned from CAR to CAB+RPV.
Abbreviations: AE, adverse event; CAB, cabotegravir; CAR, current antiretroviral; CRL, Complete Response letter; ext, extension; N, number of subjects in treatment group; n, number of subjects with adverse event; NDA, new drug application; RPV, rilpivirine; SUR, safety update report

Global Safety Database (September 12, 2019 Through January 31, 2020)

The Applicant's review of their Global Safety Database identified 14 SAEs in 10 subjects receiving CAB+RPV (Q4W). Only 1 of the 14 SAEs, Hodgkin's disease (Subject (b) (6), was considered related to CAB+RPV by the investigator and is described below. The narratives for all 14 SAEs revealed no new safety concerns and are described in Table 8.

Table 8. Summary of Serious Adverse Events From the Global Safety Database, Trial 201584

Subject ID	Event	Grade	Assessment of Relatedness[1]	Possible Alternate Cause/Confounder
(b) (6)	Gastroenteritis viral	3	No/No	None
	Intervertebral disc protrusion[2]	2	No/No	None
	Hodgkin's disease[2]	4	Yes/No	Epstein-Barr virus
	Appendicitis	1	No/No	None
	Tibia fracture	2	No/No	Fall (alcohol use)
	Liver abscess	3	No/No	Bacteremia/cholecystitis
	Cholecystitis acute	3	No/No	Bacteremia/liver abscess
	Calculus urinary	3	No/Unlikely	None
	Headache[2]	2	No/Unlikely	None
	Paresthesia[2]	3	No/Unlikely	None
	Hypoesthesia[2]	2	No/Unlikely	None
	Road traffic accident	2	No/No	Struck by car while crossing the street
	Rhabdomyolysis	3	No/Unlikely	Exercise
	Psychotic disorder	3	No/Unlikely	Marijuana and methamphetamines

Source: Adapted from the Applicant's CRL SUR (Table 9, Page 30)
[1] As determined by investigator/reviewer
[2] SAE was included in the Week 96 analysis even though onset date was after Week 96 last subject last visit
Grading based on NIH Division of AIDS Toxicity Table
Abbreviations: AIDS, acquired immune deficiency syndrome; CRL, Complete Response letter; NIH, National Institutes of Health; SAE, serious adverse event; SUR, safety update report

A 37-year-old male subject developed biopsy-confirmed Hodgkin's disease (Grade 4) while receiving CAB+RPV (Q4W). CAB+RPV were discontinued, and the investigator considered that there was a reasonable possibility that Hodgkin's disease may have been caused by CAB+RPV; however, the investigator considered the main cause of the malignancy to be related to HIV infection and Epstein-Barr virus co-infection.

7.6.3.2. Trial 201585 (ATLAS)

Week 96 Safety Analysis (Through April 16, 2019)

The SAEs reported through Week 96 were generally consistent with those reported through Week 48. No fatal SAEs and no new drug-related SAEs were reported. Table 9 shows the total number of SAEs (any event) and the SAEs that were reported in at least two subjects in any treatment group.

Table 9. Summary of Serious Adverse Events, Trial 201585

	Maintenance Phase Week 48[1]		Maintenance + Extension Phase[2,3]	Extension Phase[2,4]
Adverse Event	CAB+RPV N=308	CAR N=308	CAB+RPV N=308	Extension Switch[5] N=174
Any event	13 (4)	14 (5)	15 (5)	2 (1)
AE preferred term				
Hepatitis B	1 (<1)	0	2 (<1)	0
Colitis	0	2 (<1)	0	0

Source: Adapted from the Applicant's CRL SUR (Table 10, Page 31)
All values are expressed as n (%).
[1] Presented in Original NDA
[2] Week 96 analysis; Extension Phase includes data beyond Week 96
[3] Cumulative Data = Original NDA + Safety Update
[4] Included in the Safety Update
[5] In the Extension Switch, subjects transitioned from CAR to CAB+RPV.
Abbreviations: AE, adverse event; CAB, cabotegravir; CAR, current antiretroviral regimen; CRL, Complete Response letter; N, number of subjects in treatment group; n, number of subjects with adverse event; NDA, new drug application; RPV, rilpivirine; SUR, safety update report

Global Safety Database (April 16, 2019 Through January 31, 2020)

The Applicant's review of their Global Safety Database identified six SAEs in five subjects receiving CAB+RPV (Q4W). None of the six SAEs were considered by the investigator to be related to CAB+RPV. The narratives for all six SAEs revealed no new safety concerns and are described in Table 10.

Table 10. Summary of Serious Adverse Events From the Global Safety Database, Trial 201585

Subject ID	Event	Grade	Assessment of Relatedness[1]	Possible Alternate Cause/Confounder
(b) (6)	Squamous cell carcinoma	3	No/No	Human papillomavirus
	Colonic abscess	2	No/No	Diverticulitis
	Staphylococcal infection	3	No/No	Pressure ulcer
	Arthritis infective	3	No/No	Knee fluid (*Staphylococcus aureus)*
	Acute hepatitis C	2	No/No	None
	Cholelithiasis	2	No/Unlikely	Elderly, obese female

Source: Adapted from the Applicant's CRL SUR (Table 11, Page 34)
Grading based on NIH Division of AIDS Toxicity Table
[1] As determined by investigator/reviewer
Abbreviations: AIDS, acquired immune deficiency syndrome; CRL, Complete Response letter; NIH, National Institutes of Health; SUR, safety update report

7.6.3.3. Trial 207966 (ATLAS-2M)

Week 48 Safety Analysis (Through June 6, 2019)

The Week 48 safety results were generally similar in both CAB+RPV treatment groups (Q8W and Q4W) and were consistent with those reported through Week 48 in the phase 3 trials 201584 (FLAIR) and 201585 (ATLAS). The most frequently reported SAE was pneumonia (two subjects in each group) and no new drug-related SAEs were reported (b) (4) Table 11 summarizes the total number of SAEs (any event) and the SAEs that were reported in at least two subjects in either treatment group.

Table 11. Summary of Serious Adverse Events, Trial 207966

Adverse Event	CAB+RPV Q8W N=522	CAB+RPV Q4W N=523
Any event	27 (5)	19 (4)
AE preferred term		
Pneumonia	2 (<1)	2 (<1)
Appendicitis	2 (<1)	0
Hemorrhoids	2 (<1)	0

Source: Adapted from the Applicant's CRL Safety Update (Table 12, Page 34)
All values are expressed as n (%).
Abbreviations: AE, adverse event; CAB, cabotegravir; CRL, Complete Response letter; N, number of subjects in treatment group; n, number of subjects with adverse event; RPV, rilpivirine; Q4W, every 4 weeks; Q8W, every 8 weeks

Global Safety Database (June 6, 2019 Through January 31, 2020)

The Applicant's review of their Global Safety Database identified 20 subjects with 21 SAEs reported in subjects receiving CAB+RPV. Three of the 21 SAEs (myocardial infarction, osteonecrosis, and drug hypersensitivity) were considered by the investigator to be possibly related to CAB+RPV. The narratives for all 21 SAEs revealed no new safety concerns and are described in Table 12.

Table 12. Summary of Serious Adverse Events From the Global Safety Database, Trial 207966

Subject ID	Event	Grade	Assessment of Relatedness[1]	Possible Alternate Cause/Confounding Factor
(b) (6)	Gastroenteritis	3	No/Unlikely	None reported
	Breast abscess	3	No/No	Previous piercing
	Acute myocardial infarction	3	No/Unlikely	50-year-old male; risk factors (hypertension, smoking, positive family history)
	Drug hypersensitivity	3	Yes/Yes	None reported
	Testicular neoplasm	4	No/No	None reported
	Osteoarthritis	2	No/Unlikely	None reported
	Myocardial infarction	3	Yes/Unlikely	47-year-old male; risk factors (smoking, amphetamine use)
	Peritoneal perforation	4	No/No	Diverticulosis
	Gastrointestinal procedural complication	2	No/No	Sigmoiditis
	Pneumonia	3	No/No	Smoking; Blood culture (*Enterobacter cloacae*)
	Breast cancer	3	No/Unlikely	None reported
	Osteonecrosis	3	Yes/Unlikely	Recent fall (injured hip), history of chemotherapy and corticosteroid treatment for lymphoma
	Appendicitis	3	No/Unlikely	None reported
	Myocardial infarction	4	No/Unlikely	57-year-old male; risk factors (hypertension, hyperlipidemia, type 2 diabetes)
	Coronary artery disease	4	No/Unlikely	
	Pneumonia	3	No/Unlikely	None reported
	Transient ischemic attack	2	No/Unlikely	Smoking, frequent alcohol
	Osteonecrosis	3	No/Unlikely	None reported
	Cellulitis	1	No/No	Sexual encounter (penile cellulitis)
	Completed suicide	5	No/Unlikely	Longstanding history of depression and anxiety
	Nasal abscess	2	No/No	None reported

Source: Adapted from the Applicant's CRL Safety Update (Table 13, Page 38)
Grading based on NIH Division of AIDS Toxicity Table
[1] As determined by investigator/reviewer
Abbreviations: AIDS, acquired immune deficiency syndrome; CRL, Complete Response letter; NIH, National Institutes of Health

7.6.3.4. Trial 200056 (LATTE-2)

The Week 256 safety results in the Maintenance + Extension Phase (randomized Q8W/Q4W) were generally consistent with those reported through Week 160. Table 13 summarizes the total number of SAEs (any event) and the SAEs that were reported in at least two subjects in either treatment group through January 21, 2020.

Table 13. Summary of Serious Adverse Events in Maintenance + Extension Phase, Trial 200056

	Week 160[1]		Week 256[2]	
Adverse Event	**CAB+RPV Q8W N=115**	**CAB+RPV Q4W N=115**	**CAB+RPV Q8W N=115**	**CAB+RPV Q4W N=115**
Any event	17 (15)	21 (18)	25 (22)	27 (23)
AE preferred term				
Acute kidney injury	1 (<1)	0	2 (2)	1 (<1)
Suicide attempt	2 (2)	1 (<1)	2 (2)	1 (<1)
Chest pain	0	1 (<1)	0	2 (2)
Intervertebral disc protrusion	0	0	0	2 (2)
Overdose	0	0	0	2 (2)
Toxicity to various agents	0	1 (<1)	0	2 (2)

Source: Adapted from the Applicant's CRL SUR (Table 14, Page 40)
All values are expressed as n (%).
[1] Presented in original NDA
[2] Cumulative data = Original NDA + Safety Update
Abbreviations: AE, adverse event; CAB, cabotegravir; CRL, Complete Response letter; N, number of subjects in treatment group; n, number of subjects with adverse event; NDA, new drug application; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SUR, safety update report

Table 14 summarizes the total number of SAEs (any event) and the SAEs that were reported in at least one subject in the Extension Switch Phase (optimized) through January 21, 2020.

Table 14. Summary of Serious Adverse Events, Extension Switch Phase, Trial 200056

	Week 160[1]		Week 256[2]	
Adverse Event	**Optimized CAB+RPV Q8W N=34**	**Optimized CAB+RPV Q4W N=10**	**Optimized CAB+RPV Q8W N=34**	**Optimized CAB+RPV Q4W N=10**
Any event	2 (6)	0	6 (18)	1 (10)
AE preferred term				
Pneumonia	1 (3)	0	2 (6)	0
Gastroenteritis viral	0	0	1 (3)	0
Abdominal pain upper	0	0	1 (3)	0
Anal neoplasm	0	0	1 (3)	0
Pneumothorax	0	0	1 (3)	0
Road traffic accident	0	0	1 (3)	0
VIth nerve paralysis	0	0	0	1 (10)

Source: Adapted from the Applicant's CRL SUR (Table 15, Page 44)
All values are expressed as n (%).
[1] Presented in the original NDA
[2] Cumulative data = Original NDA + Safety Update
Abbreviations: AE, adverse event; CAB, cabotegravir; CRL, Complete Response letter; N, number of subjects in treatment group; n, number of subjects with adverse event; NDA, new drug application; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine; SUR, safety update report

Between Week 160 and Week 256, SAEs were reported in seven additional subjects (not reported in the 60-day SUR), including two subjects with SAEs that were considered to be related to CAB+RPV. The narratives for the SAEs in the seven subjects revealed no new safety concerns and are described in Table 15.

Table 15. Summary of Serious Adverse Events Between Week 160 and Week 256, Trial 200056

Subject ID	Event	Grade	Assessment of Relatedness[3]	Possible Alternate Cause/Confounder
(b) (6)	Postinjection reaction[1]	1-2	Yes/Yes	None
	Delusion	3	Yes/Unlikely	Previous hospitalization for depression and obsessive-compulsive disorder
	Hepatic failure	4	No/Unlikely	History of alcohol abuse
	Depression suicidal	4	No/Unlikely	
	Syncope	4	No/Unlikely	None
	Mania	3	No/Unlikely	Social stressors
	Bipolar disorder[2]	2	No/Unlikely	History of anxiety disorder
	Psychotic behavior	3	No/Unlikely	History of depression, anxiety, and insomnia
	Bipolar disorder	3	No/Unlikely	

Source: Reviewer
Grading based on NIH Division of AIDS Toxicity Table
[1] SAEs: abdominal pain, dyspnea, chest pain, and flushing
[2] Event listed as depression (Grade 2) in the 60-day SUR
[3] As determined by investigator/reviewer
Abbreviations: AIDS, acquired immune deficiency syndrome; NIH, National Institutes of Health; SAE, serious adverse event; SUR, safety update report

Global Safety Database (January 21, 2020 Through January 31, 2020)

The Applicant's review of their Global Safety Database did not identify any new reported SAEs.

7.6.3.5. Supporting Trials

Twelve SAEs were reported in nine subjects during the reporting period (through January 31, 2020) in trials 209035 (POLAR) and 209493 (CUSTOMIZE). The narratives of all 12 SAEs revealed no new safety concerns and are described by individual trial below.

Trial 209035 (POLAR)

Five subjects had seven SAEs; only injection site reaction was considered by the investigator to be related to CAB+RPV. The seven SAEs are described in Table 16.

Table 16. Summary of Serious Adverse Events, Trial 209035

Subject ID	Event	Grade	Assessment of Relatedness[1]	Possible Alternate Cause/Confounder
(b) (6)	Cholecystitis acute	3	No/Unlikely	None reported
	Orchitis	4	No/No	Urine culture (*Escherichia coli*)
	Urinary tract infection bacterial	4	No/No	
	Proctitis	4	No/Unlikely	None reported
	Anal abscess	4	No/Unlikely	
	Cholelithiasis	3	No/Unlikely	None reported
	Injection site reaction	2	Yes/Yes	None reported

Source: Adapted from the Applicant's CRL SUR (Table 27, Page 72)
Grading based on NIH Division of AIDS Toxicity Table
[1] As determined by investigator/reviewer
Abbreviations: AIDS, acquired immune deficiency syndrome; CRL, Complete Response letter; NIH, National Institutes of Health; SUR, safety update report

Trial 209493 (CUSTOMIZE)

Four subjects had five SAEs; only neurological symptom was considered by the investigator to be related to CAB+RPV. The five SAEs are described in Table 17.

Table 17. Summary of Serious Adverse Events, Trial 209493

Subject ID	Event	Grade	Assessment of Relatedness[1]	Possible Alternate Cause/ Confounder
(b) (6)	Chest pain	2	No/Unlikely	None reported
	Gunshot wound	4	No/No	None reported
	Staphylococcus infection	3	No/No	Cut finger on a plate
	Abscess limb	3	No/No	History of *Staphylococcus aureus* abscess
	Neurological symptom[2]	3	Yes/Unlikely	Unspecified positive drug test

Source: Adapted from the Applicant's CRL SUR (Table 28, Page 74)
Grading based on NIH Division of AIDS Toxicity Table
[1] As determined by investigator/reviewer
[2] SAEs: Visual disturbance, vertigo, headache, ataxia
Abbreviations: AIDS, acquired immune deficiency syndrome; CRL, Complete Response letter; NIH, National Institutes of Health; SAE, serious adverse event; SUR, safety update report

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

No new safety concerns were identified after reviewing the AEs leading to withdrawal in the four key trials with CAB+RPV in the CRL SUR. The AEs leading to withdrawal were either consistent with proposed labeling or unlikely related to CAB+RPV and do not warrant labeling at this time. The AEs leading to withdrawal from the four key trials are briefly summarized by individual trial below.

Trial 201584 (FLAIR)

The AEs leading to withdrawal through September 12, 2019, were generally consistent with those reported through Week 48. During the Maintenance Phase to Week 96, the new AEs leading to withdrawal were either unrelated to CAB+RPV or consistent with the proposed labeling. The AEs included depression (n=2), hepatitis A (n=1), and injection site pain (n=1). The two AEs of depression were nonserious and considered related to CAB+RPV. In the Extension Phase (Extension Switch) from CAR to CAB+RPV group, one subject experienced an AE (injection site pain) that led to withdrawal. Table 18 provides a summary of the total number of AEs leading to withdrawal and the AEs leading to withdrawal that were reported in at least two subjects in any treatment group.

Table 18. Summary of Adverse Events Leading to Withdrawal, Trial 201584

	Maintenance Phase				Maintenance + Ext Phase[2,3]	Ext Phase[3,4]
	Week 48[1]		Week 96[2]			
Adverse Event	CAB+RPV N=283	CAR N=283	CAB+RPV N=283	CAR N=283	CAB+RPV N=283	Ext Switch[5] N=232
Any withdrawal	9 (3)	4 (1)	14 (5)	4 (1)	15 (5)	2 (<1)
AE preferred term						
Acute hepatitis B	2 (<1)	0	2 (<1)	0	2 (<1)	0
Hepatitis A	2 (<1)	0	3 (1)	0	3 (1)	0
Injection site pain	2 (<1)	0	3 (1)	0	3 (1)	1 (<1)
Depression	0	0	2 (<1)	0	2 (<1)	0

Source: Adapted from the Applicant's CRL SUR (Table 16, Page 48)
All values are expressed as n (%).
[1] Presented in original NDA
[2] Cumulative data = Original NDA + Safety Update
[3] Week 96 analysis; Extension Phase includes data beyond Week 96
[4] Safety Update
[5] In the Extension Switch, subjects transitioned from CAR to CAB+RPV.
Abbreviations: AE, adverse event; CAB, cabotegravir; CAR, current antiretroviral regimen; CRL, Complete Response letter; Ext, extension, N, number of subjects in treatment group; n, number of subjects with adverse event; NDA, new drug application; RPV, rilpivirine; SUR, safety update report

Trial 201585 (ATLAS)

The AEs leading to withdrawal through April 16, 2019, were generally consistent with those reported through Week 48. From Week 48 to Week 96, the new AEs leading to withdrawal were either unrelated to CAB+RPV or included in the 60-day SUR; the AEs included hepatitis B (n=1) and fear (n=1). During the Maintenance + Extension Phase to Week 96, the only new AE leading to withdrawal was hepatitis B. In the Extension Phase (Extension Switch) from CAR to CAB+RPV group, one subject experienced an AE (injection site pain) that led to withdrawal. Table 19 provides a summary of the total number of AEs leading to withdrawal and the AEs leading to withdrawal that were reported in at least two subjects in any treatment group.

Table 19. Summary of Adverse Event Leading to Withdrawal, Trial 201585

	Maintenance Phase Week 48[1]		Maintenance + Extension Phase[2,3]	Extension Phase[2,4]
Adverse Event	CAB+RPV N=308	CAR N=308	CAB+RPV N=308	Extension Switch[5] N=174
Any withdrawal	13 (4)	5 (2)	16 (5)	1 (<1)
AE preferred term				
Acute hepatitis B	1 (<1)	0	2 (<1)	0
Injection site pain	4 (1)	2 (<1)	4 (1)	1 (<1)
Headache[6]	2 (<1)	0	1 (<1)	0
Hepatitis A[6]	2 (<1)	0	1 (<1)	0

Source: Adapted from the Applicant's CRL Safety Update (Table 17, Page 50)
All values are expressed as n (%).
[1] Presented in original NDA
[2] Week 96 analysis; Extension Phase includes data beyond Week 96
[3] Cumulative data = Original NDA + Safety Update
[4] Safety Update
[5] In the Extension Switch, subjects transitioned from CAR to CAB+RPV
[6] AEs classified as leading to withdrawal Week 48; then changed to "did not lead to withdrawal" in the database prior to Week 96
Abbreviations: AE, adverse event; CAB, cabotegravir; CAR, current antiretroviral regimen; CRL, Complete Response letter; N, number of subjects in treatment group; n, number of subjects with adverse event; NDA, new drug application; RPV, rilpivirine

Trial 207966 (ATLAS-2M)

At Week 48 (through June 6, 2019), the AEs leading to withdrawal were generally consistent with those reported through Week 48 in the phase 3 trials 201584 (FLAIR) and 201585 (ATLAS). The most frequently reported AEs leading to withdrawal were injection site reactions (ISRs), which occurred in five subjects in each treatment group. Table 20 provides a summary of the non-ISR AEs leading to withdrawal that were reported in at least two subjects (combined).

Table 20. Summary of Non-Injection Site Reaction Adverse Events Leading to Withdrawal, Trial 207966

AE Preferred Term	CAB+RPV Q8W N=522	CAB+RPV Q4W N=523
Fatigue	1 (<1)	2 (<1)
Hyperhidrosis	0	2 (<1)
Abnormal dreams	0	2 (<1)
Acute hepatitis B	1 (<1)	1 (<1)
Headache	1 (<1)	1 (<1)
Presyncope	1 (<1)	1 (<1)
Pyrexia	1 (<1)	1 (<1)

Source: Adapted from the Applicant's CRL Safety Update (Table 18, Page 52)
All values are expressed as n (%).
Abbreviations: AE, adverse event; CAB, cabotegravir; CRL, Complete Response letter; N, number of subjects in treatment group; n, number of subjects with adverse event; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine

Trial 200056 (LATTE-2)

The AEs leading to withdrawal at Week 256 (randomized Q8W/Q4W) were generally consistent with those reported through Week 160. With the exception of injection site pain, all of the other individually reported AEs leading to withdrawal had an incidence of one subject in either group at both time points. Table 21 provides a summary of AEs leading to withdrawal that were reported in at least two subjects in any treatment group.

Table 21. Summary of Maintenance and Extension Period Adverse Events Leading to Withdrawal, Trial 200056 (Randomized Q8W/Q4W)

	Week 160[1]		Week 256[2]	
Adverse Event	CAB+RPV Q8W N=115	CAB+RPV Q4W N=115	CAB+RPV Q8W N=115	CAB+RPV Q4W N=115
Any withdrawal	3 (3)	12 (10)	3 (3)	20 (17)
AE preferred term				
Injection site pain	2 (2)	0	2 (2)	1 (<1)

Source: Adapted from the Applicant's CRL Safety Update (Table 20, Page 54)
All values are expressed as n (%).
[1] Presented in original NDA
[2] Cumulative data = Original NDA + Safety Update
Abbreviations: AE, adverse event; CAB, cabotegravir; CRL, complete response letter; N, number of subjects in treatment group; n, number of subjects with adverse event; NDA, new drug application; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine

In the Extension Switch (optimized Q8W/Q4W) through Week 256, one withdrawal occurred in a subject because of lumbar pain, conjunctival infection, facial erythema, general redness, and urticarial papular erythematous rash. These events were nonserious (Grade 1) and were considered by the investigator to be related to CAB+RPV.

7.6.1. Discontinuation Due to Liver Events

No new safety concerns were identified after reviewing the discontinuations that occurred due to liver events in the four key trials with CAB+RPV in the CRL SUR. There were four additional subjects who discontinued CAB+RPV due to liver events; these events were not included in the original NDA submissions or in the 60-day SUR. Three of the four events were associated with acute viral hepatitis (hepatitis B [n=2] and hepatitis A [n=1]), and one of the four events was described as drug-induced liver injury (DILI), which was likely related to CAB+RPV and was resolved after discontinuation of CAB+RPV. These liver events are consistent with the proposed CAB+RPV labeling and are briefly summarized by individual trial below.

Trial 201584 (FLAIR)

At Week 96, one additional subject met liver stopping criteria and withdrew from the trial. The subject was diagnosed with acute hepatitis A, which was assessed by the investigator as not related to CAB+RPV.

Trial 207966 (ATLAS-2M)

Through Week 48, three subjects withdrew from the trial due to liver events. Two of the three subjects met liver stopping criteria and were diagnosed with acute hepatitis B; both events were assessed by the investigator as not related to CAB+RPV. The third subject developed a possible case of DILI and is described below.

Subject (b) (6)

A 20- to 30-year-old female was randomized at baseline to the Q4W group after previously receiving lopinavir, ritonavir, ABC, and 3TC as part of trial 201585 (ATLAS). After receiving 28 days of oral CAB+RPV during the OLI period, the subject developed an asymptomatic increase in ALT and aspartate aminotransferase (AST) with no elevation in bilirubin; ALT was 206 U/L (>4× ULN) and AST was 137 U/L (>3× ULN). The OLI was extended while the subject was investigated for alternative causes; however, investigations were negative for viral hepatitis, syphilis, and an autoimmune screen. During this time, ALT and AST remained elevated (ALT 6× ULN and AST >3× ULN), total bilirubin was within normal limits, liver stopping criteria were not met, and the subject was withdrawn from the trial after receiving a total of 11 weeks of oral CAB+RPV. After the subject initiated abacavir, lamivudine, and dolutegravir, both ALT and AST returned to normal after 12 weeks. The case was submitted to the Hepatic Adjudication Committee for review as a case of potential interest, and the committee concluded that this was a possible case of DILI related to CAB+RPV.

7.6.2. Adverse Events of Special Interest

Refer to the review completed on December 19, 2019.

Risks or potential risks related to AEs were identified primarily through the AESI list, including:

- Injection reactions
- Hypersensitivity reactions and rash

- Hepatobiliary events
- Psychiatric events (including depressive disorders)
- Neurologic events (including seizure)
- Gastrointestinal events (including pancreatitis)
- Musculoskeletal events related to injection or rhabdomyolysis
- Weight gain
- Pregnancy and risk of embryo-fetal toxicity

The CRL SUR did not include a specific summary of new AESIs.

7.6.3. Most Common Adverse Events (≥5%)

No new safety concerns were identified after reviewing the most common AEs (≥5%) occurring in the four key trials with CAB+RPV in the CRL SUR. AEs were either consistent with proposed labeling or unlikely to be related to CAB+RPV and therefore do not warrant labeling at this time. The most common AEs from the four key trials are briefly summarized by individual trial below.

Trial 201584 (FLAIR)

The most common AEs reported through Week 96 (through September 12, 2019) were similar to those reported through Week 48. For the Maintenance Phase at Week 96, the most common AEs reported in the CAB+RPV group were injection site pain (83%), nasopharyngitis (28%), injection site nodule (20%), and headache (18%). In the Maintenance + Extension Phase, the most common AEs reported in the CAB+RPV group were injection site pain (84%), nasopharyngitis (29%), injection site nodule (22%), and headache (19%). In the Extension Switch group, the most common AEs were injection site pain (60%), injection site induration (5%), and injection site nodule (4%); however, the period of time and cumulative number of injections administered per subject in the Extension Switch group were lower than in the ongoing CAB+RPV group.

Trial 201585 (ATLAS)

The most common AEs reported through Week 96 (through April 16, 2019) were similar to those reported through Week 48. During the Maintenance + Extension Phase at Week 96, the most common AEs reported in the CAB+RPV group were injection site pain (75%), nasopharyngitis (19%), injection site nodule (12%), upper respiratory tract infection (12%), headache (11%), and injection site induration (10%). In the Extension Switch group, the most common AEs were injection site pain (45%), nasopharyngitis (6%), injection site induration (5%), and influenza (5%). However, the period of time and cumulative number of injections administered per subject in the Extension Switch group were lower than in the ongoing CAB+RPV group.

Trial 207966 (ATLAS-2M)

The Week 48 safety results (through June 6, 2019) were generally consistent with those reported through Week 48 in trials 201584 (FLAIR) and 201585 (ATLAS). The most common AEs

reported in both treatment groups were injection site pain (71% Q8W; 69% Q4W), nasopharyngitis (14% Q8W; 14% Q4W), injection site nodule (10% Q8W; 17% Q4W), and upper respiratory tract infection (10% Q8W; 14% Q4W).

Trial 200056 (LATTE-2)

The Week 256 safety results (through January 21, 2020) during the Maintenance + Extension Phase (randomized Q8W/Q4W) were generally consistent with those reported through Week 160. The most common AEs reported at Week 256 in both treatment groups were injection site pain (97% Q8W; 100% Q4W), nasopharyngitis (43% Q8W; 46% Q4W), injection site nodule (35% Q8W; 43% Q4W), and injection site swelling (34% Q8W; 34% Q4W).

The Week 256 safety results (through January 21, 2020) during the Maintenance + Extension Phase (Extension Switch) were generally consistent with those reported through Week 160. The most common AEs reported at Week 256 in both treatment groups were injection site pain (88% Q8W; 80% Q4W), injection site nodule (35% Q8W; 40% Q4W), injection site swelling (18% Q8W; 20% Q4W), and nasopharyngitis (18% Q8W; 50% Q4W).

7.6.4. Laboratory Findings

Refer to the review completed on December 19, 2019.

7.7. Review Issues Relevant to the Evaluation of Risk

Refer to the review completed on December 19, 2019.

No new review issues were identified during the review of the CRL SUR.

8. Therapeutic Individualization

Refer to the review completed on December 19, 2019.

8.1. Intrinsic and Extrinsic Factors

Refer to the review completed on December 19, 2019.

8.2. Drug Interactions

Refer to the review completed on December 19, 2019.

8.3. Pediatric Labeling/Plans for Pediatric Drug Development

Refer to the review completed on December 19, 2019.

8.4. Pregnancy and Lactation

Refer to the review completed on December 19, 2019.

Ten new confirmed pregnancies were reported among subjects receiving CAB+RPV in the CRL SUR; these pregnancies were not included in the original NDA submissions or the 60-day SUR. Of the 10 confirmed pregnancies, 6 resulted in live births, 2 resulted in spontaneous abortions, and 2 were terminated electively. No congenital anomaly was reported with the live births. The review of the new reported pregnancies in the CRL SUR revealed no new safety concerns and are described by individual trial below.

Trial 201584 (FLAIR)

- Subject (b) (6) (CAB+RPV) had a spontaneous abortion at less than 22 weeks gestation; the investigator assessed the event as not related to study drugs.
- Subject (b) (6) (CAB+RPV) delivered a healthy male infant of 40 weeks gestation.
- Subject (b) (6) (CAB+RPV) had an ongoing pregnancy at the time of the Week 96 analysis; information received from the site following the data cutoff for this safety update indicated the birth of a healthy male infant. The approximate gestation period was 40 weeks, 4 days.
- Subject (b) (6) (Extension Switch to CAB+RPV) had a positive pregnancy test during the OLI period and did not receive IM CAB+RPV prior to withdrawal. Information received after the cutoff date indicated that a healthy male baby was delivered.

Trial 201585 (ATLAS)

- Subject (b) (6) (CAB+RPV) had an ongoing pregnancy at the time of data cutoff date. Information received after the cutoff date indicated that a healthy infant was born.

Trial 207966 (ATLAS-2M)

- Subject (b) (6) (Q4W group) had a spontaneous abortion; the investigator assessed the event as not related to study drugs.
- Subject (b) (6) (Q4W group) had an elective abortion for nonmedical reasons.
- Subject (b) (6) (Q8W group) had an elective abortion for nonmedical reasons; the subject was withdrawn from the trial during the OLI period and did not receive IM CAB+RPV prior to withdrawal.
- Subject (b) (6) (Q4W group) had a live birth at approximately 39 weeks gestation and no birth defects were observed. The delivery was complicated by Grade 2 chorioamnionitis, which was assessed by the investigator as not related to CAB+RPV and was resolved 2 days later. The subject was withdrawn from the trial during the OLI period and did not receive IM CAB+RPV prior to withdrawal.

Trial 200056 (LATTE-2)

- Subject (b) (6) delivered a healthy infant at approximately 36 weeks.

Supporting Trials

No new pregnancies were reported in the supporting trials (209035, 209493, 201767, 208580, and 204843).

As summarized in the December 19, 2019, review, no trials have been conducted with CAB+RPV in pregnant women, and pregnant women were excluded from the CAB+RPV development program. Females who became pregnant during a trial had CAB+RPV discontinued. There are insufficient human data on the use of CABENUVA during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. CABENUVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus or the patient.

9. Product Quality

Approval—The Office of Pharmaceutical Quality review team has assessed NDA 212887 (VOCABRIA) and NDA 212888 (CABENUVA) with respect to Chemistry, Manufacturing, and Controls, and has determined that they meet all applicable standards to support the identity, strength, quality, and purity that they purport. The Office of Pharmaceutical Quality recommends approval of these NDAs from a quality perspective.

9.1. Device or Combination Product Considerations

Refer to the review completed on December 19, 2019.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

Refer to the review completed on December 19, 2019.

11. Advisory Committee Summary

CAB+RPV was not taken to an FDA advisory committee because no unexpected significant safety or efficacy issues were identified, and no controversial or challenging issues arose that would benefit from advisory committee discussion.

III. Appendices

Refer to the review completed on December 19, 2019.

12. References

Centers for Disease Control and Prevention, 2019, HIV in the United States and Dependent Areas, https://www.cdc.gov/hiv/statistics/overview/ataglance.html.

ClinicalInfo, 2019, What's New in the Guidelines?, https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines.

Guidance for Industry, Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (November 2015)

13. Review Team Acknowledgments

Refer to the review completed on December 19, 2019.

Table 22. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Debra Birnkrant, MD	OND/DAV	Enter sections. ☐ Authored ☒ Approved Section 1 and Section II
Division Director	**Signature:** Debra B. Birnkrant -S Digitally signed by Debra B. Birnkrant -S Date: 2021.01.19 11:55:57 -05'00'		
Clinical	Kimberly Struble, PharmD	OND/DAV	Enter sections. ☒ Authored Section I: Executive summary, Benefit-Risk Conclusions ☒ Approved Section II
Cross-Disciplinary Team Lead	**Signature:** Kimberly A. Struble -S Digitally signed by Kimberly A. Struble -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300077275, cn=Kimberly A. Struble -S Date: 2021.01.19 09:59:45 -05'00'		
Clinical	Timothy Jancel, PharmD, MHS	OND/DAV	Enter sections. ☒ Authored Section II: Section 7, 8.4 ☒ Approved Section II
Primary Reviewer	**Signature:** Timothy J. Jancel -S Digitally signed by Timothy J. Jancel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0013382980, cn=Timothy J. Jancel -S Date: 2021.01.19 11:50:47 -05'00'		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW A GENTLES
01/19/2021 12:55:26 PM

JOHN J FARLEY
01/19/2021 01:45:14 PM

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Integrated Review

Category	Application Information
Application type	NDA
Application number(s)	212887
Priority or standard	Priority
Submit dates	4/29/2019
Received dates	4/29/2019
PDUFA goal date	12/29/2019
Division/office	Division of Antiviral Products (DAVP)
Review completion date	11/1/2019
Established name	Cabotegravir Tablets
(Proposed) trade name	VOCABRIA
Pharmacologic class	Cabotegravir: integrase strand transfer inhibitor [INSTI]
Code name	Cabotegravir: CAB, GSK1265744
Applicant	ViiV Healthcare
Dose form/formulation(s)	Tablet
Dosing regimen	30 mg of cabotegravir taken orally once daily for approximately one month in combination with one 25 mg tablet of EDURANT (rilpivirine) orally once daily prior to the initiation of CABENUA to assess tolerability of cabotegravir and rilpivirine
Applicant proposed indication(s)/population(s)	(b) (4) - Oral lead-in (OLI) to assess the tolerability of cabotegravir prior to administration of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions -Oral therapy for patients who will miss planned injection dosing with CABENUVA injectable suspension
Proposed SNOMED indication	(b) (4)
Regulatory action	Complete response
Approved indication(s)/population(s) (if applicable)	Not applicable because the NDA will receive a Complete Response action. If an approval action was recommended the following is the indication as agreed by FDA and ViiV VOCABRIA, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), is indicated in combination with EDURANT, oral rilpivirine, for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as: - Oral lead-in to assess the tolerability of cabotegravir prior to administration of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions - Oral therapy for patients who will miss planned injection dosing with CABENUVA injectable suspensions

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Category	Application Information
Approved SNOMED indication	Not applicable because the NDA will receive a Complete Response action. If the NDA received an approval action the SNOMED indication is as follows: 40780007: Human immunodeficiency virus I infection (disorder)

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Category	Application Information
Application type	NDA
Application number(s)	212888
Priority or standard	Priority
Submit dates	4/29/2019
Received dates	4/29/2019
PDUFA goal date	12/29/2019
Division/office	Division of Antiviral Products (DAVP)
Review completion date	11/1/2019
Established name	Cabotegravir extended-release injectable suspension; Rilpivirine extended-release injectable suspension
(Proposed) trade name	CABENUVA
Pharmacologic class	Cabotegravir: integrase strand transfer inhibitor [INSTI] Rilpivirine: nonnucleoside reverse transcriptase inhibitor [NNRTI]
Code name	Cabotegravir: CAB, GSK1265744 Rilpivirine: RPV, TMC278, GSK1329758
Applicant	ViiV Healthcare
Dose form/formulation(s)	Injectable suspension
Dosing regimen	Initiate injections of CABENUVA (3 mL) on the final day of OLI and continue with injections of CABENUVA (2 mL) every month thereafter
Applicant proposed indication(s)/population(s)	(b) (4)
Proposed SNOMED indication	(b) (4)
Regulatory action	Complete response
Approved indication(s)/population(s) (if applicable)	Not applicable because the NDA will receive a Complete Response action. If an approval action was recommended the following is the indication as agreed by FDA and ViiV CABENUVA, a 2-drug copackaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 nonnucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.
Approved SNOMED indication	Not applicable because the NDA will receive a Complete Response action. If the NDA received an approval action the SNOMED indication is as follows: 40780007: Human immunodeficiency virus I infection (disorder)

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Glossary

3TC	lamivudine
ABC	abacavir
ACCEPT	Chronic Treatment Acceptance questionnaire
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATLAS	Antiretroviral Therapy as Long-Acting Suppression
ATV	atazanavir
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BIC	bictegravir
BLA	biologics license application
BMI	body mass index
BQL	below the limit of quantitation
CAB	cabotegravir
CAB LA	long-acting cabotegravir
CAM	chorioallantoic membrane
CAR	current first-line antiretroviral regimen
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CI	confidence interval
CK	creatine kinase
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel Haenszel
COA	clinical outcome assessment
CVF	confirmed virologic failure
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAVP	Division of Anti-viral Products
DDI	drug-drug interaction
DILI	drug-induced liver injury
DNP	Division of Neurology Products
DTG	dolutegravir
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
EFV	efavirenz

EPR	essential performance requirement
ERDF	efficacy-related discontinuation/failure
ESRD	end-stage renal disease
EVG	elvitegravir
FDA	Food and Drug Administration
FLAIR	First Long-Acting Injectable Regimen
FTC	emtricitabine
GD	gestation day
GI	gastrointestinal
GLP	good laboratory practice
HAART	highly active antiretroviral treatment
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIVTSQ	HIV Treatment Satisfaction Questionnaire
HIVTSQc	HIV Treatment Satisfaction Questionnaire – status change
HPMC	hydroxypropyl methylcellulose
HPTN	HIV-1 prevention trial number
HR	health-related
HAS	human serum albumin
HSR	hypersensitivity reaction
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IM	intramuscular
IN	integrase
IND	investigational new drug
INI	integrase inhibitor
INSTI	integrase strand transfer inhibitor
ISR	injection site reaction
ITT-E	intention-to-treat exposed
KLH	keyhole limpet hemocyanin
LAI	long-acting injectable
LATTE	Long-Term Anastrozole vs. Tamoxifen Treatment Effects
LOCF	last observation carried forward
LSC	liver stopping criteria
LTFU	long-term follow-up
LTR	long terminal repeat
MC4R	melanocortin-4 receptor
NDA	new drug application
NNRTI	nonnucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRS	Numeric Rating Scale
NRTI	nucleoside reverse transcriptase inhibitor
NTD	neural tube defect

OAT	organic anion transporter
OLI	oral lead-in
PBMC	peripheral blood mononucleocyte
PBPK	physiologically-based pharmacokinetic
PCFT	proton-coupled folate transporter
PCR	polymerase chain reaction
PDE	permitted daily exposure
PGx	pharmacogenomics
PHIV	pseudo-HIV
PI	protease inhibitor
PIN	Perception of Injection
PK	pharmacokinetics
PMR	postmarketing requirement
PND	postnatal day
popPK	population pharmacokinetics
PP	per protocol
PPND	pre- and postnatal development
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PT	preferred term
QoL	quality of life
RAL	raltegravir
RAS	resistance-associated substitution
RFC	reduced folate carrier
RHD	recommended human dose
RNA	ribonucleic acid
RPR	rapid plasma reagin
RPV	rilpivirine
RPV LA	long-acting rilpivirine, also referred to as TMC-LA and TMC278 LA
RT	reverse transcriptase
SAE	serious adverse event
SOC	system organ class
SUR	safety update report
TDAR	T-cell–dependent antibody response
TDF	tenofovir disoproxil fumarate
TEAE	treatment-emergent adverse event
TK	toxicokinetics
TQT	thorough QT
TRDF	treatment-related discontinuation/failure
ULN	upper limit of normal
USPI	United States Prescribing Information
VPC	visual predictive check
WOCBP	women of childbearing potential

I. Executive Summary

1. Summary of Regulatory Action

These new drug applications (NDAs) for VOCABRIA, an oral formulation of cabotegravir (CAB), and CABENUVA, an extended-release, injectable, two-drug copackaged product containing CAB and rilpivirine (RPV), were submitted by ViiV Healthcare. CAB is a new integrase strand transfer inhibitor (INSTI) and RPV is a previously approved nonnucleoside reverse transcriptase inhibitor (NNRTI). These NDAs were reviewed by the multidisciplinary review team.

The intended indication for VOCABRIA is use in combination with oral RPV for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV, for use as one) an oral lead-in (OLI) to assess the tolerability of CAB prior to administration of CABENUVA and 2) as an oral therapy (up to 2 consecutive months) for patients who will miss planned dosing with CABENUVA injectable suspensions.

The intended indication for CABENUVA is a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen (CAR) in those who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV. CABENUVA is administered by a healthcare provider every 4 weeks.

Each discipline (clinical, virology, clinical pharmacology, pharmacology/toxicology statistics and regulatory) did not identify any issues that preclude approval. I, the signatory authority, agree the benefit/risk assessment favors approval. However, the Agency will issue a Complete Response action for this application due to deficiencies observed at the GLAXO OPERATIONS UK LIMITED manufacturing facility for NDA 212888 (CABENUVA). Specifically, preliminary [redacted] (b) (4) (b) (4) Furthermore, the Drug Master File for RPV was found inadequate to support approval for NDA 212888. Please refer to the Complete Response letter for further details.

Each discipline (clinical, virology, clinical pharmacology, pharmacology/toxicology, statistics, CMC and regulatory) did not identify any issues that preclude approval for NDA 212877 (VOCABRIA). I, the signatory authority, agree the benefit/risk assessment favors approval. However, a Complete Response action will be issued for NDA 212887 because the approval of VOCABRIA is contingent on the approval of CABENUVA.

ViiV submitted two adequate and well-controlled phase 3 trials that provided substantial evidence of efficacy for the indications approved. No significant issues were identified during the review relevant to the benefit of CAB+RPV. The two-drug CAB+RPV regimen was

noninferior to controls (subjects remain on their current three-drug ARV regimen). Higher virologic failure rates were seen in females, subjects with body mass index (BMI) ≥30 kg/m^2, and females with BMI ≥30 kg/m^2 compared to their counterparts. Further post hoc exploratory analyses did not reveal a singular explanation for the higher virologic failure rates. These post hoc exploratory analyses were limited by sample size, and further analyses from ongoing trials are needed to assess these findings.

Oral CAB and extended-release injectable suspension forms of CAB and RPV are safe for the intended use. Aside from local and systemic injection site reactions (ISRs), no new or unexpected safety findings were noted. The adverse event (AE) profile was consistent with previous trials with RPV and INSTIs. The use of oral CAB and RPV as a 4-week OLI was adequate to assess the tolerability of CAB and RPV prior to receiving CAB and RPV injections. Discontinuations during the OLI phase were infrequent. We concur the identified risks can be mitigated through labeling and further evaluated during routine pharmacovigilance.

The “long-acting” (LA) properties of CABENUVA have potential advantages and disadvantages. The extended-release injectable formulations eliminate the need for adherence to oral daily medications and can be administered every 4 weeks. However, because residual concentrations of CAB and RPV can remain for prolonged periods (12 months or longer), careful selection of patients who agree to the required monthly injection dosing schedule is imperative. Nonadherence to the monthly injections or missed injections can lead to loss of virologic response and development of resistance to CAB, RPV, or the INSTI and NNRTI drug classes.

For detailed information supporting the basis for the benefit-risk assessment please refer to the details in this integrated assessment document. Please also refer to the Product Quality Review for the deficiencies observed resulting in the overall Complete Response action.

2. Benefit-Risk Assessment

Table 1. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Human immunodeficiency virus type 1 (HIV-1) is a transmissible virus that attacks CD4+ cells and thereby weakens the immune system. Without effective treatment, HIV-1 infection leads to progressive destruction of the immune system, acquired immunodeficiency syndrome (AIDS)-defining illnesses, and premature death in almost all cases. • In the United States, 1.1 million people were living with HIV at the end of 2015, and 38,739 people were newly diagnosed with HIV in 2017.[1] • The goals of HIV treatment are to durably suppress HIV RNA, preserve and restore the immune system, reduce HIV-associated morbidity, and ultimately improve long-term survival.	HIV-1 continues to be a significant public health concern, both globally and domestically. Without effective treatment, HIV-1 leads to progressive destruction of the immune system and therefore is a serious, life-threatening condition. With effective management, however, HIV-1 is a controllable chronic condition. Effective viral load suppression can also provide the additional public health benefit of decreased HIV-1 transmission.
Current Treatment Options	• The current antiretroviral (ARV) treatment armamentarium is robust. Excluding fixed-dose combination (FDC) products and different formulations, 29 individual ARV drugs and 2 drugs (cobicistat and ritonavir) which inhibit metabolic enzymes and enhance the exposure of ARVs are approved and available for the treatment of HIV-1. (A complete list is provided in Appendix III.12). • The current recommended standard of care for most people with HIV is a three-drug regimen, typically an integrase strand transfer inhibitor (INSTI) plus two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) (Panel on Antiretroviral Guidelines for Adults and Adolescents and Department of Health and Human Services). • In clinical practice, patients may choose to switch from an initially effective three-drug ARV regimen for a variety of reasons, including adverse event (AE), drug–drug or drug−food interactions, or a desire for a simpler regimen with fewer pills. In this situation, current guidelines recommend switching to an alternative regimen that maintains viral suppression without jeopardizing future treatment options.	Optimal management of HIV-1 is complex and must consider patients' individual needs. The expansion of the HIV treatment armamentarium with another ARV that is efficacious, well-tolerated, with relatively few clinically relevant drug−drug interactions benefits virologically suppressed patients who want to switch from their current ARV regimen to another. A two-drug extended-release injectable regimen, administered monthly by a healthcare professional would be expected to be beneficial for some patients. The monthly two-drug injectable regimen would reduce the complexity of ARV treatment, decrease the risk of adverse reactions of the third drug in a regimen, and provide an option to address pill-fatigue associated non-adherence with daily medication. One would anticipate more effective treatment of HIV-1 in some patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of CAB+RPV (cabotegravir and rilpivirine) in the virologically suppressed (HIV RNA <50 copies/mL) population was established in two randomized phase 3 trials: – FLAIR and ATLAS were trials with similar designs that compared CAB+RPV extended-release injectable versus a three-drug regimen (with INSTI, protease inhibitor (PI), or NNRTI as the third agent). – Together, the trials enrolled 1,182 subjects: with 591 each in CAB+RPV treatment group and the pooled control group. • Both trials included the primary endpoint HIV RNA ≥50 copies/mL at week 48 to measure the effectiveness of sustaining virologic suppression from baseline. A key secondary endpoint included threshold for virologic response with HIV-1 RNA <50 copies/mL. This endpoint is well-established as a clinically meaningful endpoint and correlates with clinical benefits. • In the stratified pooled analysis of FLAIR and ATLAS, the week 48 adjusted treatment difference and 95% CI was 0.2 (-1.4, 1.7). The result met the threshold for noninferiority to the three-drug comparator group. The results from the individual trials were consistent with the pooled analysis result. • Higher virologic failure rates were seen for the CAB+RPV treatment group versus the control group among the following subgroups compared to their counterparts: female subjects, subjects with BMI ≥30 kg/m^2, and female subjects with BMI ≥30 kg/m^2. • The presence of pre-existing NNRTI resistance-associated substitutions (RAS) could potentially reduce the virologic response to RPV and contribute to virologic failure on the CAB+RPV regimen. However, the limited data from the FLAIR trial did not suggest the presence of RT K103N NNRTI RAS at screening is associated with virologic failure.	The submitted clinical trial data demonstrated a meaningful benefit of CAB+RPV in treating virologically suppressed, HIV-1–infected patients. The efficacy of CAB+RPV, a two-drug extended-release injectable regimen is noninferior to the comparator three-drug regimens. The review did not identity significant issues with trial design or conduct. Limited data are available on the durability of a two-drug regimen to maintain virologic suppression beyond 48 weeks. Other uncertainties as described below are from exploratory analyses and cannot be addressed with the current data, primarily due to limited sample size. Therefore, additional evaluation for differences in outcome among these subgroups is warranted. • Although the presence of RT K103N resistance-substitution is generally a concern for patients initiating an NNRTI-based regimen, the limited data from the FLAIR trial did not suggest the presence of the RT K103N NNRTI RAS at screening is associated with virologic failure to CAB+RPV. Additional data are needed to further assess the presence of the K103N substitution on the effectiveness of CAB+RPV regimen before recommending an indication for this subpopulation. • Virologic failure rates were higher for the CAB+RPV treatment group versus the control treatment group among females, baseline BMI ≥30 kg/m^2, and females with baseline BMI ≥30 kg/m^2 compared to their counterparts. Our review further focused on the females with baseline BMI ≥30 kg/m^2 subgroup. Drug exposure or baseline virologic characteristics did not explain this finding. Despite these current results, limitation of use is not recommended at this time. We view the results

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		from our analyses as hypothesis-generating because the outcomes were based on a post hoc, exploratory subgroup analysis; did not apply multiplicity adjustment; and had limited sample size. Additional evaluation for differences in outcome among these subgroups is warranted. Further assessment with more data from other independent trial(s) is necessary to confirm the observed higher virologic failure rate in the CAB+RPV treatment arm in females with baseline BMI ≥30 kg/m^2 and to explore the possible explanations for the higher virologic failure rate.
Risk and Risk Management	• Deficiencies were identified during the inspection of the NDA 212888 CAB drug product manufacturing facility. • The safety data from the FLAIR and ATLAS trials exceeded the 300 to 500 subjects recommended for safety evaluations in the FDA HIV Treatment Guidance (November 2015).[2] The safety data are also supplemented by extensive experience with RPV, marketed either as individual drugs or as part of other FDCs. Data from the phase 2 trials (LATTE and LATTE-2), and safety reports from ongoing trials (ATLAS-2M, HPTN083 and HPTN084), also provided supportive safety data/information for CAB. • The 4-week oral lead-in was adequate to assess the tolerability of CAB and RPV prior to initiating extended-release CAB and RPV injections. Few subjects discontinued oral therapy prior to receiving CAB and RPV injections. • The most common adverse drug reactions during treatment with CAB+RPV extended-release were injection site reactions (ISRs). Additionally, systemic reactions such as pyrexia, musculoskeletal pains, and sciatica were associated with injections. • Other common adverse reactions include pyrexia, fatigue, headache, nausea, musculoskeletal pain, sleep disorders, dizziness, and rash.	Satisfactory resolution of the identified manufacturing deficiencies is required before the CAB+RPV application can be approved and subsequently the oral CAB application. Overall, the safety data are adequate to assess the safety of CAB+RPV for the proposed indication, dosage regimen, duration, and patient populations. The safety profile of CAB+RPV has been well-characterized, and none of the identified safety issues would preclude approval of CAB+RPV. Except for injection-related events, the overall safety profile of CAB+RPV was generally similar to the anticipated profile for an INSTI and the known profile of RPV. An oral lead-in to assess the tolerability of CAB+RPV prior to initiating dosing with the extended-release injections may not be needed in the future. Review of the data from ATLAS-2M will help determine if CAB+RPV extended-release can be administered without an oral lead-in. Although FLAIR and ATLAS trials were not designed to show a benefit on the basis of any specific safety outcome, the descriptive safety analyses showed that the two-drug regimen lacked the additional safety concerns associated with a third drug (e.g., NRTIs). While the risk of development of resistance or cross-resistance among virologic failures is shared across

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The most serious AEs (or potential events), including depressive disorders, HSR, and hepatotoxicity, are adequately labeled under WARNINGS and PRECAUTIONS. These events are associated with other INSTIs. NNRTIs, including RPV, are also labeled for similar events. Neuropsychiatric events, including suicide-related events, have been described with RPV use and as a potential class-associated safety concern with INSTI use. While serious or severe HSRs were not observed during the phase 3 clinical trials, cases such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been observed with RPV. Additionally, HSRs have been described with other INSTIs and thus considered a potential safety concern with CAB. • Weight increase is an emerging important safety issue with INSTI use. Weight increase was observed among CAB+RPV-treated subjects as well as among abacavir/dolutegravir/lamivudine (ABC/DTG/3TC)-treated subjects in FLAIR. Additional long-term follow-up data are anticipated to further assess cardiovascular and/or metabolic risks associated with weight gain. • Emergence of resistance to both CAB and RPV occurred frequently among virologic failures in the CAB+RPV treatment group; the incidence of emergent resistance was also higher than the control group. • The combination of HIV subtype A1 and presence of the baseline IN L74I polymorphism were associated with virologic failure. The IN L74I polymorphism alone was only associated with virologic failure in subjects with subtype A1. Subtype A1 is prevalent in Russia. However, no detectable phenotypic resistance to CAB was conferred by the IN L74I substitution at baseline. • The CAB and RPV resistance substitutions selected during exposure to CAB+RPV confer cross-resistance to other INSTIs and NNRTIs, respectively. Thus, future treatment options with other INSTIs and NNRTIs may be compromised for CAB+RPV virologic failures. • The concentrations of CAB and RPV can be detected at least 52 weeks after the last injections. An extended-release formulation may	ARVs, the prolonged window for risk of resistance development during the residual concentration of CAB and RPV is unique. To address this concern, the DOSAGE and ADMINISTRATION section clearly outlines the importance of selecting the right patient population prior to initiating CAB+RPV and counseling patients on the importance of adherence/compliance to the scheduled monthly visits for CAB+RPV administration. The DOSAGE and ADMINISTRATION section also instructs to initiate a suppressive regimen within 30 days.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	help with adherence or compliance by eliminating pill burden or pill fatigue for some patients. On the other hand, the prolonged exposures cause concern for the development of resistance to CAB+RPV and cross-resistance to the INSTI and NNRTI classes in patients who do not comply with monthly injections or fail to initiate an alternative, effective regimen after discontinuing CAB+RPV.	

Conclusions Regarding Benefit-Risk

Infection with HIV-1 continues to be a significant public health concern both domestically and internationally. Although the HIV treatment armamentarium is robust, additional effective antiretroviral (ARV) treatment options that provide greater flexibility in meeting patients' individual needs and facilitating their tolerance for and adherence to lifelong HIV-1 treatment are needed. The extended-release injectable formulations of CAB and RPV offer patients the advantage of once monthly dosing and eliminate the need for daily oral medication. However, the prolonged residual exposure is an important consideration for the appropriate selection of patients who can adhere to monthly in-office injections.

The submitted evidence clearly demonstrates CAB+RPV is effective as a two-drug complete regimen for patients who are virologically suppressed and plan to replace their current regimen with CAB+RPV. We can also conclude that CAB+RPV is noninferior to a three-drug regimen, with the caveat that uncertainty remains about the durability of these benefits beyond 48 weeks of treatment. While higher virologic failure rates were seen in some subgroups (females, subjects with BMI $\geq$30 kg/m^2, and females with BMI $\geq$30 kg/m^2), these results are from exploratory subgroup analyses with limited sample size. More data are needed to assess the higher virologic failure rates in these subgroups. Also, the efficacy of CAB+RPV in patients who have a baseline K103N substitution, acquired INSTI or NNRTI resistance, or with history of treatment failure is unknown.

The safety evaluation for CAB+RPV was adequate, and the demonstrated safety profile of CAB+RPV in the virologically suppressed HIV-1 population is acceptable for the indicated dose and population. With the exception of local and systemic ISRs, the overall safety profile of CAB+RPV was consistent with prior trials with RPV and INSTIs. No new or unexpected safety concerns were identified. Other safety findings, specifically those identified with prior experience with RPV or the INSTI class, can be adequately addressed in labeling and by routine pharmacovigilance. The CAB and RPV OLI dosing was safe, and few patients discontinued prior to the injection phase. Data from the Antiretroviral Therapy as Long-Acting Suppression (ATLAS)-2M trial will provide additional data regarding the need for an oral lead in prior to CAB and RPV injections.

With all factors considered, the benefits of an all-injectable two-drug regimen clearly outweigh the risks. CAB+RPV is the first all-injectable two-drug regimen to be approved as a complete regimen for HIV-1–infected, virologically suppressed adults to replace

their current ARV regimen. Once the CMC deficiencies are adequately addressed, the availability of CAB+RPV will offer patients and providers another safe and effective option to manage this complex chronic disease.

II. Interdisciplinary Assessment

3. Introduction

This review serves as the interdisciplinary assessment for two NDAs, VOCABRIA® (NDA 212887) and CABENUVA® (NDA 212888).

VOCABRIA (CAB) 30-mg tablet, in combination with EDURANT (RPV) 25-mg tablet, is for use as an OLI to assess the tolerability of CAB prior to administration of CABENUVA and as a short-term oral therapy for patients who will miss planned CABENUVA injections. The (b) (4)

CABENUVA contains CAB extended-release injectable suspension copackaged with RPV extended-release injectable suspension. CABENUVA is intended for use as a complete replacement regimen to treat HIV-1–infected adults who are virologically suppressed (HIV RNA <50 copies/mL) on a stable ARV regimen, with no history of treatment failure, and no known substitutions associated with resistance to the individual components of CABENUVA. The indication for CABENUVA requires a 4-week lead-in treatment with oral CAB 30-mg and RPV 25-mg tablets.

CAB is a new molecular entity and an INSTI. RPV is an HIV-1 NNRTI. While RPV extended-release for injection is an investigational ARV agent, oral RPV is an approved ARV product. EDURANT (RPV) is approved for the treatment of HIV infection in combination with other ARVs. Oral RPV is also approved as a component of the fixed-dose combination products COMPLERA, ODEFSEY, and JULUCA.

JULUCA is currently the only oral two-drug complete regimen for use in virologically suppressed HIV-1–infected patients. CABENUVA will be the first all-injectable, two-drug complete regimen for use in virologically suppressed HIV-1–infected patients.

(b) (4) ViiV, in collaboration with Janssen, subsequently submitted another IND to investigate the dual regimen, CAB and RPV oral tablets once daily, followed by CAB+RPV injections to maintain viral suppression.

During the development program, the Applicant considered two safety-related matters that led to the decision to include a four-week OLI dosing prior to the initiation of the extended-release injections. The first safety consideration was the lack of robust safety data for CAB. Unlike RPV, CAB was early in its clinical development with limited safety data. To minimize the potential safety risks, the Applicant designed the phase 2 and 3 clinical trials with an OLI for a minimum of 4 weeks. The second consideration was to allow for a subject-level risk

management and mitigation strategy by assessing the short-term safety of oral CAB+RPV for that individual prior to switching to CAB+RPV injections. Refer to Sections 7.6.6 and III.17 for discussion on the AEs during the OLI period.

Two similar phase 3 clinical trials (201584 (FLAIR) and 201585 (ATLAS)) were conducted to assess the safety and establish the noninferiority of CAB+RPV injections compared to an all-oral, three-drug regimen containing an INSTI, NNRTI, or protease inhibitor (PI), plus two NRTIs. The primary assessment was planned at 48 weeks, which is included in this initial submission. The FLAIR trial is ongoing to assess the long-term efficacy through at least week 96. The ATLAS trial has concluded, and subjects were rolled over to ATLAS-2M to evaluate the efficacy of CAB+RPV injections administered bimonthly compared to monthly.

Note, the review team acknowledges that LA is not formally recognized by the FDA as nomenclature to describe extended-release formulations. This review document may reference CAB+RPV as LA to imply CABENUVA is an extended-release product. The term “long-acting” has been extensively used within the HIV community to describe extended-release products in development for the treatment or prevention of HIV infection. The term is also referenced in the FDA guidance for industry for systemic drug development for the treatment or prevention of HIV infection.[3]

The review team identified two review issues relevant to the evaluation of benefit (Section 6.5) and include the effect of pre-existing NNRTI resistance-associated substitutions (RAS, K103N substitution) on virologic response to CAB+RPV and the potential differences in virologic failure rates among the following subgroups compared to their counterparts: female subjects, subjects with BMI $\geq$30 kg/m^2, and female subjects with BMI $\geq$30 kg/m^2. These issues are based on exploratory analyses. As such, any interpretations should be made with caution.

Before the review process began, several potential risks were identified for CABENUVA based on prior knowledge on the characteristics of the individual drug products. These risks (or potential risks) are multidisciplinary and include concerns such as the selection of the appropriate population that will adhere to the required monthly injection dosing schedule; the consequences of nonadherence or noncompliance, namely the development of resistance on or off therapy; certain adverse reactions; drug-drug interactions (DDIs); and the nonclinical safety signals. At the conclusion of this NDA review, the team identified the following risks that remained significant or potentially significant and were important to highlight in the overall benefit risk assessment (please refer to Section 7.7).

- Resistance
  - Development of resistance to CAB and RPV in virologic failures
  - Virologic failure associated with the IN L74I polymorphism at baseline in HIV subtype A1
  - Cross-resistance with INSTI and NNRTI drug classes in virologic failures
- Risks associated with nonadherence or noncompliance in the setting of residual CAB and RPV concentrations
  - Failure to adhere to the dosing schedule or initiate suppressive regimen within 30 days after last dose
  - Importance of patient selection and counseling

- Potential risk of embryo-fetal toxicity
  - Structural similarity to dolutegravir (DTG) and risk of neural tube defect (NTD)
- AEs
  - Risks of local and systemic reaction in association with CAB+RPV injections
  - Risk of weight-gain in association with INSTI exposure, including CAB

3.1. Approach to the Review

Table 2 provides an overview of the clinical trials to support the benefit-risk assessment for CAB+RPV and includes 48-week data from two similarly-designed phase 3 clinical trials 201584 (FLAIR) and 2015853 (ATLAS). The safety, dose selection, and initial demonstration of antiviral activity of CAB+RPV were supported by the phase 2 clinical trials—(LATTE) and LATTE-2. Additionally, safety information from the ongoing phase 3b trial (ATLAS-2M) in HIV-infected subjects and safety reports from completed or ongoing HIV-1 prevention trials (HPTN077, HPTN083, and HPTN084) were also reviewed. The safety update report (SUR) for the phase 3 trials and the registrational and postmarketing experience with oral RPV also contributed to the benefit-risk assessment of CAB+RPV treatment.

Table 2. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Cabotegravir+Rilpivirine (CAB+RPV)

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
204584 FLAIR	Treatment naïve at enrollment; Induction phase: ABC/DTG/3TC for 20 weeks to achieve virologic suppression (HIV RNA <50 copies/mL; day 1: switch to CAB/RPV as maintenance regimen	Control Type: AC Randomization: R Blinding: OL Biomarkers: HIV RNA Innovative design features: Switch Trial	Drug: CAB+RPV oral tablets; CAB LA+RPV LA for injection Dose: CAB 30 mg + RPV 30 mg PO QD; CAB LA×400 mg + RPV LA×600mg IM Q4 weeks Number treated: 283 in the CAB/RPV treatment arm Duration (quantity and units): 48 wk	Primary: HIV-1 RNA ≥50 copies/mL RNA Secondary: HIV RNA <50 copies/mL	Planned: 570 Randomized: 566	11 countries; 108 sites
204585 ATLAS	Virologically suppressed with current regimen at enrollment; day 1: switch to CAB/RPV as maintenance regimen	Control Type: AC Randomization: R Blinding: OL Biomarkers: HIV RNA Innovative design features: Switch Trial	Drug: CAB+RPV oral tablets and LA for injections Dose: CAB 30 mg + RPV 30 mg PO QD; CAB LA×400mg + RPV LA×600mg IM Q4 weeks Number treated: 308 in the CAB/RPV treatment arm Duration (quantity and units): 48 wk	Primary: HIV RNA ≥50 copies/mL Secondary: HIV RNA <50 copies/mL	Planned: 570 Randomized: 616	13 countries; 115 sites

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
LAI116482 LATTE	HIV-infected, treatment naïve	Control Type: AC Randomization: 1:1:1:1 Blinding: OL Biomarkers: HIV RNA Innovative design features: N/A	Drug: CAB+RPV oral tablets Dose: 10 mg, 30 mg, 60 mg Number treated: 60; 60; 61 Duration (quantity and units): 144 wk	Primary: HIV RNA <50 copies/mL Secondary: HIV RNA ≥50 copies/mL	Randomized: 244	2 countries; 48 centers
200056 LATTE-2	HIV-infected, treatment naïve	Control type: AC Randomization: 2:2:1 Blinding: OL Biomarkers: HIV RNA Innovative design features: N/A	Drug: CAB+ABC/3TC PO QD CAB+RPV IM Q4 CAB+RPV IM Q8 Dose: CAB 30 mg QD CAB+RPV 400/600 mg Q4 MO CAB+RPV 600/900 mg Q8 MO Number treated: 115;115; 56 Duration (quantity and units): 96 wk	Primary: HIV RNA <50 copies/mL Secondary: HIV RNA ≥50 copies/mL	Randomized: 286	5 countries; 50 centers

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: 3TC = lamivudine, ABC = abacavir, AC = acting control, CAB = cabotegravir, DTG = dolutegravir, IM = intramuscular, LA = long-acting, MO = monthly, OL = open-label, PO = by mouth, Q4 = every four, QD = once a day, R = randomized, RPV = rilpivirine

4. Patient Experience Data

Based on patient experience data, the Applicant is seeking (b) (4) During development of the phase 3 clinical trial protocol, the Applicant included patient-reported outcome (PRO) measures as secondary endpoints. The measures included Perception of Injection (PIN), HIV Treatment Satisfaction Questionnaire (HIVTSQ), HIV Patient Satisfaction Questionnaire status-change (HIVTSQc), Pain Numeric Rating Scale (NRS) and the Chronic Treatment Acceptance Questionnaire (ACCEPT), which assesses patients' acceptance of long-term medication. For several reasons (b) (4)

(b) (4)

Table 3. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome (PIN, HIVTSQ, HIVTSQc, NRS, ACCEPT)	Section III.20.1
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data was submitted by Applicant, indicate here.**	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Clinical pharmacology properties of CAB and RPV were comprehensively evaluated (Table 4, Table 5). The clinical pharmacology review focused on the following issues:

- Exposure–response relationships for efficacy and safety
- Clinical significance of the effect of intrinsic and extrinsic factors on the pharmacokinetics (PK) of CAB and RPV
- Impact of residual concentrations of CAB and RPV following discontinuation on potential for drug interactions with subsequent ARV medications or non-ARV medications
- Labeling recommendations for planned and unplanned missed injections

Table 4. Summary of General Clinical Pharmacology and Pharmacokinetics of Cabotegravir

Characteristic	Drug Information
Pharmacologic activity	
Established pharmacologic class (EPC)	CAB is an HIV-1 integrase strand transfer inhibitor (INSTI)
Mechanism of action	CAB inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration.
Antiviral activity	CAB had antiviral activity against laboratory strains (subtype B, n=4) with mean EC_{50} values of 0.22 to 1.7nM and against HIV-1 Group M subtypes A to G with median EC_{50} values ranging from 0.05 to 0.36nM (median EC_{50} value for subtype B =0.05nM).
Active moieties	CAB
QT prolongation	In a thorough QT study, cabotegravir did not prolong the QTc interval.
General information	
Bioanalysis	CAB was measured in pivotal studies using LC/MS/MS. The calibration range is 0.025-25 µg/mL. The assay was validated according to FDA guidance and is acceptable.
Healthy subjects versus patients	CAB exposures were not found to be significantly affected by HIV infection status.

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Characteristic	Drug Information

Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (mcg•h/mL)	C_{max} (mcg/mL)	C_{tau} (mcg/mL)
Oral Lead-In[c]	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
Initial Injection[d]	600 mg IM Initial Dose	1,591 (714, 3,245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
Monthly Injection[e]	400 mg IM monthly	2,415 (1,494, 3,645)	4.2 (2.5, 6.5)	2.8 (1.7, 4.6)

[a] Pharmacokinetic parameter values based on individual post hoc estimates from separate cabotegravir and rilpivirine population pharmacokinetic models (pooled FLAIR and ATLAS, n=581), except for oral rilpivirine (see footnote e).
[b] tau is dosing interval: 24 hours for oral cabotegravir and rilpivirine; 1 month for cabotegravir and rilpivirine extended-release injectable suspensions.
[c] Oral lead-in pharmacokinetic parameter values represent steady-state.
[d] Initial injection $AUC_{(0\text{-}tau)}$ and C_{max} values primarily reflect values following oral dosing because the initial injection was administered on the same day as the last oral dose; however, the Ctau value at week 4 reflects the initial injection.
[e] Monthly injection pharmacokinetic parameter values represent week 48 data.

Maximally tolerated dose or exposure	The highest CAB exposures were observed in a QT study. CAB 150 mg orally did not affect the QT interval and resulted in a mean C_{max} of 22.5 µg/mL and mean $AUC_{0\text{-}24h}$ of 386 µg·h/mL.
Dose proportionality	At oral doses of 5-60 mg, CAB exposures increased proportionally or slightly less than proportionally (within 15%). Comparing CAB 30 mg and 150 mg orally, C_{max} and AUC increased <3-fold, which is much less than proportionate with dose. At CAB LA doses of 100 mg to 800 mg, CAB exposures increased proportionally with dose.
Accumulation	Oral CAB accumulation is 2.5-fold and CAB LA accumulation is 56%.
Time to achieve steady-state	Oral CAB reaches steady-state by day seven. Because elimination half-life of CAB LA is driven by the slow absorption from the injection site, the time to reach steady-state is approximately 44 weeks.
Bridge between to-be-marketed and clinical trial formulations	The final to-be-marketed oral and LA formulations were used in the pivotal trials.
Absorption	
Bioavailability	The absolute BA of oral or IM CAB is unknown. Relative bioavailability of CAB oral relative to the IM formulation is 76%.
T_{max}	Oral: 2 hours LA: 5 days
Food effect (fed/fasted) geometric least square mean and 90% CI	CAB 30 mg orally with a high-fat meal (53% fat, 870 calories) vs. fasted $AUC_{0\text{-}\infty}$: 1.14 (1.02, 1.28) C_{max}: 1.14 (1.03, 1.27) T_{max}: Median of 3.0 hours in both groups

Characteristic	Drug Information
Distribution	
Apparent volume of distribution	5.3 L
Plasma protein binding	99.9% bound at a CAB concentration range of 1–20 µg/mL
Blood-to-plasma ratio	0.5
CSF-to-plasma concentration ratio (median [range])	0.003 (0.002–0.004)
Drug as substrate of transporters	CAB is a substrate of BCRP and P-gp. CAB is not a substrate of OATP1B1, OATP1B3, or OCT1
Elimination	
Mass balance results	27% of the CAB dose was eliminated in urine (0% unchanged), and 59% of the dose was eliminated in feces (47% unchanged)
Apparent clearance	0.151 L/h for both CAB oral and LA
Half-life	Oral: 41 hours LA: 5.6-11.5 weeks
Metabolic pathway(s)	CAB is primarily metabolized by UGT1A1, with a minor contribution by UGT1A9
Primary excretion pathways	Metabolism
Drug interaction liability (drug as perpetrator)	
Inhibition/induction of metabolism	CAB is not a clinically relevant inhibitor of CYP1A2, 681 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17. CAB is not an inducer of CYP1A2, 2B6 or 3A4.
Inhibition/induction of transporter systems	CAB is not a clinically relevant inhibitor of P-gp, BCRP, BSEP, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE 2-K, MRP2, or MRP4. CAB is an in vitro inhibitor of OAT1 and OAT3. However, based on PBPK modeling, no clinically relevant interaction is expected.

Abbreviations: BA = bioavailability, BCRP = breast cancer resistance protein, BSEP = bile salt export pump, CAB = Cabotegravir, CI = confidence interval, EC_{50} = half maximal effective concentration, IM = intramuscular, LA = long-acting, LC/MS/MS = liquid chromatography technique coupled with tandem mass spectrometry, PBPK = physiologically-based pharmacokinetic, P-gp = P-glycoprotein

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics of Rilpivirine

Characteristic	Drug Information
Pharmacologic activity	
Established pharmacologic class (EPC)	RPV is a nonnucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1.
Mechanism of action	RPV noncompetitively inhibits the virus-encoded reverse transcriptase and thereby disrupts viral replication.
Antiviral activity	RPV had antiviral activity against wild-type laboratory strain HIV-1_{IIIB} in the MT4 T-cell line with a median EC_{50} value of 0.73nM and against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01nM
Active moieties	RPV
QT prolongation	At a dose of 75 mg (three times the approved oral dose), RPV prolongs the QT interval. At a dose of 25 mg (approved oral dose), RPV does not prolong the QT interval.

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td>General information</td><td></td></tr>
<tr><td>Bioanalysis</td><td>RPV was measured in pivotal studies using LC/MS/MS. The calibration range was 1-2000 ng/mL. The assay was validated according to FDA guidance and is acceptable.</td></tr>
<tr><td>Healthy subjects vs. patients</td><td>RPV exposures were not found to be significantly affected by HIV-infection status.</td></tr>
<tr><td>Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)</td><td>
<table>
<tr><th rowspan="2">Dosing Phase</th><th rowspan="2">Dosage Regimen</th><th colspan="3">Geometric Mean (5th, 95th Percentile)[a]</th></tr>
<tr><th>AUC(0-tau)[b] (ng•h/mL)</th><th>Cmax (ng/mL)</th><th>Ctau (ng/mL)</th></tr>
<tr><td>Oral Lead-In[c]</td><td>25 mg once daily</td><td>2,083 (1,125, 3,748)</td><td>116 (48.6, 244)</td><td>78.9 (32.2, 180)</td></tr>
<tr><td>Initial Injection[d]</td><td>900 mg IM Initial Dose</td><td>41,069 (20,062, 76,855)</td><td>139 (87.6, 219)</td><td>37.2 (19.4, 69.2)</td></tr>
<tr><td>Monthly Injection[e]</td><td>600 mg IM monthly</td><td>65,603 (37,239, 113,092)</td><td>116 (66.8, 199)</td><td>82.2 (47.5, 140)</td></tr>
</table>
[a] Pharmacokinetic parameter values based on individual post hoc estimates from separate cabotegravir and rilpivirine population pharmacokinetic models (pooled FLAIR and ATLAS, n=581), except for oral rilpivirine (see footnote e).
b tau is dosing interval: 24 hours for oral cabotegravir and rilpivirine; 1 month for cabotegravir and rilpivirine extended-release injectable suspensions.
[c] Oral lead-in pharmacokinetic parameter values represent steady-state.
[d] Initial injection $AUC_{(0\text{-}tau)}$ and C_{max} values primarily reflect values following oral dosing because the initial injection was administered on the same day as the last oral dose; however, the C_{tau} value at week 4 reflects the initial injection.
[e] Oral rilpivirine: $AUC_{(0\text{-}tau)}$ based on population pharmacokinetic estimates of rilpivirine 25 mg once daily from pooled phase 3 trials with EDURANT; C_{tau} based on observed data from FLAIR and ATLAS; C_{max} based on observed data for rilpivirine 25 mg once daily from a pharmacokinetic substudy in pooled phase 3 trials with EDURANT.
</td></tr>
<tr><td>Maximally tolerated dose or exposure</td><td>QT prolongation is associated with RPV at a dose of 75 mg orally but not at a dose of 25 mg orally. RPV 25 mg is considered the maximally tolerated dose.</td></tr>
<tr><td>Dose proportionality</td><td>Exposures from oral RPV are dose proportional between 25-150 mg. Exposures from RPV LA are dose proportional between 300-1200 mg.</td></tr>
<tr><td>Accumulation</td><td>The accumulation ratio of oral RPV is 3. The accumulation ratio of RPV LA is 4.2.</td></tr>
<tr><td>Time to achieve steady-state</td><td>Oral RPV reaches steady-state by 10 days, and RPV LA is expected to reach steady-state after 2.2 years.</td></tr>
<tr><td>Bridge between to-be-marketed and clinical trial formulations</td><td>The approved oral and final to-be-marketed LA formulations were used in pivotal trials.</td></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Bioavailability</td><td>The absolute BA of oral or IM RPV is unknown. Based on $AUC_{0\text{-}tau}$ for oral RPV 25 mg daily vs. RPV 600 IM monthly, the relative BA of oral RPV is similar to RPV LA.</td></tr>
<tr><td>T_{max}</td><td>The T_{max} of oral RPV is 4-5 hours. The T_{max} of RPV LA is 3-4 days.</td></tr>
<tr><td>Food effect (fed/fasted)
Geometric least square mean and 90% CI</td><td>RPV 75 mg orally, moderate-fat meal (35% fat, 533 calories) vs. fasted
$AUC_{0\text{-}\infty}$: 1.57 (1.24, 1.98)
C_{max}: 1.84
T_{max}: Median of 4 hours fasted and 5 hours with a moderate-fat meal

RPV 75 mg orally, high-fat meal (54% fat, 928 calories) vs. fasted
$AUC_{0\text{-}\infty}$: 1.72 (1.36, 2.16)
C_{max}: 1.64
T_{max}: Median of 4 hours fasted and 5 hours with a high-fat meal</td></tr>
</table>

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Characteristic	Drug Information
Distribution	
Apparent volume of distribution	132 L
Plasma protein binding	99.7% at an RPV concentration range of 10-3,000 ng/mL
Blood-to-plasma ratio	0.7
CSF-to-plasma concentration ratio (median [range])	0.01 (BQL to 0.02)
Drug as substrate of transporters	RPV has only been evaluated as a substrate of P-gp and is not a substrate of P-gp.
Elimination	
Mass balance results	85% of the RPV dose was eliminated in urine (26% unchanged), and 6% of the dose was eliminated in feces (<1% unchanged).
Apparent clearance	7.1 L/h for oral RPV and 5.1h for RPV LA
Half-life	50 hours for oral RPV and 13-28 weeks for RPV LA
Metabolic pathway(s)	RPV is primarily metabolized by CYP3A with a potential contribution of CYP2C19.
Primary excretion pathways	Metabolism
Drug interaction liability (drug as perpetrator)	
Inhibition/induction of metabolism	Based on in vitro studies, conflicting results were obtained for inhibition of CYP2C8. RPV is a possible inhibitor of CYP 2C9 and 2D6. RPV did not inhibit CYP 1A2. RPV was found to potentially induce CYP1A2. Based on human studies, RPV is not an inhibitor or inducer of CYP 2C19, 2E1, or 3A. Based on in vitro data and a DDI study with methadone, RPV is a weak inducer of CYP 2B6.
Inhibition/induction of transporter systems	RPV is not an inhibitor of P-gp. Inhibition of other transporters has not been evaluated.

Abbreviations: BA = bioavailability, BQL = below the limit of quantification, CI = confidence interval, DDI = drug-drug interaction, EC_{50} = half maximal effective concentration, IM = intramuscular, LA = long-acting, LC/MS/MS = liquid chromatography with tandem mass spectrometry, P-gp = P-glycoprotein, RPV = rilpivirine

Exposure–Response Relationships for Efficacy and Safety

In pivotal studies where the proposed dosage regimen was administered, increased CAB exposure quartile and increased RPV exposure quartile were both numerically associated with decreased virologic failure rate. However, overall failure rate in the pooled pivotal studies was 1.5%, and the Applicant noted several limitations to their analysis, thus the association between exposure and failure rate was not deemed clinically significant (Section III.14.2.3). CAB and RPV exposures did not differ between subjects with or without anxiety, depression, pancreatitis, pyrexia, sleep disorder, and weight gain (Section III.14.2.4).

Effect of Intrinsic and Extrinsic Factors on the PK of CAB and RPV

No dose adjustments for CAB or RPV are required based on age, sex, race/ethnicity, BMI, presence of UGT1A1 polymorphisms, renal impairment (mild to severe), or hepatic impairment (mild or moderate). Oral CAB and oral RPV should be taken with a meal. As CAB and RPV are >99% protein bound, dialysis is not expected to alter exposures of CAB or RPV. Effects of end-stage renal disease (ESRD) (not on dialysis) or severe hepatic impairment on the PK of CAB or RPV are unknown (Section 8.1.3).

No new RPV DDI studies were conducted for these NDAs.

In DDI studies, no significant changes in CAB PK parameters (geometric mean ratios of PK parameters were within 1.00 to 1.14) were observed when coadministered with etravirine or RPV. Use of CAB is contraindicated in patients taking rifabutin or rifampin. Based on physiologically-based PK (PBPK) modeling, UGT1A1/9 inhibitors are not expected to interact with CAB (Section 8.2).

When coadministered with CAB in clinical DDI studies, no significant changes in PK parameters of ethinyl estradiol, levonorgestrel, midazolam, or RPV were observed (geometric mean ratios of PK parameters ranged from 0.92 to 1.12). Based on PBPK modeling, CAB has the potential to result in increased exposures of organic anion transporter 1/3 (OAT1/3) substrates (Section 8.2).

Residual CAB and RPV Concentrations After Discontinuation

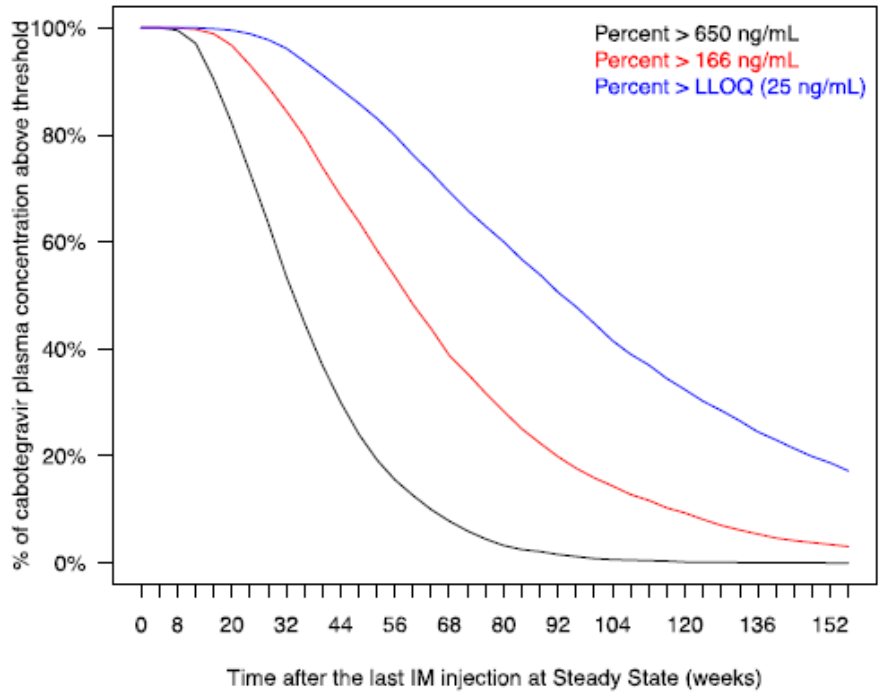
After discontinuation of CAB and RPV IM injections due to the slow absorption rate from the injection site, residual CAB and RPV concentrations are expected to be detectable in the systemic circulation for more three years after the last injections. The predicted median time to CAB concentrations below the limit of quantification (BQL) after discontinuation is ~96 weeks for females, ~44 weeks for males, and ~182 weeks (42 months) for RPV regardless of sex (Section III.14.2.6; Figure 1, Figure 2, and Figure 3).

One potential concern was that residual concentrations of CAB and/or RPV after discontinuation may interact with subsequent ARV or non-ARV medications. After discontinuation, CAB and RPV concentrations will decline, so there is no concern that subsequent medications will result in clinically significant increases or decreases in CAB or RPV concentrations.

CAB and RPV have some potential effects on other drugs (Section 8.2). However, due to relatively low CAB and RPV concentrations after discontinuation, there is minimal concern that CAB or RPV will significantly affect the PK of subsequent ARV or non-ARV drugs.

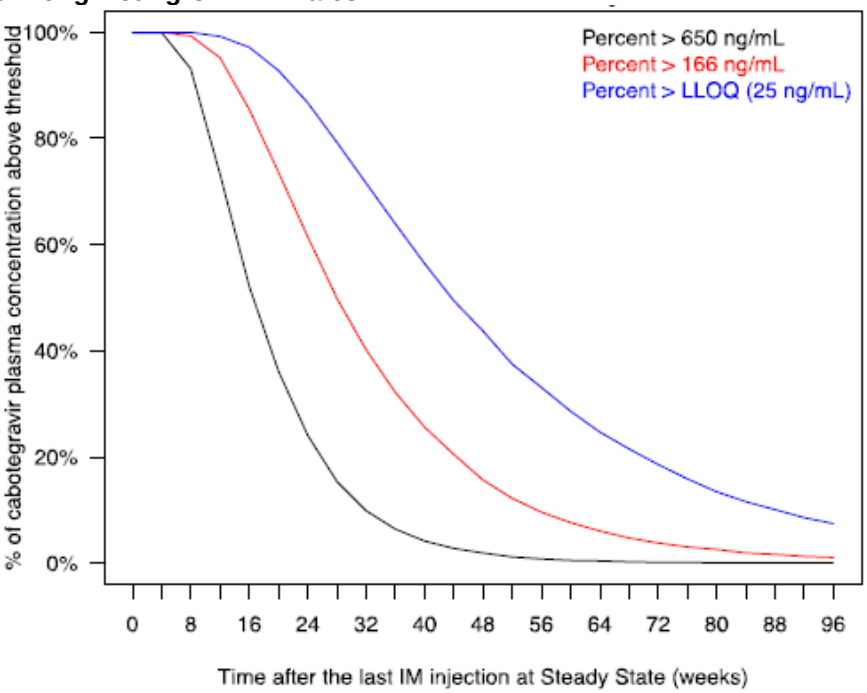
Another concern is that residual concentrations of CAB and/or RPV after discontinuation may result in development of resistance. Potential exists for development of resistance if another suppressive regimen is not started within 30 days after the last IM injection of CAB/RPV (Section 7.7.2).

Figure 1. Predicted Time to Undetectable Cabotegravir (CAB) Exposure Following Discontinuation of CAB LA in Females



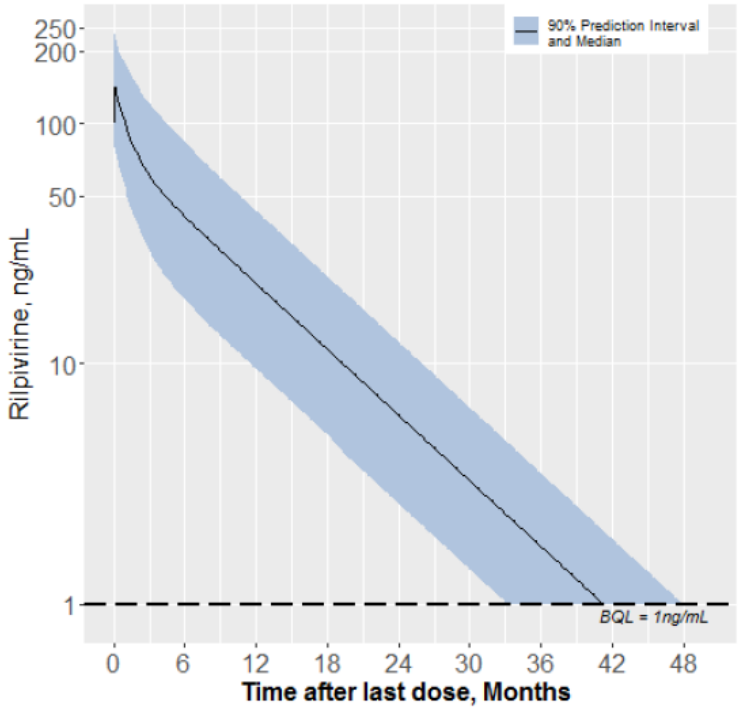
Source: CAB popPK report, page 91.
Abbreviations: IM = intramuscular, LA = long-acting, LLOQ = lower limit of quantification

Figure 2. Predicted Time to Undetectable Cabotegravir (CAB) Exposure Following Discontinuation of Long-Acting CAB in Males



Source: CAB popPK report, page 148.
Abbreviations: IM = intramuscular, LLOQ = lower limit of quantification

Figure 3. Predicted Time to Undetectable Rilpivirine (RPV) Exposure Following Discontinuation of Long-Acting RPV



BQL, below the quantification limit; Q4W, every 4 weeks; RPV, rilpivirine.

Source: RPV popPK report, page 137.
Abbreviations: BQL = below the limit of quantification

Appropriateness of Missed Injection Strategy

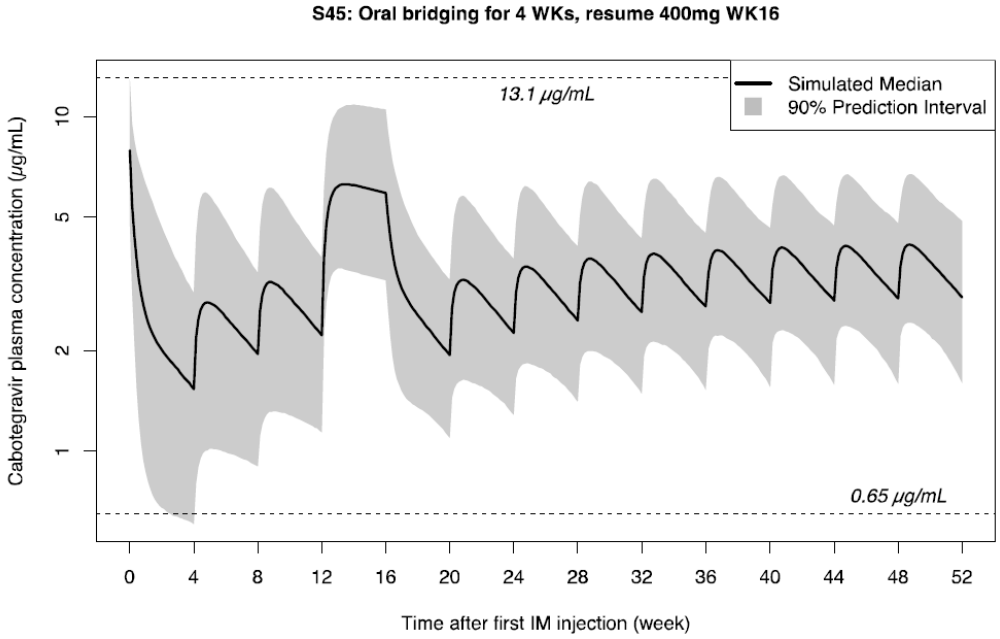
After the initial loading dose injections of CAB 600 mg and RPV 900 mg, the recommended monthly maintenance dose injections are a single 400-mg (2-mL) gluteal IM injection of CAB and a single 600-mg (2-mL) gluteal IM injection of RPV. CAB and RPV injections are to be administered monthly ±7 days as was done in the pivotal studies. In the pivotal studies, 79 subjects received injections outside of the seven day window and none had virologic failure at week 48 (Section III.16; Figure 51; Figure 52).

Although adherence to the monthly injection dosing schedule is strongly recommended, the Applicant conducted simulations to assess the impact of planned and unplanned missed injections on CAB and RPV exposures. From an efficacy perspective, acceptability of dosing recommendations for missed injections was based on ensuring that most subjects exceed the 5th percentile of CAB and RPV C_{min} after the initial injection in phase 3 studies. The target C_{min} is 0.65 µg/mL for CAB and 17.3 ng/mL for RPV. Target concentrations for safety were identified as the median maximum plasma concentration (C_{max}) at an oral CAB dose of 60 mg (13.1 µg/mL) and the highest RPV concentration that does not prolong the QT interval (551 ng/mL).

Planned Missed Injections (Oral Dosing to Replace Up to Two Consecutive Monthly Injections)

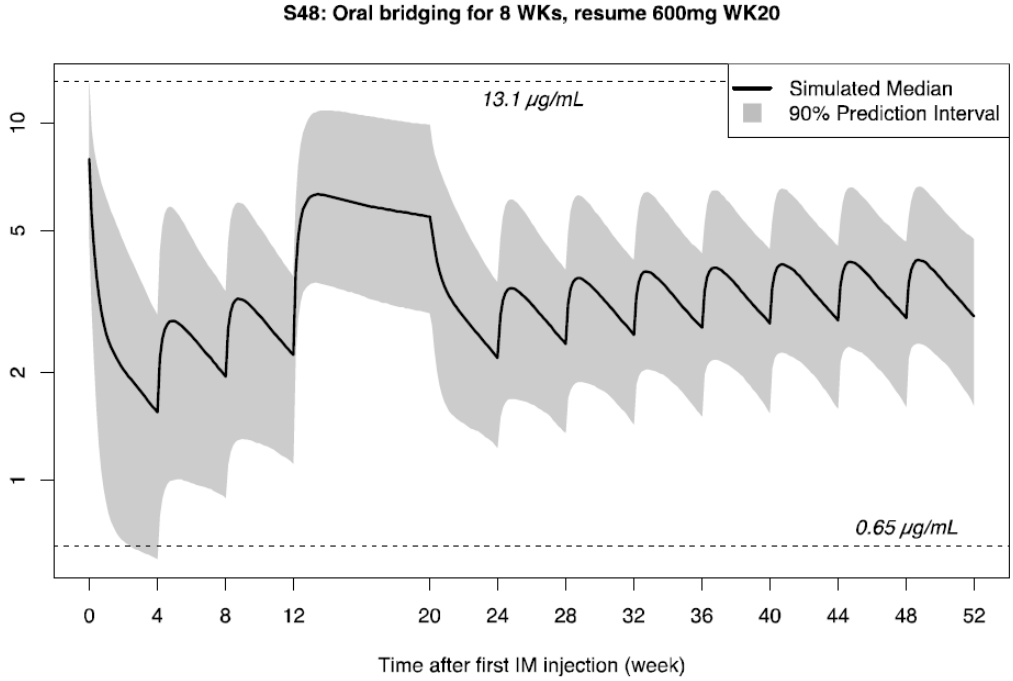
If a patient plans to miss a scheduled injection visit by more than 7 days, daily oral CAB 30 mg and oral RPV 25 mg should be used to replace up to two consecutive monthly injection visits. In the pivotal studies, 16 subjects used oral bridging for missed injections; the duration of oral bridging was 4 days to 2 months. There was no apparent association between the use of oral bridging and HIV-1 RNA increase (Section III.16; Table 165; Figure 55). In addition, 72 weeks of safety and efficacy data of oral CAB and oral RPV are available from a prior study, LATTE. CAB and RPV concentrations are expected to stay above the efficacy targets when oral CAB and RPV are used to replace up to two consecutive monthly IM injections (Figure 4, Figure 5, Figure 6, Figure 7).

Figure 4. Simulated Cabotegravir (CAB) Concentration-Time Profile When Oral Bridging Is Used Between Missed Injections for 4 Weeks



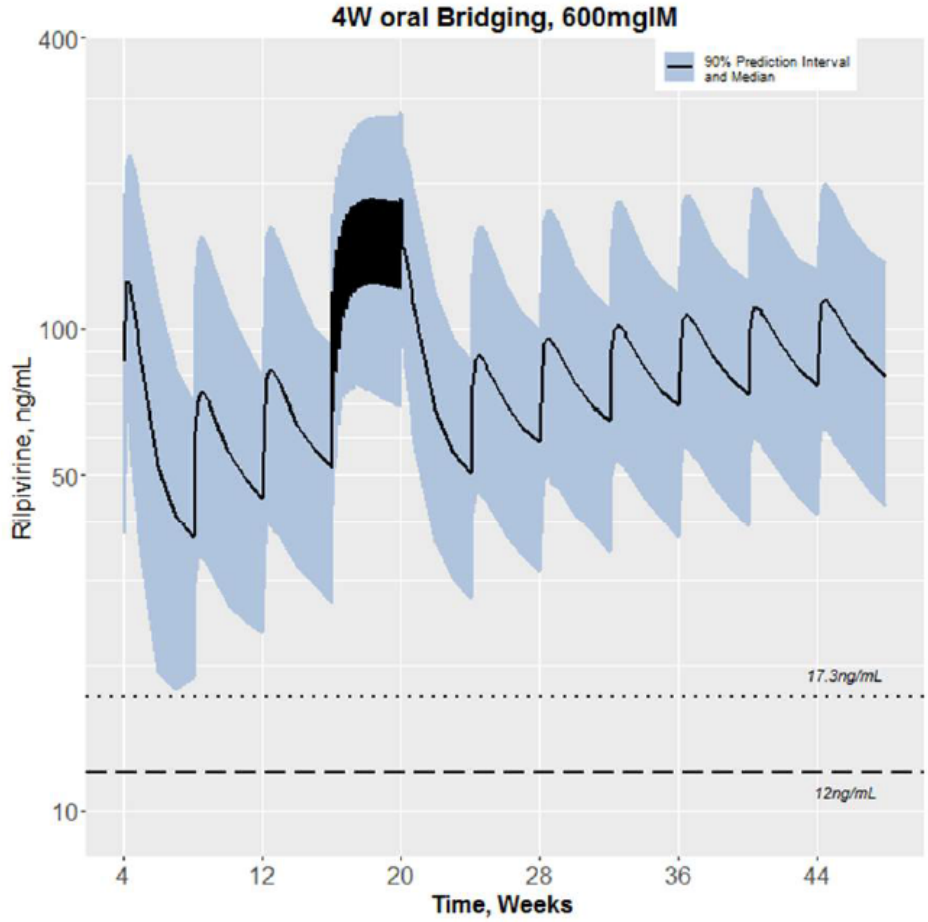
Source: CAB popPK report, page 87. 600 mg IM on week 0; 400 mg IM on weeks 4 and 8; 30 mg PO daily on weeks 12 to 16; 400 mg IM every 4 weeks on weeks ≥16.
Abbreviations: IM = intramuscular

Figure 5. Simulated Cabotegravir (CAB) Concentration-Time Profile When Oral Bridging Is Used Between Missed Injections for 8 Weeks



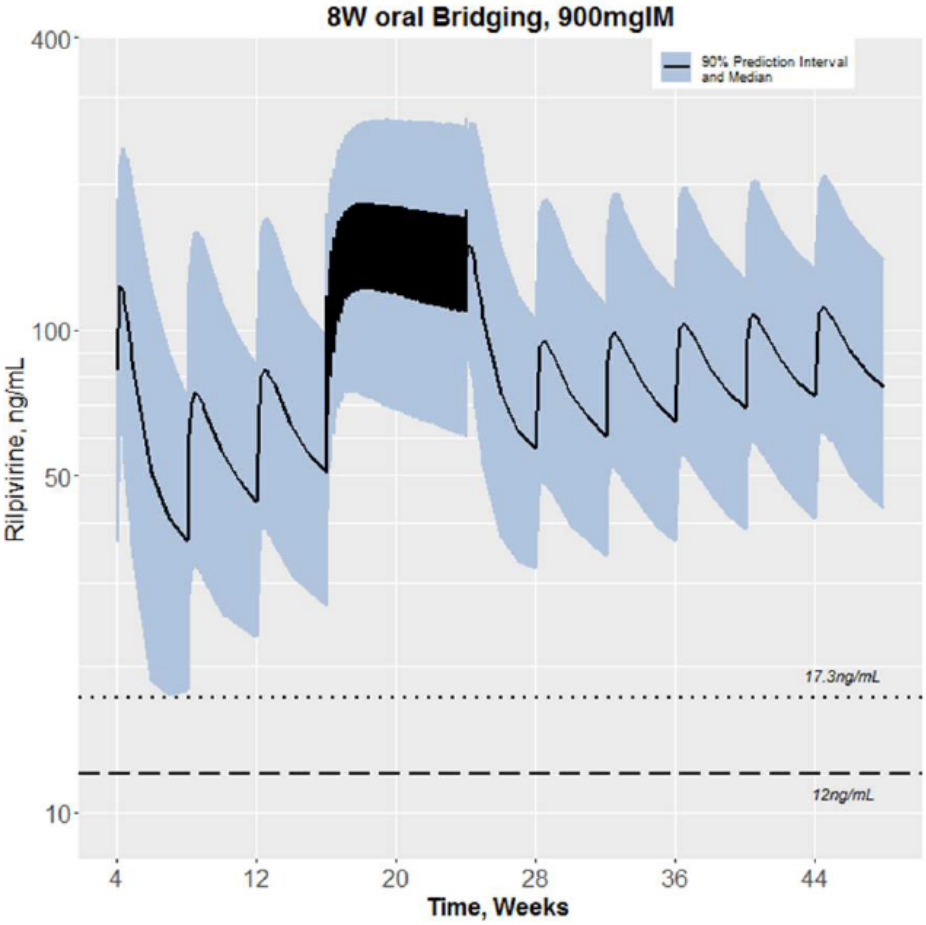
Source: CAB popPK report, page 87. 600 mg IM on week 0; 400 mg IM on weeks 4 and 8; 30 mg PO daily on weeks 12 to 20; 600 mg IM on week 20; 400 mg IM every 4 weeks on weeks ≥24.
Abbreviations: IM = intramuscular

Figure 6. Simulated Rilpivirine (RPV) Concentration-Time Profile When Oral Bridging Is Used Between Missed Injections for 4 Weeks



Source: NDA 212888 SDN 19, page 19. RPV 900 mg IM on week 4; 600 mg IM on weeks 8 and 12; 25 mg PO daily on weeks 16-20; 600 mg IM every 4 weeks on weeks ≥20.
Abbreviations: IM = intramuscular

Figure 7. Simulated Rilpivirine (RPV) Concentration-Time Profile When Oral Bridging Is Used Between Missed Injections for 8 Weeks

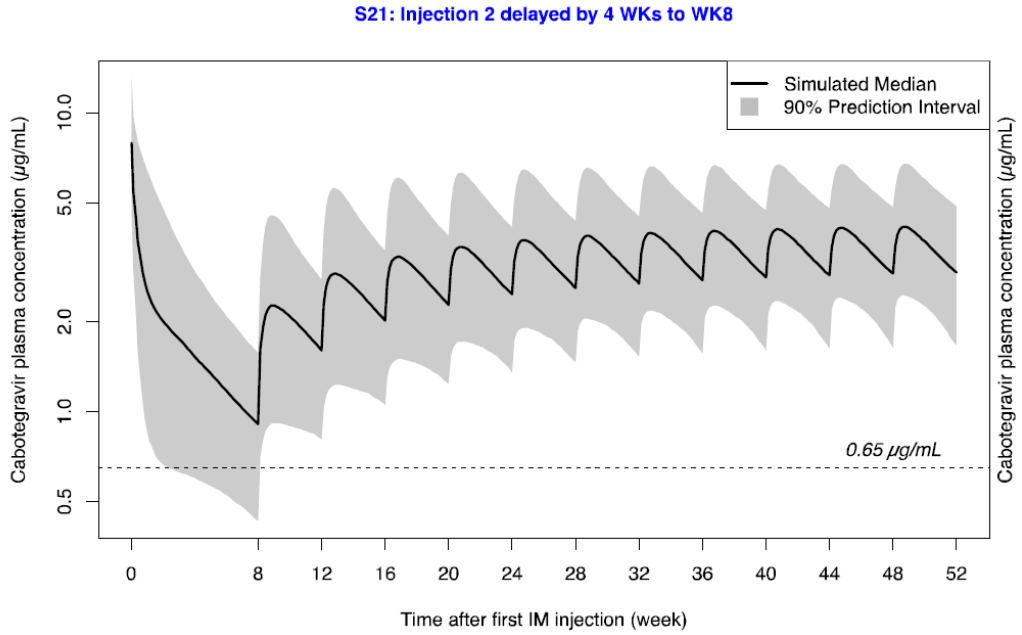


Source: NDA 212888 SDN 19, page 19. RPV 900 mg IM on week 4; 600 mg IM on weeks 8 and 12; 25 mg PO daily on weeks 16 to 24; 900 mg IM on week 24; 600 mg IM every 4 weeks on weeks ≥28.
Abbreviations: IM = intramuscular

Unplanned Missed Injections

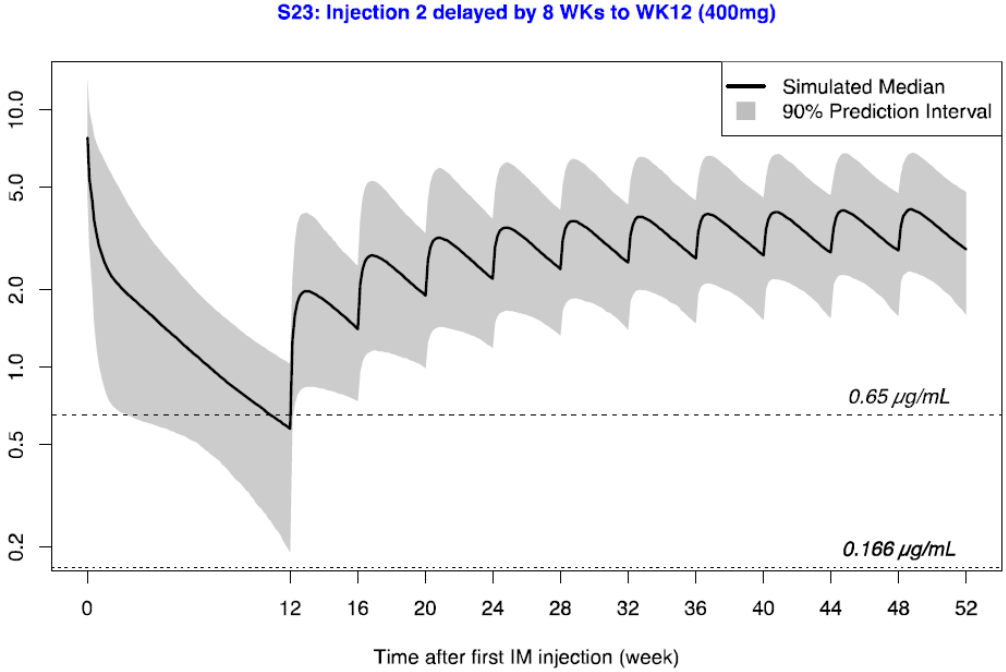
If monthly injections are missed or delayed by >7 days and oral therapy has not been taken in the interim to replace monthly injections, the prescriber should clinically reassess the patient to determine if resumption of injection dosing remains appropriate. Based on simulations, most subjects who resume IM injection dosing (loading doses if the time since last injections was ≥2 months, maintenance doses if the time since last injections was <2 months) are expected to have CAB and RPV concentrations within the safety and efficacy targets (Figure 8, Figure 9, Figure 10, Figure 11).

Figure 8. Simulated Cabotegravir Concentration-Time Profile When the Second Injection Is Delayed by 4 Weeks



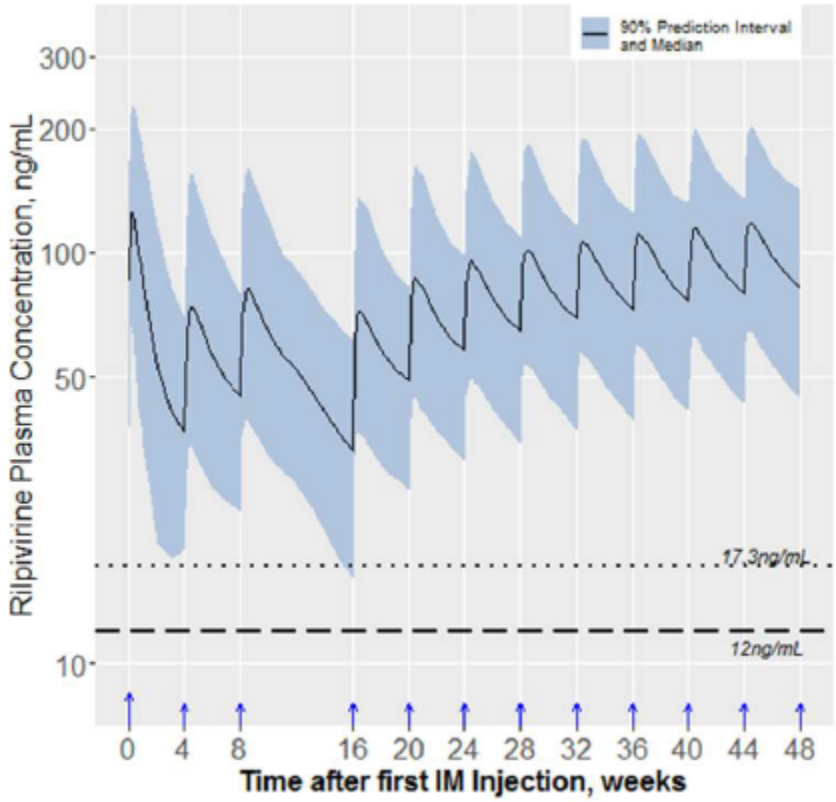
Source: CAB popPK report, page 86. 600 mg IM on week 0; 400 mg IM every 4 weeks on weeks ≥8.
Abbreviations: IM = intramuscular

Figure 9. Simulated Cabotegravir Concentration-Time Profile When the Second Injection Is Delayed by 8 Weeks



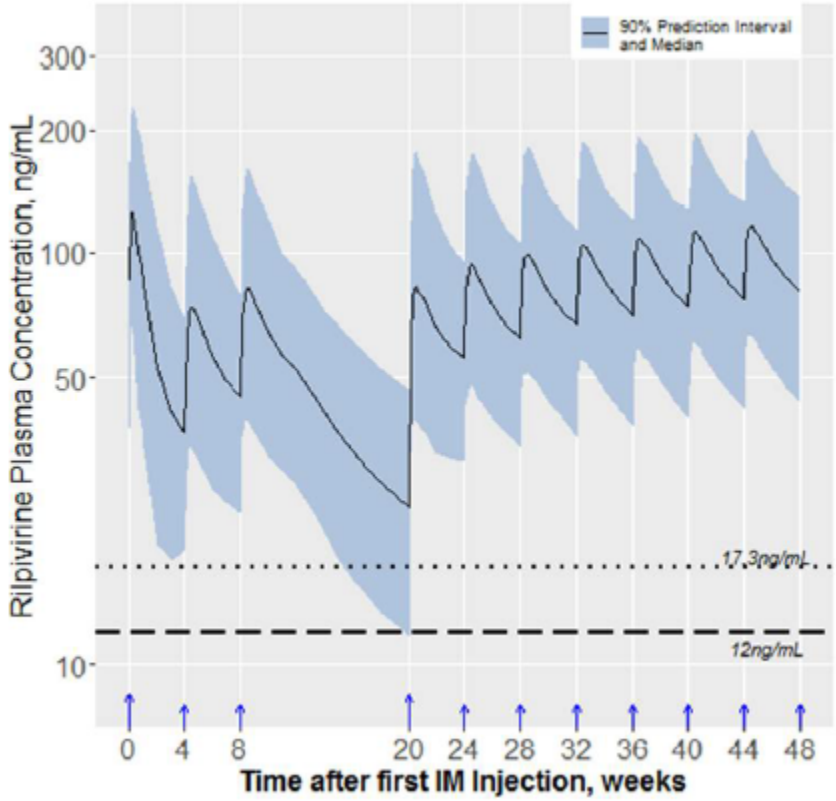
Source: CAB popPK report, page 86. 600 mg IM on week 0; 600 mg IM on week 12; 400 mg IM every 4 weeks on weeks ≥16.
Abbreviations: IM = intramuscular

Figure 10. Simulated Rilpivirine Concentration-Time Profile When the Second Injection Is Delayed by 4 Weeks



Source: NDA 212888 SDN 19, page 19. RPV 900 mg IM on week 0; 600 mg IM on weeks 4 and 8; 600 mg IM every 4 weeks on weeks ≥16.
Abbreviations: IM = intramuscular

Figure 11. Simulated Rilpivirine Concentration-Time Profile When the Second Injection Is Delayed by 8 Weeks



Source: NDA 212888 SDN 19, page 19. RPV 900 mg IM on week 0; 600 mg IM on weeks 4 and 8; 900 mg IM on week 20; 600 mg IM every 4 weeks on weeks ≥24.
Abbreviations: IM = intramuscular

Resumption of Injection Dosing After Missed IM Injections

Based on the above simulations for planned or unplanned injections, we agree with proposed labeling for resumption of injection dosing after missed IM injections (Table 6).

Table 6. Injection Dosing Recommendations After Missed Injection[a]

Time Since Last Injection	Recommendation
Less than 2 months	Resume with 400 mg (2 mL) of cabotegravir and 600 mg (2 mL) of rilpivirine intramuscular monthly injections as soon as possible.
2 months or greater	Re-initiate the patient with 600 mg (3 mL) of cabotegravir and 900 mg (3 mL) of rilpivirine intramuscular injections then continue to follow the 400-mg (2-mL) cabotegravir and 600-mg (2-mL) rilpivirine intramuscular monthly injection dosing schedule.

[a] Refer to oral dosing recommendations if a patient plans to miss a scheduled injection visit.

5.1. Nonclinical Assessment of Potential Effectiveness: CAB

The nonclinical data support the effectiveness of CAB for the treatment of HIV-1 infection and is based on the following findings:

- Biochemical and virologic studies support the mechanism of action of CAB; CAB inhibits HIV integrase (IN) by binding to the IN active site and blocking the strand transfer step of retroviral DNA integration.
- CAB demonstrated good antiviral activity in cell culture that can be achieved in vivo without inducing toxic effects to cells.
- CAB showed broad antiviral activity against HIV-1 and HIV-2 isolates in cell culture and is expected to have clinical antiviral activity in HIV-1–infected patients who are virologically suppressed and have no resistance to CAB.
- Based on cell culture data, antagonism of CAB is not a concern in a clinical setting, and it can be combined with RPV.
- Phenotypic and genotypic characterization of CAB-resistant virus indicated that cross-resistance with approved INSTIs is possible. See Sections 7.7.1 and III.18.3.2.

These nonclinical data (summarized below) supported further clinical development of CAB.

Mechanism of Action

CAB is an INSTI and has the same mechanism of action as the other members in the INSTI class of anti-HIV-1 drugs (i.e., bictegravir [BIC], DTG, elvitegravir [EVG], and raltegravir [RAL]). Using full-length recombinant HIV IN isolated from *Escherichia coli* complexed with biotinylated donor DNA and tritiated target DNA substrate, CAB inhibited HIV-1 IN catalyzed strand transfer with a mean half maximal inhibitory concentration (IC_{50}) value of 3.0nM. Additional support that CAB targets the IN protein includes the selection of amino acid substitutions in the IN after serial passage of HIV-1 with CAB in cell culture selection experiments and that these selected IN substitutions conferred decreased susceptibility to CAB. Refer to Section III.18.1 for the complete review of mechanism of action.

Antiviral Activity of Cell Culture

The median half maximal effective concentration (EC_{50}) value for recombinant virus with IN from clinical isolates was 1.3nM (range 1.0 to 1.6nM, n=13). The median EC_{50} value of CAB against clinical HIV-1 isolates was 0.19nM (range 0.02nM to 1.06nM, n=24). Against HIV-2 isolates, the median EC_{50} value of CAB was 0.12nM (range 0.10nM to 0.14nM, n=4). The mean EC_{50} value for individual HIV-1 subtypes A to G ranged from 0.10nM to 0.38nM and was 0.64nM for group O isolates (refer to Section III.18.2 for the complete review of Cell Culture Antiviral Activity studies).

5.2. Nonclinical Assessment of Potential Effectiveness: RPV

The nonclinical virology assessments of RPV were previously reviewed in NDA202022. The key findings are below.

- RPV is an NNRTI of HIV-1 and inhibits HIV-1 replication by noncompetitive inhibition of HIV-1 reverse transcriptase (RT).

- RPV demonstrated antiviral activity against a wild-type laboratory strain with a median EC_{50} value of 0.73nM and a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07nM to 1.01nM.
- RPV was less active against group O primary isolates with EC_{50} values ranging from 2.9nM to 8.5nM and demonstrated limited activity in cell culture against HIV-2 with a median EC_{50} value of 5,220nM (range 2,510nM to 10,830nM).
- Based on cell culture data, antagonism of RPV is not a concern in a clinical setting, and it can be combined with CAB and other approved ARVs.
- Resistance to RPV results in cross-resistance to other approved NRTIs.

6. Evidence of Benefit (Assessment of Efficacy)

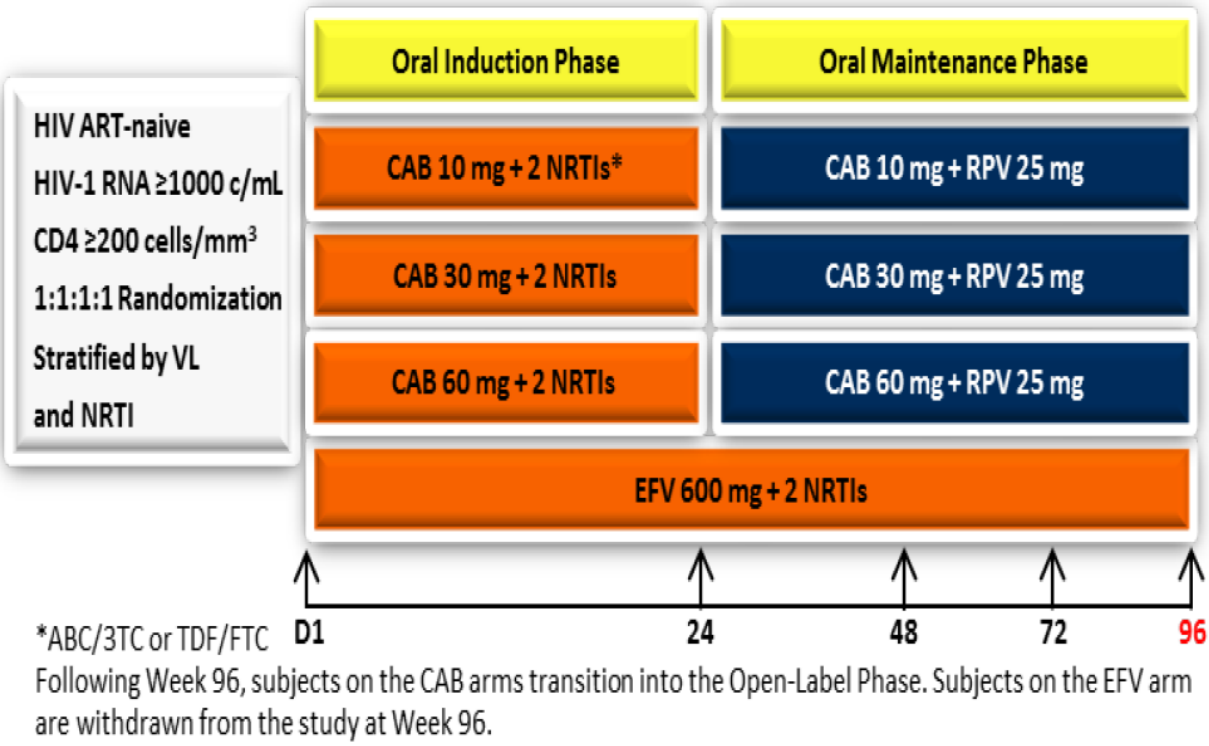
6.1. Assessment of Dose and Potential Effectiveness: CAB

The doses of CAB selected for evaluation in phase 1b through phase 3 are acceptable based on virology, human PK, and exposure–response data.

Two monotherapy trials (ITZ112929 and ITZ111451) were conducted to evaluate the short-term antiviral activity of oral CAB. Trial ITZ112929 evaluated oral CAB 5-mg (n=7) monotherapy versus placebo (n=2) once daily for 10 days in HIV-1–infected subjects without prior HIV integrase inhibitor (INI) therapy. CAB oral 5-mg monotherapy resulted in a mean 2.2 $\log_{10}$ copies/mL decrease from baseline in HIV-1 RNA (Section III.14.1.2). Trial ITZ111451 evaluated oral CAB 30 mg (n=8) versus placebo (n=3) once daily for 10 days in HIV-1–infected subjects. CAB oral 30-mg monotherapy resulted in a mean 2.3 $\log_{10}$ copies/mL decrease from baseline in HIV-1 RNA (Section III.14.1.2).

Subsequently, a phase 2b dose-ranging trial (LAI116482, LATTE) was conducted in ARV treatment-naïve subjects, who received oral CAB plus two NRTIs (induction phase) followed by oral CAB in combination with oral RPV 25 mg daily (maintenance phase; Figure 12) compared to efavirenz (EFV)+two NRTIs. The primary endpoint was the proportion of subjects with HIV-1 RNA <50 copies/mL at week 48. At week 24, the proportion of subjects with HIV-1 RNA <50 copies/mL (per snapshot algorithm) was 88%, 85%, 87%, and 74% for the CAB 10 mg, 30 mg, 60 mg, and EFV groups, respectively. No difference in virologic outcome was noted in subjects with baseline HIV-1 RNA <100,000 copies/mL versus ≥100,000 copies/mL. At week 48, the proportion of subjects with HIV-1 RNA <50 copies/mL was 71% in the EFV arm and approximately 80% (and comparable) across CAB 10 mg, 30 mg, and 60 mg groups (Table 7). Based on these results, CAB 30 mg was selected as the dose for CAB OLI for phase 3 studies. The Division of Antivirals (DAV) agreed with use of CAB 30 mg orally for phase 3 studies at the end of the phase 2 meeting.

Figure 12. LATTE Study Design



Source: http://regist2.virology-education.com/2015/16HIVHEP/10_Spreen.pdf
Abbreviations: 3TC = lamivudine, ART = antiretroviral therapy, ABC = abacavir, CAB = cabotegravir, FTC = emtricitabine, EFV = efavirenz, NRTI = nucleotide reverse-transcriptase inhibitor, RPV = rilpivirine, TDF = tenofovir, VL = viral load

Table 7. LATTE Week 48 Virologic Response Rates

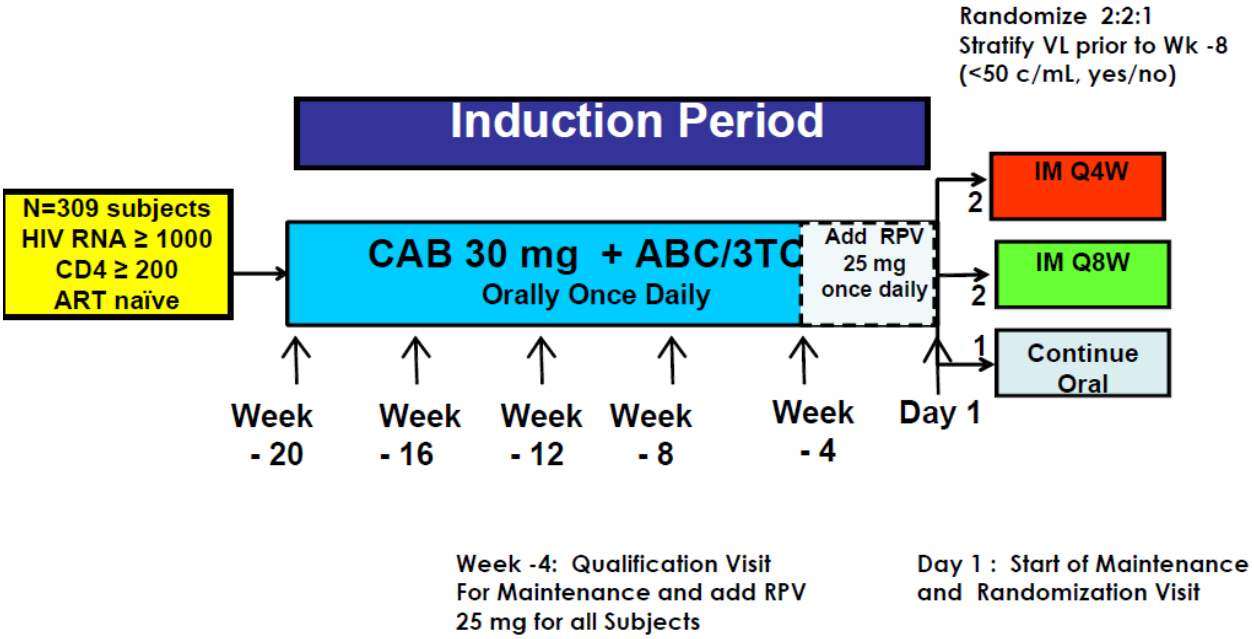
Visit		GSK744 10 mg N=60	GSK744 30 mg N=60	GSK744 60 mg N=61	GSK744 Subtotal N=181	EFV 600 mg N=62
Week 48	n (%) 95% CI	48 (80) (70, 90)	48 (80) (70, 90)	53 (87) (78, 95)	149 (82) (77, 88)	44 (71) (60, 82)

Source: LATTE week 48 CSR, page 70. GSK744 = CAB.
Abbreviations: CI = confidence interval, EFV = efavirenz

Prior to initiation of the phase 3 studies, the Applicant conducted an additional phase 2b trial (LATTE-2) to evaluate the CAB+RPV IM regimen for maintenance of virologic suppression after an induction period with a once daily regimen of CAB 30 mg orally plus two NRTIs in treatment-naïve adults. RPV was added during the last 4 weeks of the oral regimen prior to initiating the injectable dosing (Figure 13).

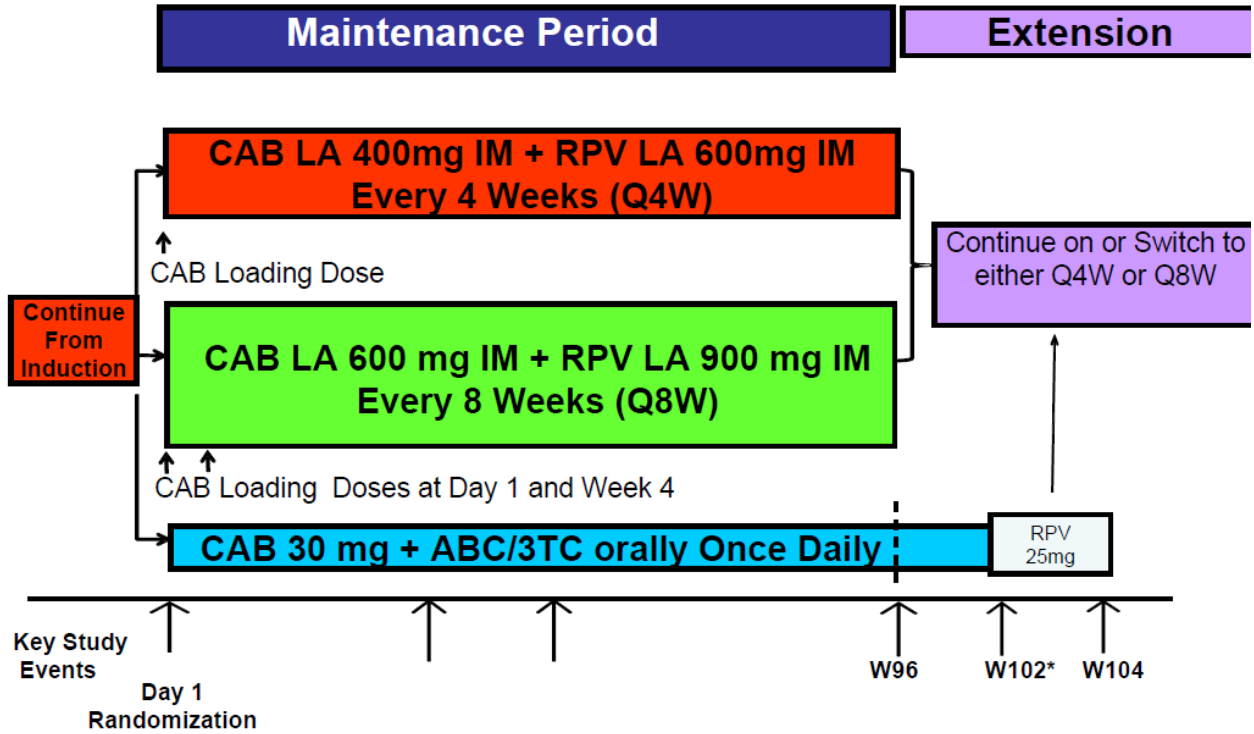
VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Figure 13. LATTE-2 Induction Period Trial Design



Source: http://regist2.virology-education.com/2015/16HIVHEP/10_Spreen.pdf
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, IM = intramuscular, Q4W = every 4 weeks, Q48 = every 8 weeks, RPV = rilpivirine, VL = viral load

Figure 14. LATTE-2 Maintenance Period Trial Design



Source: http://regist2.virology-education.com/2015/16HIVHEP/10_Spreen.pdf.
Abbreviations: CAB = cabotegravir, IM = intramuscular, LA = long-acting, Q4W = every 4 weeks, Q8W = every 8 weeks, RPV = rilpivirine

Virologic response rates were similar across CAB oral and IM treatment groups (Table 8).

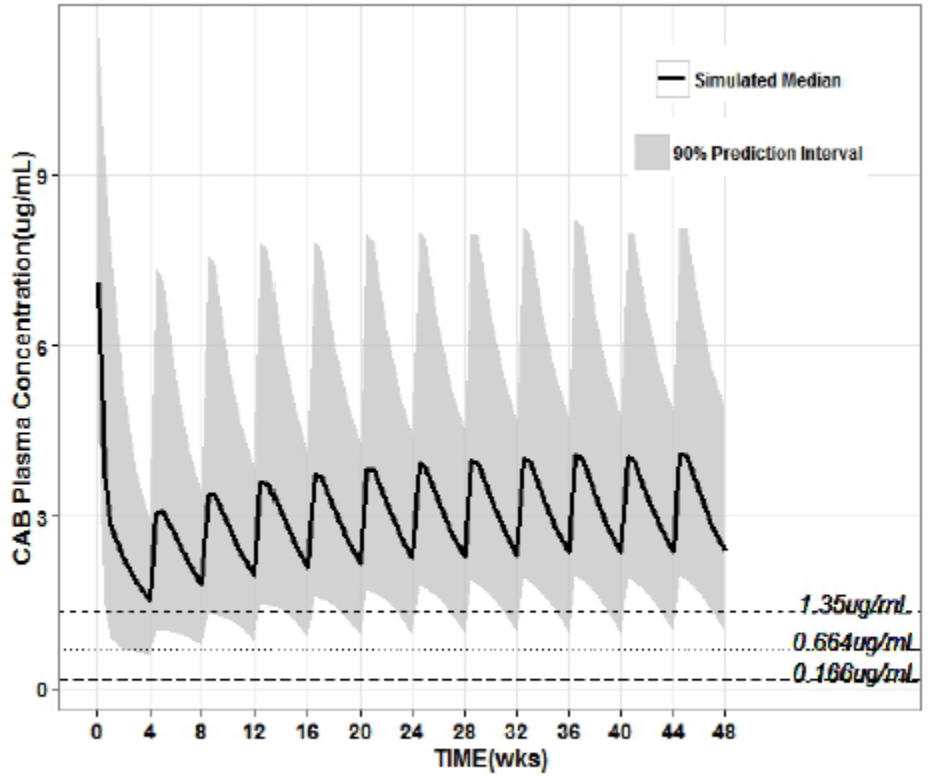
Table 8. Summary of Study Outcome at Week 48, LATTE-2

Outcome	Q8W IM N=115 n (%)	Q4W IM N=115 n (%)	CAB 30 mg N=56 n (%)	Subtotal IM N=230 n (%)
Virologic Success, n (%)	106 (92)	105 (91)	50 (89)	211 (92)
Virologic Failure, n (%)	8 (7)	1 (<1)	1 (2)	9 (4)
Data in window not below threshold	6 (5)	1 (<1)	0	7 (3)
Discontinued for lack of efficacy	1 (<1)	0	1 (2)	1 (<1)
Discontinued for other reason while not below threshold	1 (<1)	0	0	1 (<1)
No Virologic Data	1 (<1)	9 (8)	5 (9)	10 (4)
Discontinued due to AE or Death	0	6 (5)	2 (4)	6 (3)
Discontinued for Other Reasons	1 (<1)	3 (3)	3 (5)	4 (2)

Source: Page 92, LATTE-2 CSR
Abbreviations: AE = adverse event, CAB = cabotegravir, IM = intramuscular, Q4W = every 4 weeks, Q8W = every 8 weeks

The CAB extended-release injectable dosing regimen (once-daily 30-mg tablet orally administered on month 1, 600-mg loading dose on month 2, followed by 400 mg every 4 weeks) proposed for evaluation in phase 3 studies was supported by modeling and simulation data. Geometric mean C_{min} (1.35 µg/mL) following oral CAB 10 mg once daily in LATTE was used as a target concentration, and CAB exposures from the proposed phase 3 regimen were expected to exceed the target for most subjects (Figure 15). Based on the week 32 efficacy outcome and overall safety profile from LATTE-2 along with modeling and simulation data, DAV agreed with the long-acting cabotegravir (CAB LA) dosing regimen proposed for evaluation in phase 3 studies.

Figure 15. Predicted Median (90% Prediction Interval) Cabotegravir (CAB) Concentrations Corresponding to a CAB 600-mg Loading Dose and CAB 400-mg LA Maintenance Dose



Medium dashed line at 1.35μg/mL corresponds to the geometric mean C_T following oral CAB 10mg once daily (LATTE) and is equivalent to 8x PA-IC_{90}.
Dotted line at 0.664μg/mL corresponds to 4x PA-IC_{90}.
Long dashed line at 0.166 μg/mL corresponds to the PA-IC_{90}.

Source: IND 109678 SDN 168, page 2.
Abbreviations: CAB = cabotegravir, LA = long-acting, PA-IC_{50} = protein-adjusted half minimum inhibitory concentration

6.2. Assessment of Dose and Potential Effectiveness: RPV

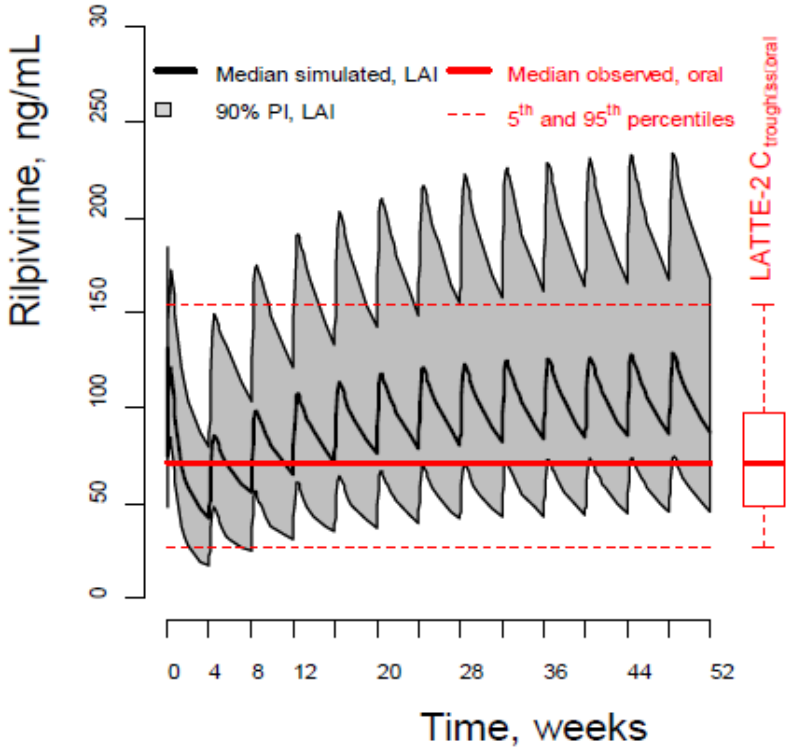
The RPV oral and LA dosing selected for the pivotal studies was reasonable. The assessment of dose and potential effectiveness of oral RPV for the treatment of HIV-1 infection was previously reviewed in NDA 202022. The approval of oral RPV was based on proof-of-concept trials, dose-finding trials, and confirmed in phase 3 trials. In addition, the efficacy results from the LATTE (Table 8) trial provided support for the use of CAB+RPV as a two-drug complete regimen.

The RPV IM dosing regimen (900-mg loading dose on month 2 followed by 600 mg every 4 weeks) proposed for phase 3 studies was supported by efficacy data from LATTE-2 (Figure 13, Table 8) and modeling and simulation data.

In the modeling and simulation analysis, the distribution of observed RPV C_{min} concentrations from oral RPV 25 mg dosing in study LATTE-2 were used as target concentrations. The distribution of RPV C_{min} for the RPV IM regimen proposed for phase 3 studies was expected to

exceed the target for most subjects (Figure 16). DAVP agreed with the RPV IM dosing regimen proposed for evaluation in phase 3 studies.

Figure 16. Predicted Median (90% Prediction Interval) Rilpivirine (RPV) Concentrations Corresponding to an RPV 900-mg Loading Dose and RPV 600-mg LA Maintenance Dose



Source: IND 109678 SDN 168, page 3.
Abbreviations: LA = long-acting, LAI = long-acting injectable, PI = prediction interval

6.3. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.3.1. Trial Design

Two phase 3 trials were submitted to support the benefit evaluation. Please refer to Section III.15 for a detailed description of the protocol overview and conduct.

FLAIR was a randomized, open-label, active-controlled, noninferiority trial conducted in HIV-1–infected antiretroviral therapy (ART)-naïve adult subjects. All subjects enrolled were first entered into the 20-week induction phase where ABC/DTG/3TC was administered. Subjects who had HIV-1 RNA <50 copies/mL at week −4 (4 weeks before the end of the 20-week induction phase) were randomized (1:1) to either stay on their CAR or receive oral CAB 30 mg + RPV 25 mg once daily for a minimum of 4 weeks (OLI) followed by CAB LA+long-acting RPV (RPV LA) every 4 weeks thereafter. Patients in the CAR arm would have the opportunity of switching to CAB+RPV regimen at the end of week 100. Randomization was stratified by subject's induction phase HIV-1 RNA (<100,000 or ≥100,000 copies/mL) and sex at birth.

ATLAS was a randomized, open-label, active-controlled, noninferiority switch trial conducted in HIV-1–infected virologically suppressed adult subjects. All subjects were on a stable (uninterrupted) regimen for at least 6 months prior to enrollment and had documented evidence of at least two plasma HIV-1 RNA <50 copies/mL within the prior 12 months. At the randomization visit, subjects were randomized (1:1) to either stay on their original CAR or switch to a once daily regimen of oral CAB 30 mg+RPV 25 mg for a minimum of 4 weeks (OLI) followed by CAB LA+RPV LA every 4 weeks thereafter. Patients in the CAR arm would have the opportunity of switching to CAB+RPV regimen at the end of week 52. Randomization was stratified by subject's baseline third agent class (INSTI, NNRTI, or PI) and sex at birth.

Although FLAIR started with treatment-naïve subjects, all subjects were required to have HIV-1 RNA <50 copies/mL before being randomized to CAB+RPV or CAR. Therefore, both trials were considered switch trials, and the noninferiority design was appropriate. The primary efficacy endpoint for both trials was the proportion of virologic failure (defined as HIV-1 RNA ≥50 copies/mL) using FDA snapshot algorithm at week 48, which is consistent with the FDA guidance of *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015).[2]

The FDA guidance[2] also recommends a noninferiority margin of 4% based on the endpoint of HIV-1 RNA ≥50 copies/mL to be used for switch trials. However, the Applicant requested a 6% margin for each trial. The Division found this approach acceptable based on the consideration that CAB LA+RPV LA regimen may offer important advantages over the standard 3-drug oral regimen, so a 6% margin for the individual trials and a 4% margin for the combined trials was considered acceptable. Accordingly, both individual trials should satisfy the 6% margin criteria prior to the integration of the data for the pooled analysis that would be evaluated using a 4% margin.

The secondary efficacy endpoints at week 48 included comparisons between treatment arms for the following:

- Proportion with HIV-1 RNA <50 copies/mL and <200 copies/mL
- Proportion with confirmed virologic failure (CVF) (two consecutive plasma HIV-1 RNA ≥200 copies/mL after prior suppression to <200 copies/mL)
- Absolute values and change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) and CD4+ cell count
- Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS], and death)

The above endpoints will also be evaluated at week 96 for FLAIR. As specified, those are secondary endpoints. The Applicant will submit the week 96 data later when they are available.

A detailed summary of the trial design is presented in Section III.15.

6.3.2. Eligibility Criteria

Both FLAIR and ATLAS enrolled HIV-1–infected subjects who were at least 18 years of age at the time of screening. Because the two trial designs were not identical, some differences between the two trials with respect to inclusion criteria are outlined below.

For FLAIR, subjects who were ART naïve and had a screening HIV-1 RNA ≥1,000 copies/mL were eligible for enrollment.

For ATLAS, subjects must be on a stable (uninterrupted) regimen for at least 6 months prior to screening; any prior changes of a single drug or multiple drugs for treatment failure or resistance were not permitted. An acceptable stable ART regimen included two NRTIs plus INSTI (except ABC/DTG/3TC), NNRTI, or a PI with either cobicistat or ritonavir. Subjects should have at least 2 plasma HIV-1 RNA <50 copies/mL in the 12 months prior to screening with 1 within the 6 to 12 window and 1 within the 6-month window, and also had HIV-1 RNA <50 copies/mL at screening.

Both FLAIR and ATLAS excluded subjects who were pregnant or breast feeding, had an active Centers for Disease Control and Prevention (CDC) stage 3 disease, known moderate to severe hepatic impairment, unstable liver disease, liver cirrhosis, pancreatitis, untreated syphilis, ongoing malignancy, significant cardiovascular disease, allergy to the study drug, alanine aminotransferase (ALT) ≥3×upper limit of normal (ULN), estimated creatinine clearance <50 mL/min/1.73 m^2, were in need of chronic anticoagulant, were coinfected with hepatitis B virus (HBV) or required hepatitis C virus (HCV) therapy before or during the 48 weeks of the study treatment period, or who had a pre-existing physical or mental condition that may interfere with subject's ability to comply with trial conduct or a high risk of seizures that were unstable or poorly controlled (reference Section 7.6.6 for details on seizure-like AEs).

6.3.3. Statistical Analysis Plan

The Applicant and the review division agreed on the FLAIR and ATLAS statistical analysis plan (SAP) prior to the trial completion.

The target sample size of 285 subjects per arm for both FLAIR and ATLAS trials was estimated to have 97% power to demonstrate noninferiority using a margin of 6% for the primary efficacy endpoint for individual trials, and a combined sample size of 570 per arm (using weighted pooling of the data from FLAIR and ATLAS) would achieve 90% power for concluding noninferiority using a margin of 4%, all using one-sided α level 0.025.

The primary efficacy analysis was performed in the intent-to-treat exposed (ITT-E) population defined as all randomized subjects who received at least one dose of study drug. The primary efficacy analysis compared the proportion of subjects with a week 48 HIV-1 RNA ≥50 copies/mL between the two arms (CAB+RPV – CAR) using FDA snapshot algorithm. This was performed using stratified Cochran-Mantel Haenszel (CMH) method, adjusting induction baseline HIV-1 RNA (<100,000 or ≥100,000 copies/mL) and sex at birth for FLAIR, and baseline third agent class (INSTI, NNRTI, or PI) and sex at birth for ATLAS. For the pooled analysis using CMH test, a total of 10 strata were applied. This approach performs well for the stratified analysis that compares two proportions. Adjusted CMH estimates of the treatment difference and 95% CIs were calculated, and the upper bound of the 95% CI was compared to the prespecified noninferiority margin. A conclusion of noninferiority of CAB+RPV compared to CAR can be determined if the upper bound of the 95% CI is less than the noninferiority margin.

An interim analysis that evaluated accumulative efficacy results was conducted for the two individual trials when approximately 50% of the subjects reached week 24. A futility rule based

on Bayesian posterior predictive probability was applied to assess the probability that CAB+RPV is noninferior to CAR. An independent data monitoring committee (IDMC) was unblinded and evaluated the efficacy results, while the Applicant remained blinded. No alpha(α) was spent on the interim analysis because there was no hypothesis test conducted, and the Applicant remained blinded to the randomization and the interim results.

The Applicant will perform secondary analyses for the week 96 efficacy endpoints once FLAIR data are completed for the week 96 visit.

The week 48 analysis cut-off date was August 30, 2018 for FLAIR and June 5, 2018 for ATLAS.

6.4. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

This section summarizes the subject disposition, baseline demographics, and disease characteristics and primary efficacy results to support the efficacy of CAB+RPV in treatment-naïve subjects who had viral suppression before switching to CAB+RPV.

6.4.1. Disposition, Baseline Demographics, and Characteristics

Patient disposition information for both trials, FLAIR and ATLAS, is presented in Table 9. In FLAIR and ATLAS, 566 and 616 subjects—respectively—were randomized, and all received study drugs. FLAIR was designed to have randomized treatment period for 100 weeks. Therefore, no subject has completed the study for the current submission; hence, subjects have various treatment exposure time at data cut-off date. Thus, it would be more reasonable to look at patient disposition based on a fixed exposure period (48 weeks) so that data are comparable between the treatment and control groups. For the same consideration, patient disposition for ATLAS is presented through week 52. In ATLAS trial, numerically more subjects withdrew from the study in the CAB+RPV arm compared to CAR arm, 8.4% versus 5.8%, and the reason for the higher withdrawal rate was mainly due to AEs. Similarly, in FLAIR trial, more subjects withdrew from the study due to AE, 3.2% versus 1.1%, and 2 subjects withdrew due to intolerance of injections. The remaining reasons for trial discontinuation were generally similar between the two arms.

Table 9. Patient Disposition, FLAIR and ATLAS

	FLAIR		ATLAS	
	Through Week 48		Through Week 52	
Patient Disposition	**CAB+RPV**	**CAR**	**CAB+RPV**	**CAR**
Population				
Randomized	283 (100%)	283 (100%)	308 (100%)	308 (100%)
ITT-E	283 (100%)	283 (100%)	308 (100%)	308 (100%)
Safety	283 (100%)	283 (100%)	308 (100%)	308 (100%)
Per protocol	278 (98.2%)	282 (99.6%)	294 (95.5%)	292 (94.8%)
Completion status				
Completed*	0	0	281 (91.2%)	290 (94.2%)
Withdrawn	20 (7.1%)	20 (7.1%)	26 (8.4%)	18 (5.8%)

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

	FLAIR		ATLAS	
	Through Week 48		Through Week 52	
Patient Disposition	**CAB+RPV**	**CAR**	**CAB+RPV**	**CAR**
Reasons for withdrawal				
Adverse event	9 (3.2%)	3 (1.1%)	13 (4.2%)	5 (1.6%)
Lack of efficacy	4 (1.4%)	3 (1.1%)	3 (1%)	4 (1.3%)
Protocol deviation	0	1 (0.4%)	5 (1.6%)	3 (1%)
Subject met the GSK defined liver criteria	0	0	1 (0.3%)	0
Lost to follow-up	2 (0.7%)	2 (0.7%)	1 (0.3%)	1 (0.3%)
Physician decision	0	4 (1.4%)	2 (0.6%)	0
Withdrawal by subject	5 (1.8%)	7 (2.5%)	1 (0.3%)	5 (1.6%)
Intolerability of injections	2 (0.7%)	0	0	0

Source: Reviewer's analysis using ADDS.xpt
Note: Proportions are based on the ITT-E population
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, GSK = GlaxoSmithKline, ITT-E = intent-to-treat-exposed, RPV = rilpivirine
*Subjects enrolled in FLAIR are continuing the trial, hence none have reached trial completion. Subjects enrolled in ATLAS are switching to ATLAS-2M phase 3b trial after reaching the Week 48 window.

Baseline demographics and characteristics were generally balanced between arms for both trials (Table 10 and Table 11). Both trials enrolled more males, white subjects, and subjects with BMI <30 kg/m^2. In the United States alone, black/African American persons account for 44% of all new HIV infections, and women account for 19% of new HIV infections.[4] Therefore, the representation of black/African American subjects for the two trials falls below the national estimates, and the representation of women is adequate based on the national estimates. Approximately half the subjects enrolled in FLAIR were <35 years of age. In ATLAS, more subjects were between the ages of 35 and <50. The age of the enrolled subjects reflects the targeted trial population of ART-naïve in FLAIR and ART-experienced in ATLAS.

Table 10. Baseline Demographic and Clinical Characteristics, Efficacy Population, FLAIR and ATLAS

	FLAIR n(%)		ATLAS n(%)	
	CAB+RPV	CAR	CAB+RPV	CAR
Demographic	**(N=283)**	**(N=283)**	**(N=308)**	**(N=308)**
Age group				
<35	143 (50.5)	145 (51.2)	80 (26.0)	80 (26.0)
35-<50	107 (37.8)	109 (38.5)	162 (52.6)	132 (42.9)
≥50	33 (11.7)	29 (10.2)	66 (21.4)	96 (31.2)
Sex				
Male	220 (77.7)	219 (77.4)	209 (67.9)	204 (66.2)
Female	63 (22.3)	64 (22.6)	99 (32.1)	104 (33.8)
Race				
White	216 (76.3)	201 (71.0)	214 (69.5)	207 (67.2)
Nonwhite	67 (23.7)	82 (29.0)	94 (30.5)	101 (32.8)
BMI group (kg/m^2)				
<30	243 (85.9)	246 (86.9)	248 (80.5)	242 (78.6)
≥30	40 (14.1)	37 (13.1)	60 (19.5)	66 (21.4)
Smoke				
Current	122 (43.1)	108 (38.2)	93 (30.2)	80 (26.0)
Former	34 (12.0)	38 (13.4)	62 (20.1)	49 (15.9)
Never	127 (44.9)	137 (48.4)	153 (49.7)	179 (58.1)

Source: Reviewer's analysis using ADSL.xpt
Note: Proportions are based on the ITT-E population
Abbreviations: BMI = body mass index, CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

Because the eligibility of randomization was determined using HIV-1 RNA measured at −4 week in FLAIR, about 4% subjects had HIV-1 RNA at or above 50 copies/mL at the time of randomization. This rate was numerically higher compared to the rate in ATLAS, which was 1%. We found this is reasonable because the enrolled subjects in ATLAS were on a stable virologically suppressed regimen longer than those in FLAIR, and the differences were not considered clinically significant.

Table 11. Patient Screening and Baseline HIV Disease Characteristics, FLAIR and ATLAS

	FLAIR		ATLAS	
	CAB+RPV N=283	CAR N=283	CAB+RPV N=308	CAR N=308
Disease Characteristic	**n (%)**	**n (%)**	**n (%)**	**n (%)**
CDC HIV infection				
Stage 1	200 (70.7)	196 (69.3)	229 (74.4)	224 (72.7)
Stage 2	78 (27.6)	82 (29.0)	78 (25.3)	83 (26.9)
Stage 3	5 (1.8)	5 (1.8)	1 (0.3)	1 (0.3)
Induction HIV-1 RNA (copies/mL)				
<100,000	227 (80.2)	227 (80.2)		
≥100,000	56 (19.8)	56 (19.8)		
Induction CD4+ cell count (cells/mm^3)				
<350	87 (30.7)	87 (30.7)		
350 to <500	88 (31.1)	88 (31.1)		
≥500	108 (38.2)	108 (38.2)		
Baseline HIV-1 RNA (copies/mL)				
<50	272 (96.1)	272 (96.1)	305 (99.0)	305 (99.0)
≥50	11 (3.9)	11 (3.9)	3 (1.0)	3 (1.0)

	FLAIR		ATLAS	
Disease Characteristic	**CAB+RPV N=283 n (%)**	**CAR N=283 n (%)**	**CAB+RPV N=308 n (%)**	**CAR N=308 n (%)**
Baseline CD4+ cell count (cells/mm^3)				
<350	19 (6.7)	27 (9.5)	23 (7.5)	27 (8.8)
350 to <500	64 (22.6)	60 (21.2)	56 (18.2)	57 (18.5)
≥500	200 (70.7)	196 (69.3)	229 (74.4)	224 (72.7)
K103N				
Yes	2 (0.7)	3 (1.1)		
No	281 (99.3)	280 (98.9)		
Baseline third agent class				
INSTI			102 (33.1)	99 (32.1)
NNRTI			155 (50.3)	155 (50.3)
PI			51 (16.6)	54 (17.5)

Source: Reviewer's analysis using ADSL.xpt
Note: Proportions are based on the ITT-E population
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, CDC = Centers for Disease Control and Prevention, INSTI = integrase strand transfer inhibitor, NNRTI = nonnucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RPV = rilpivirine

6.4.2. Primary and Key Secondary Efficacy Results

The Applicant's primary efficacy results were confirmed by the statistical review team, and the results demonstrate noninferiority in both FLAIR and ATLAS. The upper bound of the 95% CI for the adjusted difference in the proportion of subjects with HIV-1 RNA ≥50 copies/mL at week 48 (CAB+RPV – CAR) was lower than the prespecified 6% margin for each trial. Specifically, those upper bounds were 2.1% in FLAIR and 2.5% in ATLAS. The results also demonstrate that CAB+RPV is noninferior to CAR based on the prespecified 4% margin for the stratified pooled data analysis (Table 12).

Virologic success (HIV-1 RNA <50 copies/mL) at week 48 was also evaluated for the individual trials and the pooled data as a key secondary endpoint. None of the lower bounds of the 95% CI of the adjusted difference in the proportions between CAB+RPV and CAR were lower than noninferiority margin of −10%, which supports the results for the primary efficacy endpoint.

Homogeneity of the results across the ten randomization strata was evaluated using Breslow-Day test for the pooled analyses. The result showed that the treatment effect was consistent across strata (p-value=0.2).

Table 12. Week 48 Primary and Key Secondary Efficacy (ITT-E), FLAIR and ATLAS Trials Individually and Pooled

Trial	CAB+RPV	CAR	Difference (95% CI)
Virologic failure (HIV-1 RNA ≥50 copies/mL)			
FLAIR	6/283 (2.1%)	7/283 (2.5%)	-0.4 (-2.8, 2.1)
ATLAS	5/308 (1.6%)	3/308 (1.0%)	0.7 (-1.2, 2.5)
Pooled			0.2 (-1.4, 1.7)
Virologic success (HIV-1 RNA <50 copies/mL)			
FLAIR	265/283 (93.6%)	264/283 (93.3%)	0.4 (-3.7, 4.5)
ATLAS	285/308 (92.5%)	294/308 (95.5%)	-3.0 (-6.7, 0.7)
Pooled			-1.4 (-4.1, 1.4)

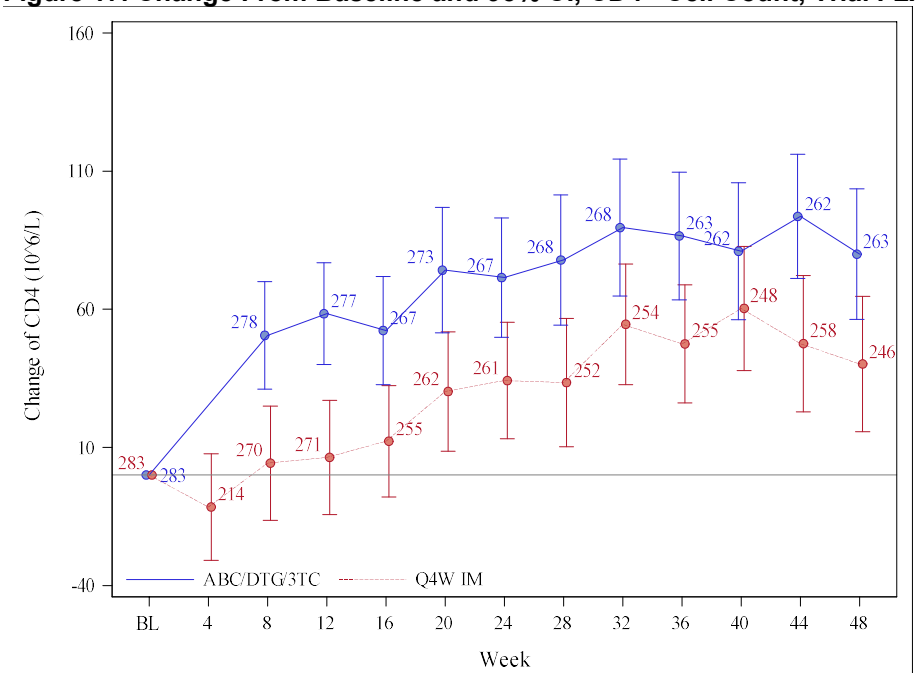
Source: Reviewer's analysis using ADEFFOUT.xpt
Note: Difference in the proportions were calculated with (CAB+RPV – CAR). CMH were applied for the stratified analyses, with stratification factors as baseline HIV-1 RNA (<100,000 or ≥100,000 copies/mL) and sex at birth for FLAIR, and baseline third agent class (INSTI, NNRTI, or PI) and sex at birth for ATLAS. The pooled analyses included all ten aforementioned stratification factors.
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, CI = confidence interval, ITT-E = intent-to-treat-exposure, RPV = rilpivirine

Change in CD4+ Cell Counts Through Week 48

In FLAIR, larger increases in CD4+ cell counts were observed through week 48 compared to ATLAS because the subjects in FLAIR had shorter time on ARV treatment (20 weeks versus on stable ART for at least 6 months in ATLAS) (Figure 17 and Figure 18). These findings were expected and consistent with the findings from similar trial designs.

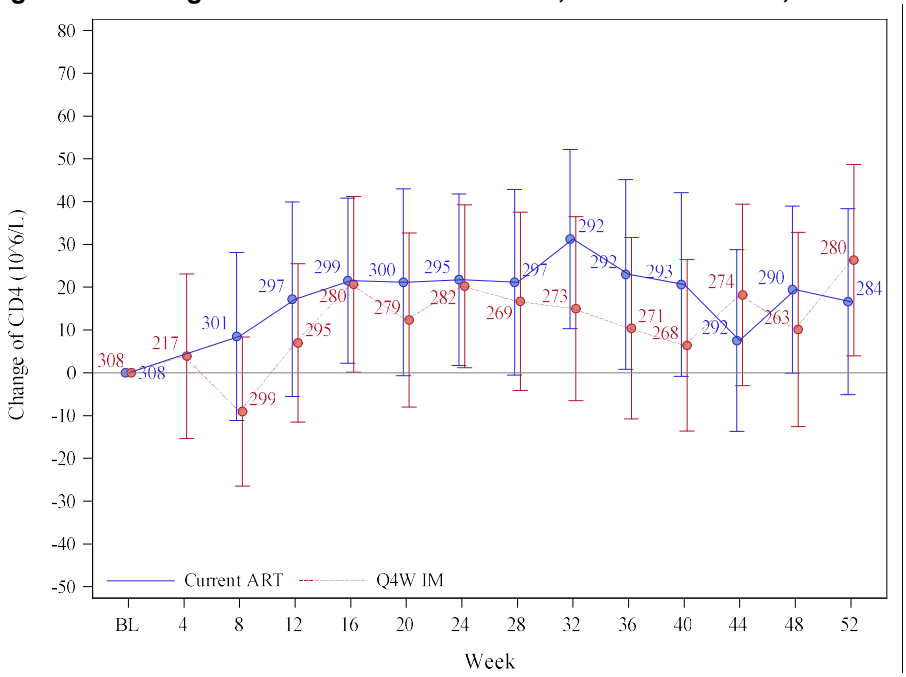
We noted that the CAB+RPV arm in both trials had consistently lower numbers of HIV-1 RNA and CD4+ cell count laboratory data at each visit compared to the CAR arms. The review team does not think those missing laboratory values would be very different from other observed values, but no explanation of the consistently higher number of missing values in the CAB+RPV arm was provided by the Applicant.

Figure 17. Change From Baseline and 95% CI, CD4+ Cell Count, Trial FLAIR, Maintenance Phase



Source: Reviewer's analysis using ADLB.xpt
Note: Numbers on the graph represent the sample size at each visit. In case more than one measurement was reported at a certain visit, the measurement value with the later date was used for calculation
Abbreviations: 3TC = lamivudine, ABC = abacavir, BL = baseline, CI = confidence interval, DTG = dolutegravir, IM = intramuscular, Q4W = every 4 weeks

Figure 18. Change From Baseline and 95% CI, CD4+ Cell Count, Trial ATLAS, Maintenance Phase



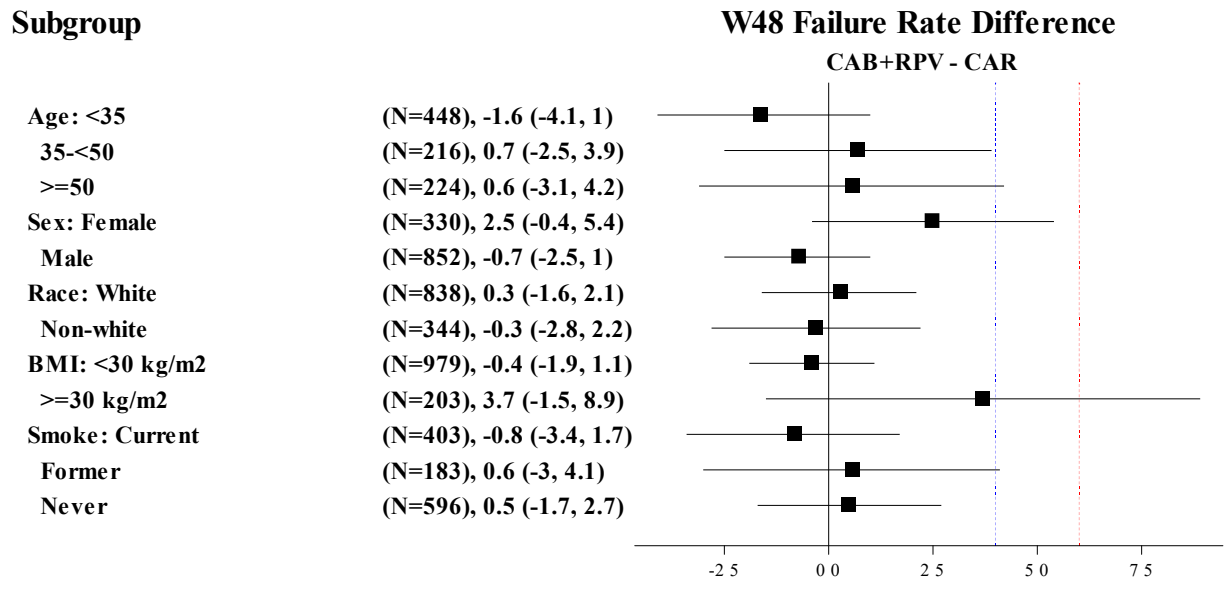
Source: Reviewer's analysis using ADLB.xpt
Note: Numbers on the graph represent the sample size at each visit. In case more than one measurement was reported at a certain visit, the measurement value with the later date was used for calculation
Abbreviations: ART = antiretroviral therapy, BL = baseline, CI = confidence interval, IM = intramuscular, Q4W = every 4 weeks

6.4.3. Subgroup Findings

For the subgroup analyses, data from FLAIR and ATLAS were combined to increase the sample size. The protocol-specified stratification factors for primary efficacy endpoint, included induction HIV-1 RNA, sex at birth, and baseline third agent class, were evaluated as subgroups. Several additional baseline demographic and disease characteristic subgroups were selected, analyzed, and evaluated. Forest plots showing the point estimates of the week 48 virologic failure rates and the associated 95% CIs are presented in Figure 19, Figure 20, and Figure 21.

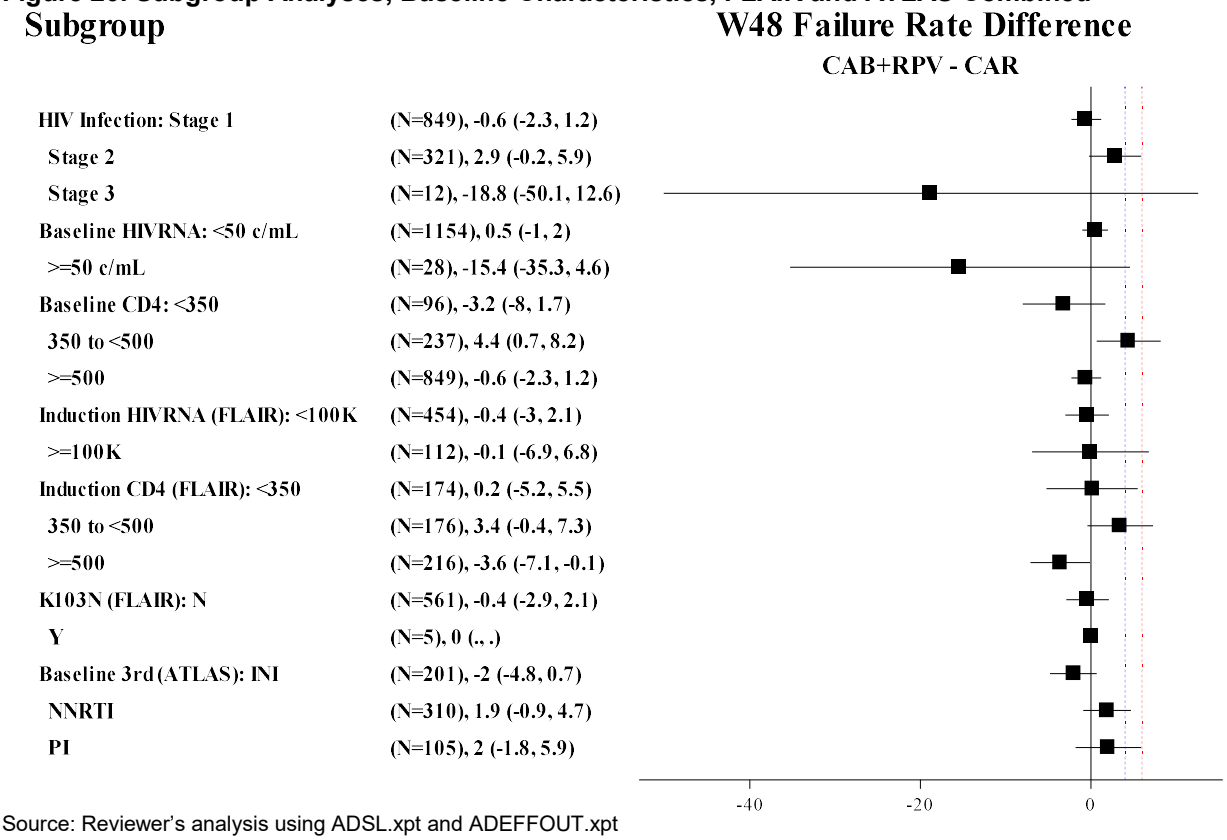
Because the sample sizes for some subgroups were relatively small, the corresponding CIs were wide. In addition, because there were multiple subgroup analyses conducted without any multiplicity adjustment, this could result in spurious findings due to chance, even if the observed result for one subgroup is seemingly very different from the other subgroups. As an example, a few subgroups had the estimated week 48 virologic failure rate difference much larger than their counterpart subgroups: the female subgroup and the subgroup with BMI ≥30 kg/m^2 (Figure 19, further discussed under Section 6.5.2). These subgroup findings should not be interpreted as statistically significant, unless the results are confirmed with additional evidence from future trial(s). Another outlier was the CD4+ cell count 350 cells/mm^3 to <500 cells/mm^3 subgroup. However, we did not think this finding was clinically relevant and was likely due to chance given the results for the CD4+ cell count <350 cells/mm^3 and ≥500 cells/mm^3 subgroups. Overall, it can be concluded that the subgroup results support the primary efficacy findings.

Figure 19. Subgroup Analyses, Baseline Demographic Characteristics, FLAIR and ATLAS Combined



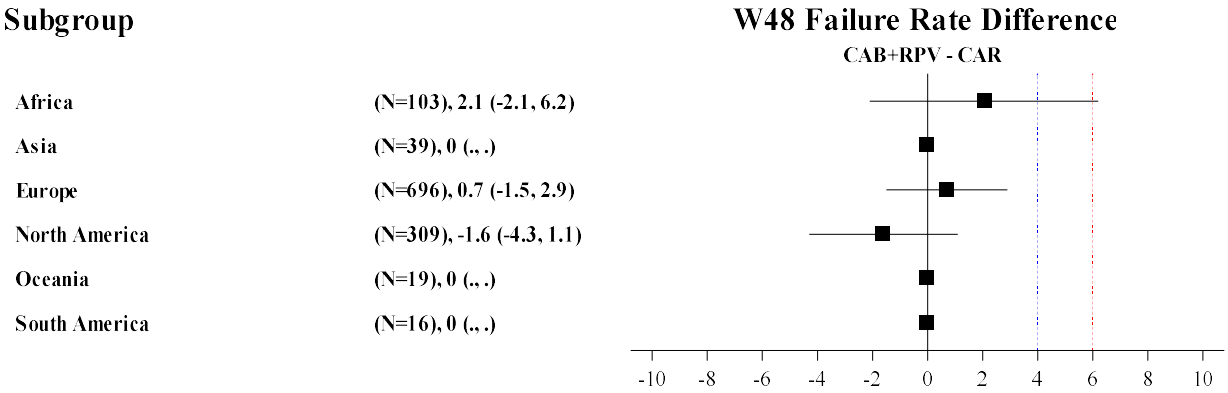
Source: Reviewer's analysis using ADSL.xpt and ADEFFOUT.xpt
Note: Difference in the proportions of virologic failure (week 48 HIV-1 RNA ≥50 copies/mL) were calculated with (CAB+RPV – CAR) using stratified CMH adjusting induction HIV-1 RNA (<100,000 or ≥100,000 copies/mL) (only pertains to FLAIR), sex at birth, and baseline third agent class (INSTI, NNRTI, or PI) (only pertains to ATLAS).
Note: Middle column includes information for sample size, point estimate of the rate difference, and 95% CI.
Note: Red and blue reference lines represent 6% and 4% noninferiority margins, respectively
Abbreviations: BMI = body mass index, CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

Figure 20. Subgroup Analyses, Baseline Characteristics, FLAIR and ATLAS Combined



Source: Reviewer's analysis using ADSL.xpt and ADEFFOUT.xpt
Note: Difference in the proportions of virologic failure (week 48 HIV-1 RNA ≥50 copies/mL) were calculated with (CAB+RPV – CAR) using stratified CMH adjusting induction HIV-1 RNA (<100,000 or ≥100,000 copies/mL) (only pertains to FLAIR), sex at birth, and baseline third agent class (INSTI, NNRTI, or PI) (only pertains to ATLAS).
Note: Because induction phase and baseline K103 substitution only pertain to FLAIR, and baseline 3rd agent only pertains to ATLAS, these subgroup analyses were based on the corresponding individual trials.
Note: Middle column includes information for sample size, point estimate of the rate difference, and 95% CI.
Note: 95% CI is not produced when both treatment groups had no subjects with HIV-1 RNA ≥50 copies/mL.
Note: Red and blue reference lines represent 6% and 4% noninferiority margins, respectively
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, INI = integrase inh bitor, NNRTI = nonnucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RPV = rilpivirine

Figure 21. Subgroup Analyses, by Region, FLAIR and ATLAS Combined



Source: Reviewer's analysis using ADSL.xpt and ADEFFOUT.xpt
Note: Difference in the proportions of virologic failure (week 48 HIV-1 RNA ≥50 copies/mL) were calculated with (CAB+RPV – CAR) using stratified CMH adjusting induction HIV-1 RNA (<100,000 or ≥100,000 copies/mL) (only pertains to FLAIR), sex at birth, and baseline third agent class (INSTI, NNRTI, or PI) (only pertains to ATLAS).
Note: Middle column includes information for sample size, point estimate of the rate difference, and 95% CI.
Note: 95% CIs are not produced when both treatment groups had no subjects with HIV-1 RNA ≥50 copies/mL.
Note: Red and blue reference lines represent 6% and 4% noninferiority margins, respectively
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

6.4.4. Exploratory Analyses

The protocols for ATLAS and FLAIR specified the injection needle, gauge, and anatomical site for administration. A 1.5" 23 gauge needle for CAB and RPV were recommended for most subjects, but various needle lengths or gauges were permitted to accommodate various body types such as those with BMI ≥30 kg/m^2. The needle length is an important consideration to ensure the injections were administered into the gluteal muscle. The review team considered the impact of needle length selection on HIV-1 RNA outcome, and exploratory analyses were conducted to evaluate whether or not the needle size used affected virologic outcome.

The needle lengths used in the trials ranged from 1 to 2.26 inches for the CAB and RPV injections. A 1.5-inch needle was used in approximately 80% of the injections administered. The gauge ranged from (b) (4) for both drug injections with about 90% of the injections using a (b) (4) -gauge needle. For the subjects who had BMI of at least 30 kg/m^2, 96% of the injections used needle length 1.5-inches or longer, and 95% of the injections selected (b) (4) -gauge needle.

Overall, no statistically significant associations between the change in HIV-1 RNA from baseline and needle length or needle gauge used for the CAB or RPV injections were observed after controlling for age, baseline BMI, baseline disease stage, baseline HIV-1 RNA, stratification factors, and visit. Details for the statistical method can be found in Section III.16.2. These exploratory analyses have some limitations in its interpretations. First, the trials were not designed to formally study the impact of the needle size on the outcome (e.g., subjects were not randomized to the needle size). Second, the trial populations were virologically suppressed before entering the trial, and because the virologic failure rate was low during the trial, the majority of the outcomes were zero or numerically very small. These factors limited our evaluation of the impact of needle size on outcome. Third, inappropriate needle sizes could have been chosen for some subjects or at some visits. However, due to the small number of subjects with virologic failure, differences in the overall outcome, if any, would be difficult to identify.

The to-be-marketed dosing kit contains two needles for IM injections (both 1.5-inches and 23-gauge). The administration instructions in the label recommend considering patient's BMI to ensure the needle length is sufficient to reach the gluteus muscle and permits use of alternative needle to the one provided in the dosing kit. For consistency, the review team recommends the label includes similar details as included in the phase 3 protocols: *"Longer needle lengths may be required for patients with higher body mass indexes (BMIs, example ≥30) to ensure that injections are administered intramuscularly as opposed to subcutaneously."*

6.4.5. Additional Analyses

Additional analyses were conducted to evaluate the subject's adherence to the injection schedule and whether the OLI or the planned oral bridging dosing were adequate to maintain the viral suppression. Those results can be found in Section III.16.2.

6.5. Review Issues Relevant to the Evaluation of Benefit

The review team concluded that the results of the phase 3 trials, FLAIR and ATLAS, support the proposed indication as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable ARV regimen with no history of treatment failure and with no known or suspected resistance to either CAB or RPV. ***The review team did not identify any issues with assessing the benefit of CAB+RPV with respect to the primary efficacy endpoint (HIV-1 RNA ≥50 copies/mL) or key secondary endpoint (HIV RNA <50 copies/mL)***; therefore, no further discussion is warranted in this subsection.

The review issues relevant to the evaluation of benefit focus on two exploratory analyses, the effect of pre-existing NNRTI resistance associated substitutions (K103N substitution) on virologic response to CAB+RPV, and the potential differences in virologic failure rates among the following subgroups compared to their counterparts: female subjects, subjects with BMI ≥30 kg/m^2, and female subjects with BMI ≥30 kg/m^2 (Figure 17 and Figure 20). However, interpretation of the apparent differences in the virologic outcome in these subgroups should be with caution because, as discussed in Section 6.4.3, the sample sizes were small, the analyses were post hoc, exploratory, and without control for multiplicity. Note, Section 6.5.2 focuses on the subgroups of sex by BMI. For analyses in subgroups sex or BMI, refer to Section 6.4.3.

6.5.1. Effect of Pre-Existing NNRTI Resistance-Associated Substitutions on Virologic Response to CAB+RPV

Issue

Subjects who had the NNRTI RAS K103N were not excluded from the FLAIR trial. The presence of pre-existing NNRTI RAS could potentially reduce the virologic response to RPV and contribute to virologic failure on the CAB+RPV regimen. Therefore, the effect of the presence of the K103 substitutions on virologic response was assessed.

Conclusion

Based on the limited data available from the FLAIR trial, the presence of RT K103 NNRTI RAS at screening was not associated with virologic failure to CAB+RPV. Additional data are needed to further assess the effect of K103 substitutions prior to recommending a specific indication for this subpopulation.

Assessment

Five subjects from FLAIR had the RT K103N NNRTI RAS at screening (Table 13). None of these five subjects were virologic failures. One subject withdrew at week 4 in the maintenance phase in the CAR arm with HIV-1 RNA <50 copies/mL. The remaining four subjects (two in the CAB arm and two in the CAR arm) were suppressed on their regimen and were successes in the trial. Additionally, there were three subjects with K103Q (one in CAB arm and two in CAR arm) and six with K103R (five in the CAB arm and one in the CAR arm), who were all virologic successes on their regimen. In this small subset of subjects, the presence of the RT K103N NNRTI RAS at screening was not associated with virologic failure to CAB+RPV. However, given the small number of subjects with the K103N substitution, no specific indication in CAB+RPV labeling is being given for subjects with the K103N substitution in their HIV-1.

Table 13. Virologic Response of Subjects with Substitutions at RT K103 at Screening in FLAIR (FDA Analysis)

Subject	ARM	Substitution at RT K103	Outcome
(b) (6)	CAB	R	Virologic success
	CAB	R	Virologic success
	CAB	R	Virologic success
	CAB	Q	Virologic success
	CAB	R	Virologic success
	CAB	N	Virologic success
	CAB	R	Virologic success
	CAB	N	Virologic success
	CAR	N	Virologic success
	CAR	Q	Virologic success
	CAR	R	Virologic success
	CAR	Q	Virologic success
	CAR	N	Virologic success
	CAR	N	Day 1 HIV-1 RNA =11,693 copies/mL and <50 copies/mL at week 4 in maintenance phase; subject withdrew

Abbreviations: CAB = cabotegravir, CAR = current antiretroviral

6.5.2. Potential Differences in Efficacy by Sex and BMI ≥30 kg/m^2

Issue

Findings from subgroup analyses by sex, baseline BMI, and sex by BMI revealed a consistent pattern of higher virologic failure rates (HIV-1 RNA ≥50 copies/mL) in the CAB+RPV treatment group among subjects who are female, have baseline BMI ≥30 kg/m^2, or who are

female with BMI ≥30 kg/m^2 compared to their counterparts. The findings in these subgroups were seen in both trials (Table 14 and Table 166 in Section III.16.2).

Conclusion

A detailed assessment of the abovementioned subgroups, including evaluation of the PK and virology data, did not reveal a singular explanation for the lower response rates observed.

The durability of a 2-drug regimen beyond 48 weeks to maintain virologic suppression remains unknown; therefore, additional evaluation for differences in outcome among these subgroups is warranted. Depending on the outcomes of those analyses, additional labeling maybe considered, including consideration for summarizing outcome data by female with BMI ≥30 kg/m^2. The product labeling presents the week 48 results by baseline BMI and by sex assigned at birth, noting the numeric differences in virologic outcome.

The long-term data from FLAIR and the ATLAS-2M trials will be submitted for review in upcoming sNDAs.

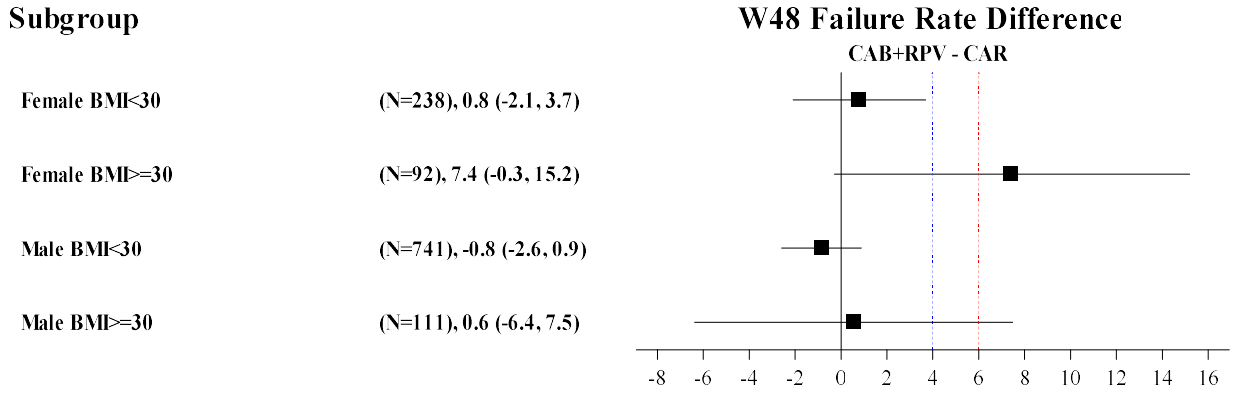
Assessment

The review team conducted a thorough assessment and attempted to identify the possible reasons for the noted numerical differences in the proportion of subjects meeting the virologic failure criterion by baseline factors. Please refer to Section 6.4.3 for details on the subgroup analyses for sex and BMI. This section further describes our assessment of the subgroups of sex by BMI combination.

No single baseline factor appeared to explain these findings. The presence of the IN L74V polymorphism complicates the assessment of those classified as HIV-1 RNA ≥50 copies/mL (by the snapshot algorithm), and thus lower CAB concentrations in these subgroups may not entirely explain the treatment differences. Our assessment is based on the following analyses.

Analyses were conducted on the pooled phase 3 data to explore the consistency of treatment effect on the subgroups of sex by BMI combination. As shown in Figure 22, the point estimates for treatment difference for the proportion of subjects with HIV-1 RNA ≥50 copies/mL was close to zero for male subjects with BMI < and ≥30 kg/m^2 and female subjects with BMI <30 kg/m^2 subgroups. However, for female subjects with BMI ≥30 kg/m^2, the treatment difference favors the CAR arm with a wide 95% CI. Overall, 3 female subjects with BMI ≥30 kg/m^2 had HIV-1 RNA ≥50 copies/mL in the CAB+RPV treatment group, compared to none in the pooled control group (Table 14). Of these three subjects, two discontinued due to “loss of efficacy”.

Figure 22. Subgroup Analyses, Sex by BMI, FLAIR and ATLAS Combined



Note: Difference in the proportions of virologic failure (week 48 HIV-1 RNA ≥50 copies/mL) were calculated with (CAB+RPV – CAR) using stratified CMH adjusting induction HIV-1 RNA (<100,000 or ≥100,000 copies/mL) (only pertains to FLAIR), sex at birth, and baseline third agent class (INSTI, NNRTI, or PI) (only pertains to ATLAS).
Note: Middle column includes information for sample size, point estimate of the rate difference, and 95% CI.
Note: Red and blue reference lines represent 6% and 4% noninferiority margins, respectively
Source: Reviewer's analysis using ADSL.xpt and ADEFFOUT.xpt
Abbreviations: BMI = body mass index, CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

Table 14. Week 48 Efficacy Results for Female With BMI ≥30 kg/m^2 Subgroup, FLAIR and ATLAS

	FLAIR		ATLAS	
Trial	**CAB+RPV**	**CAR**	**CAB+RPV**	**CAR**
HIV-1 RNA ≥50 copies/mL	2/13 (15.4%)	0	1/31 (3.2%)	0
HIV-1 RNA <50 copies/mL	11/13 (84.6%)	16/17 (94.1%)	28/31 (90.3%)	29/31 (93.5%)
No virologic data at week 48 window				
Discontinued due to adverse event or death	0	0	0	1/31 (3.2%)
Discontinued for other reasons	0	1/17 (5.9%)	2/31(6.5%)	1/31 (3.2%)
Missing data during window but on study	0	0	0	0

Source: Reviewer's analysis using ADEFFOUT.xpt
Note: Additional descriptive analyses regarding sex and BMI subgroups can be found in Section III.16
Abbreviations: BMI = body mass index, CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

We then reviewed the 11 CAB+RPV-treated subjects who were classified as HIV-1 RNA ≥50 copies/mL per the FDA snapshot algorithm in detail (Table 15). No consistent pattern with respect to sex and BMI was noted. Forty-five percent of these subjects (5/11) also had the L74V substitution at baseline, which could have contributed to virologic failure. (see Section 7.7.1.2).

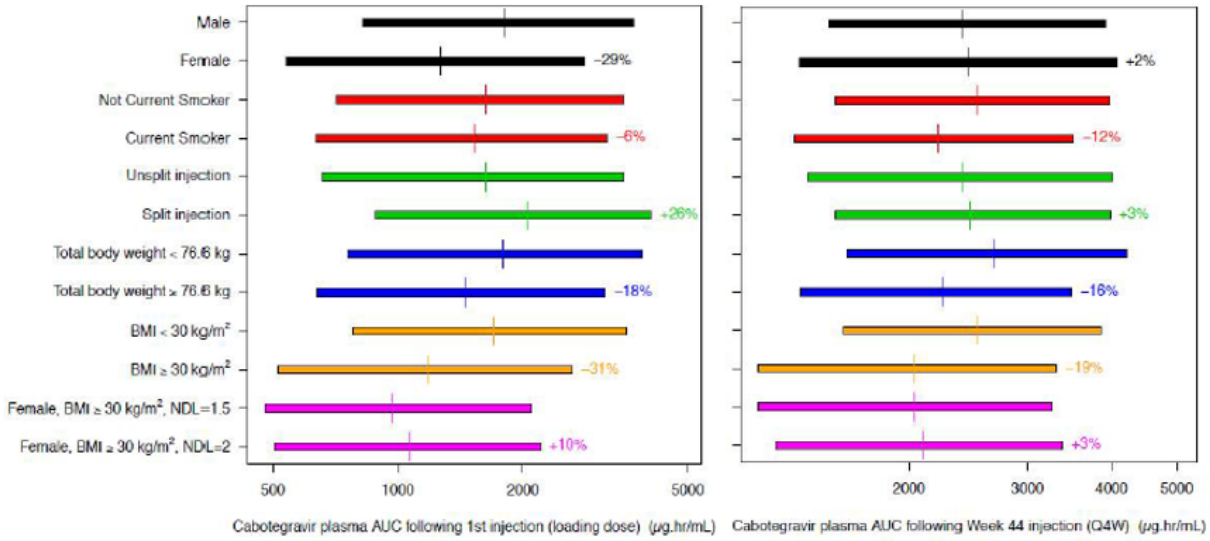
Table 15. Cabotegravir+Rilpivirine (CAB+RPV)-Treated Subjects Who Were Classified as HIV-1 RNA ≥50 Copies/mL per the FDA Snapshot Algorithm

Category	Number of Subjects	Presence of L74I at Baseline = Yes
Female + BMI ≥30	3	2
Female + BMI <30	2	1
Male + BMI ≥30	2	1
Male + BMI <30	4	1

Source: Reviewer's analysis
Abbreviations: BMI = body mass index, CAB = cabotegravir, RPV = rilpivirine

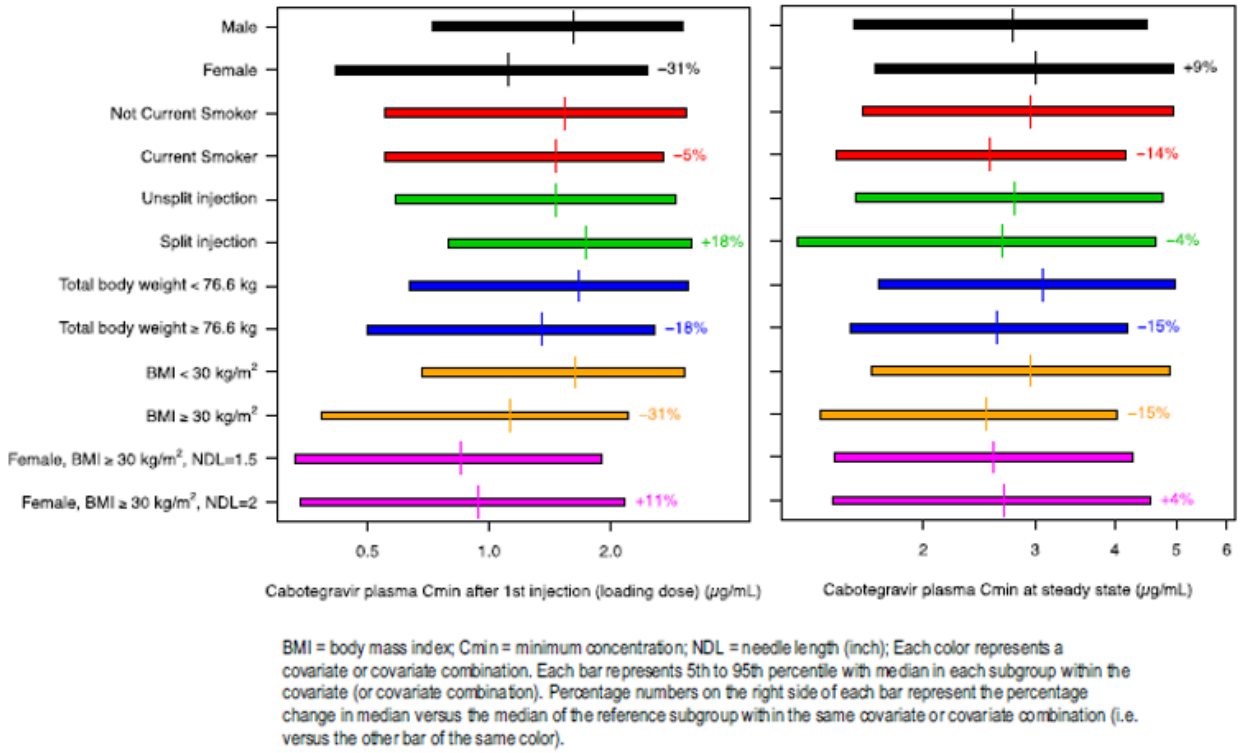
Moreover, the PK data do not entirely explain the treatment differences observed. Gender and BMI were shown to affect CAB concentrations but not RPV concentrations. After the first injection, while CAB concentrations largely overlapped between males and females and between those with BMI < and ≥30 kg/m^2, median CAB area under the concentration-time curve (AUC) and C_{min} were ~30% lower in females versus males and ~30% lower in those with BMI ≥30 kg/m^2 versus those with BMI <30 kg/m^2 (Figure 23). After the first injection, a greater fraction of subjects with CAB C_{min} lower than the efficacy target of 0.65 µg/mL is expected for females versus males and for those with BMI ≥30 kg/m^2 versus those with BMI <30 kg/m^2. However, by week 48, <5% of subjects in any subgroup are expected to have CAB C_{min} <0.65 µg/mL (Figure 24).

Figure 23. Impact of Intrinsic and Extrinsic Factors on Cabotegravir AUC After the Initial Injection (Left Panel) and at Week 48 (Right Panel)



Source: NDA 212888 SDN 19, page 8.
Abbreviations: BMI = body mass index, NDL = needle length, Q4W = every 4 weeks

Figure 24. Impact of Intrinsic and Extrinsic Factors on Cabotegravir C_{min} After the Initial Injection (Left Panel) and at Week 48 (Right Panel)



BMI = body mass index; Cmin = minimum concentration; NDL = needle length (inch); Each color represents a covariate or covariate combination. Each bar represents 5th to 95th percentile with median in each subgroup within the covariate (or covariate combination). Percentage numbers on the right side of each bar represent the percentage change in median versus the median of the reference subgroup within the same covariate or covariate combination (i.e. versus the other bar of the same color).

Source: Cabotegravir popPK report, page 75-76.

The review team assessed the potential effect of lower median CAB AUC and C_{min} in female subjects with BMI $\geq$30 kg/m^2 by evaluating the time to HIV-1 RNA $\geq$50 copies/mL. Specifically, the team assessed if females with BMI $\geq$30 kg/m^2 experienced early viral rebound, possibly due to lower CAB exposures after the first injection. As shown in Table 16, no consistent pattern was observed, suggesting that the lower median CAB AUC and C_{min} may not entirely explain the treatment differences.

Table 16. Percentage of Subjects HIV-1 RNA ≥50 Copies/mL by Visit for Female with BMI ≥30 kg/m^2 Subgroup, FLAIR and ATLAS

	FLAIR		ATLAS	
Visit	**CAB+RPV**	**CAR**	**CAB+RPV**	**CAR**
BL	0/13 (0%)	0/17 (0%)	0/31 (0%)	0/31 (0%)
W4	0/10 (0%)	0/1 (0%)	1/21 (4.8%)	---
W8	0/12 (0%)	1/16 (6.3%)	1/31 (3.2%)	1/30 (3.3%)
W12	0/13 (0%)	0/16 (0%)	2/30 (6.7%)	1/29 (3.4%)
W16	1/11 (9.1%)	0/16 (0%)	1/29 (3.4%)	0/29 (0%)
W20	1/13 (7.7%)	0/16 (0%)	0/27 (0%)	2/30 (6.7%)
W24	1/13 (7.7%)	1/16 (6.3%)	0/28 (0%)	0/30 (0%)
W28	0/11 (0%)	0/16 (0%)	1/24 (4.2%)	0/29 (0%)
W32	0/12 (0%)	0/16 (0%)	0/28 (0%)	0/30 (0%)
W36	0/12 (0%)	0/16 (0%)	0/25 (0%)	0/30 (0%)
W40	0/10 (0%)	0/16 (0%)	1/27 (3.7%)	0/29 (0%)
W44	1/12 (8.3%)	0/16 (0%)	0/28 (0%)	0/27 (0%)
W48	1/12 (8.3%)	0/15 (0%)	0/25 (0%)	0/29 (0%)

Source: Reviewer's analysis using ADLB.xpt
Abbreviations: BL = baseline, BMI = body mass index, CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

Importantly, the analyses conducted have several limitations. The sample size was relatively small. Approximately 17% of subjects entered the trial with a baseline BMI $\geq$30 kg/m^2, and 8% were in the "female+baseline BMI $\geq$30 kg/m^2" category (n=92). No multiplicity was adjusted for the subgroup analysis, and the results are from a post hoc analyses. Although the subgroup analyses generally support the primary efficacy endpoint, these findings warrant further analyses when the week 96 data are available from FLAIR or when the data from other CAB+RPV trials are submitted (ATLAS-2M).

7. Risk And Risk Management

As outlined in Section 3.1, several potential risks were identified for CABENUVA. Risks or potential risks related to AEs were identified primarily through the AEs of special interest (AESI) list, including:

- Injection reactions
- Hypersensitivity reactions and rash
- Hepatobiliary events
- Psychiatric events (including depressive disorders)
- Neurologic events (including seizure)
- GI events (including pancreatitis)
- Musculoskeletal events related to injection or rhabdomyolysis
- Weight gain
- Pregnancy and risk of embryo-fetal toxicity

After completing the interdisciplinary analysis and review, the team identified several risks that warranted additional discussion as review issues. These risks are discussed in detail in Section

7.7. The issues were selected because of their importance in contributing to the safe (and effective) use of the product or are novel issues for HIV prescribers. Additionally, factors unique to certain patient populations such as women of childbearing potential (WOCBP) and patients who are less likely to adhere to or comply with CABENUVA dosing schedule were considered when identifying the review issues.

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

7.1.1. Potential Risks or Safety Concerns: CAB

The CAB nonclinical safety studies included good laboratory practice (GLP) repeat-dose toxicology studies in mice, rats, and monkeys; reproductive and developmental toxicology studies in rats and rabbits; in vitro and in vivo safety pharmacology and genotoxicology studies; and 2-year carcinogenicity studies in mice and rats. Overall, the nonclinical safety assessment for CAB was considered acceptable to support marketplace approval from a pharmacology/toxicology perspective. All pertinent studies and findings are summarized in the following section. Full reviews for all studies are located in Section III.13.1.

Pharmacology and Pharmacokinetics

In a panel of enzymes, receptors, ion channels, transporter binding sites, and isolated tissues, CAB was shown to inhibit the MC4R. This receptor is involved in the regulation of energy homeostasis, blood pressure, glucose and lipid homeostasis, and reproductive activity, and MC4R mutations and antagonism can promote weight gain and obesity.[5,6]

Cardiovascular safety pharmacology assessments were conducted in a hERG assay; a cardiovascular function study in monkeys; and in the 2-week, 4-week, and 39-week repeat-dose studies in monkeys. An IC_{50} was not identified in the hERG assay. Increases in heart rate and mean arterial pressure were observed at 1,000 mg/kg up to 2 hours postdose in the cardiovascular function study, but no drug-related effects on these parameters were observed in the general toxicology studies up to the highest doses tested. Respiratory parameters were evaluated in a rat respiratory function study, and neurobehavioral parameters were evaluated in the 2-week repeat-dose toxicology study in rats. No drug-related findings on these parameters were observed in these studies up to the highest doses tested.

Numerous in vitro and in vivo studies were conducted to evaluate the PK of CAB. Single-dose absorption studies utilizing oral, subcutaneous, and IM formulations of CAB were conducted in mice, rats, dogs, and monkeys. CAB oral bioavailability in dogs and monkeys was 56% to 63% when administered by gavage and was 3% to 8% when administered by oral capsule. Serum half-life was approximately 5 hours when administered orally, but was extended to 8 to 12 days when administered intramuscularly. In rats, CAB exposures were generally about 20% higher in females than in males after repeated dosing and increased in a less-than-dose-proportional manner in both sexes in all species tested. Plasma protein binding of CAB was very high (≥99.3%) in rats, dogs, monkeys, and humans. In a rat tissue distribution study, CAB distributed to most tissues within 1 hour of oral dosing and remained detectable by day 28 postdose. Drug was detected in all tissues examined, but highest levels were detected in the blood, lung,

bulbourethral gland, renal medulla, adrenal medulla, and skin. Very small amounts were also detected in the brain, indicating that low levels of CAB cross the blood–brain barrier. CAB was also detected in fetal tissue in an investigative toxicokinetic (TK) study in pregnant rats. Metabolism studies identified the glucuronide metabolite of CAB to be the primary metabolite formed in all species tested (mice, rats, and monkeys). Additional metabolites, formed at much lower levels, include products of glucose and cysteine conjugation, oxidation, and glutathionylation. All human metabolites were present in the species selected for the nonclinical safety studies. Excretion of CAB occurs primarily via the feces in mice, rats, and monkeys, with minor amounts also excreted in the urine and bile in monkeys. A dedicated lactation study with CAB was not conducted, but TK data from F_1 pups on postnatal day (PND) 10 in the rat pre- and postnatal development (PPND) study demonstrated that CAB is present in the milk.

General Toxicology

Pivotal repeat-dose toxicology evaluations for CAB included GLP studies of up to 26 weeks duration in rats and 39 weeks duration in monkeys. Additional GLP studies of up to 13 weeks duration were conducted in mice to support the 2-year mouse carcinogenicity study. These species were considered appropriate based on the PK studies described above. All studies were conducted using the oral formulation of CAB, with the exception of a 3-month bridging study in rats using the subcutaneous and IM routes.

In rats, no adverse, drug-related findings were observed up to the highest doses tested in the 2-week, 4-week, and 26-week studies. Gastrointestinal (GI) findings consisting of minimal mixed cell inflammation and hemorrhage, and minimal to slight increased apoptosis in the squamous mucosa in the stomach were observed at the high dose of 1,000 mg/kg/dose in the pivotal 6-month study. However, as these were primarily minimal findings with no associated changes in body weight or food consumption, these changes were considered nonadverse. Exposure multiples at the no observed adverse effect levels (NOAELs) in the 2-week, 4-week, and 26-week rat studies are 19.8, 25.6, and 27.3, respectively. In the 3-month subcutaneous/IM rat study, adverse findings were limited to ISRs. The exposure multiple at the NOAEL for a once-monthly IM injection is 10.3.

In monkeys, no adverse findings were observed up to the highest doses tested (500 mg/kg/dose) in the 4- and 39-week studies. In the 1- and 2-week monkey study, however, emesis decreased food consumption with associated weight loss; and histopathology findings in the stomach, colon, and small intestines (minimal to moderate degeneration/regeneration, inflammation, and villous atrophy) were observed at 1,000 mg/kg/dose. Three males at this dose in the 2-week monkey study were also euthanized prematurely 4 hours postdose on day 14 due, in part, to these findings. The exposure multiples at the NOAELs in the 2-week, 4-week, and 39-week monkey studies are 1.6, 6.2, and 3.7, respectively.

No adverse findings in mice were observed up to the highest dose tested in the 2-week study. In the 13-week mouse study, however, adverse findings were limited to decreased body weight at the high dose. Exposure multiples at the NOAELs for the 2- and 13-week mouse studies are 17.7 and 9.2, respectively.

In addition, two single-dose studies were conducted in rats and monkeys in which 10 mg/kg CAB and 60 mg/kg RPV were administered intramuscularly in combination. Assessments of

local tolerance were not conducted with the combination because both drugs were administered as separate injections in two locations, but no clear additive or synergistic systemic toxicities were observed following coadministration. Because CAB and RPV will be administered clinically as two separate IM injections in separate locations, the coadministration of these two drugs in humans was considered acceptable from a pharmacology/toxicology perspective.

Genotoxicology and Carcinogenicity

CAB was negative for mutagenesis and clastogenicity in the in vitro bacterial reverse mutation assay and the in vivo micronucleus assay in rats. A 3-fold increase in mutant frequency was noted in a non-GLP in vitro mouse lymphoma assay in the absence of S9 only, but no drug-related changes were observed in a subsequent GLP in vitro mouse lymphoma assay. As a result, CAB was also considered negative in this assay. Two-year carcinogenicity studies were conducted in mice and rats. In mice, no drug-related increases in tumor incidence were observed up to 75 mg/kg/dose in males and 35 mg/kg/dose in females (8× [males] and 7× [females] higher than human exposure at the proposed human dose). In rats, no drug-related increases in tumor incidence were observed up to 75 mg/kg/dose (26× higher than human exposure at the proposed human dose).

Reproductive and Developmental Toxicology

Reproductive toxicology studies with CAB consist of a male fertility study in rats, a combined female fertility and embryo-fetal development study in rats, an embryo-fetal development study in rabbits, and PPND studies in rats. No drug-related effects on fertility parameters were observed in either sex up to 1,000 mg/kg/dose (20.2×[males] and 27.9× [females] higher than human exposure at the proposed human dose). In the combined rat fertility and embryo-fetal development study, a 6% decrease in fetal body weight was observed in the absence of maternal toxicity at 1,000 mg/kg/dose (27.9× higher than human exposure at the proposed human dose), but this was considered nonadverse due to the low magnitude of the change. No adverse, drug-related effects on embryo-fetal development were observed in rats at 1,000 mg/kg/dose (27.9× higher than human exposure at the proposed human dose).

In the rabbit embryo-fetal development study, a membranous ventricular septal defect in the heart was observed in 3/151 fetuses (1.99%) across 3/21 litters (14.29%) at the low dose, 1/159 fetuses (0.63%) in 1/21 litters (4.76%) at the mid-dose, 5/140 fetuses (3.57%) across 5/21 litters (23.81%) at the high dose, and no fetuses/litters in the control group. The increase at the high dose was also statistically significant. The historical control data from the conducting laboratory state that this malformation was observed in 15/1,942 fetuses (0.77%) across 14/295 litters (4.75%), suggesting that the high-dose finding is above historical control ranges. However, the historical data also indicates that this malformation was observed in up to four affected fetuses in four litters. In addition, an independent analysis of the background incidence of embryo-fetal developmental parameters in rabbits[7] specifies that this is a common finding in this strain (Dutch Belted rabbits), with a 30.2% chance of occurring in ≥2 out of 22 litters. As a result, this finding was considered incidental and unrelated to treatment. No drug-related effects on rabbit embryo-fetal development were observed up to 2,000 mg/kg/dose (0.7× the human exposure at the proposed human dose).

In the pivotal rat PPND study, an increase in the number of F_1 stillbirths and early postnatal deaths by PND 4 was observed at 1,000 mg/kg/dose (27.9× higher than human exposure at the proposed human dose). A slight increase in parturition time in the F_0 animals was also detected at this dose (22.7 days versus 22.2 days in controls), and no milk was present in the stomachs of some F_1 pups that died early, but it is unclear from the data if either of these factors contributed to the early F_1 pup deaths. In addition, CAB was detected in the serum of the F_1 pups on PND 10, indicating that drug is present in milk, but it was also unclear in this study if the decreases in F_1 pup viability were due to exposure during gestation or lactation. No drug-related effects on rat PPND were observed at 5 mg/kg/dose (13.4× higher than human exposure at the proposed human dose).

To determine if the increased F_1 pup deaths were due to CAB exposure during gestation or lactation, an investigational rat PPND study was conducted. In this study, similar incidences of stillbirths and early postnatal deaths were observed when rat pups born to CAB-treated dams were nursed from birth by control dams. There was no effect on neonatal survival of control pups nursed from birth by CAB-treated dams. The duration of gestation was also increased in the CAB-treated dams, with the majority of treated dams delivering on gestation day (GD) 23 rather than 22. Most stillbirths and early F_1 pup deaths, particularly those that occurred within a few hours of delivery, occurred in litters delivered on GD 23. Lastly, an investigative TK study in pregnant rats was conducted to determine if CAB accumulates in the fetus after repeat dosing and if the early neonatal deaths were due to increased fetal CAB exposures. Fetal CAB tissue concentrations increased proportionally to maternal plasma levels but did not accumulate substantially within fetal tissues with repeat dosing. Further, no correlation was seen between higher fetal drug exposures and an increased likelihood of stillbirth or early postnatal death.

Additional Toxicology Studies

CAB was negative for immunosuppression in a T-cell–dependent antibody response (TDAR) study in rats, and was not associated with skin sensitization, skin irritation, ocular irritation, or phototoxicity. An in vitro folate transporter and receptor-binding study showed no meaningful inhibition of the proton-coupled folate transporter (PCFT) or RFC up to 100µM CAB. Folate receptor α was inhibited 36.7% at 25.8µM CAB only, and an IC_{50} was not determined. Additional nonclinical studies evaluating the effect of CAB on the folate pathway are ongoing.

Exposure Multiples

Exposure multiples, based on a proposed human dose of either 30 mg once daily (oral) or 400 mg once monthly (IM), are presented in Table 17.

Table 17. Cabotegravir Exposure Multiples

Study	NOAEL (mg/kg/dose)	Adverse Findings	Nonclinical AUC (µg·hr/mL)	Exposure Multiple[a]
Repeat-dose studies (oral)				
2-week mouse	1000	None	2,586.5[c]	17.7
13-week mouse	75	Weight loss	1,345[d]	9.2
2-week rat	300	None	2,893.7[c]	19.8
4-week rat	1000	None	3,735[e]	25.6
26-week rat	1000	None	3,992[f]	27.3
2-week monkey	25	Weight loss, gastrointestinal effects, immunosuppression	232.2[c]	1.6
4-week monkey	500	None	902.5[e]	6.2
39-week monkey	500	None	547[g]	3.7
Repeat-dose studies (intramuscular, once monthly)				
3-month rat	10	Injection site reactions	25467.5[h]	10.3[b]
Carcinogenicity studies				
2-year mouse	75/35[i]	None	1140/1060[i,f]	7.8/7.3[i]
2-year rat	75	None	3820[f]	26.2
Reproductive toxicology studies				
Fertility and early embryonic development				
Rat	1000/1000[i]	None	2958/4079[i,j]	20.3/27.9[i]
Embryo-fetal development				
Rat	1000/1000[k]	Fetal weight loss	4079/1951[k,j]	27.9/27.9[k]
Rabbit	500/2000[k]	Maternal weight loss and decreased food consumption	47.4/96.1[k,l]	0.3/0.7[k]
Pre- and postnatal development				
Rat	1000/5[m]	Increased stillbirths and neonatal deaths by PND 4, increased gestation time	4079/1951[m,j]	27.9/13.4[m]

[a] Based on mean steady-state exposures in healthy human volunteers receiving 30 mg once daily oral cabotegravir (AUC_{0-24h}r =146 µg•hr/mL), unless otherwise noted
[b] Based on mean steady-state exposures in healthy human volunteers receiving 400 mg once monthly cabotegravir intramuscular injection (AUC_{0-t} =2461 µg•hr/mL)
[c] Day 14 data
[d] Week 13 data
[e] Day 28 data
f Week 26 data
[g] Week 39 data
[h] Day 91 data
[naïve] Presented as "male/female"
[j] Male and female exposure data are from the 26-week rat study (study #RD2009/00031, week 13 data)
[k] Presented as "maternal/embryo-fetal"
[l] Gestational day 11 data
[m] Presented as "maternal/pre- and postnatal"
Abbreviations: NOAEL = no observed adverse effect level, PND = postnatal day

7.1.2. Potential Risks or Safety Concerns: RPV

Nonclinical toxicology studies to support oral RPV were reviewed under NDA 202022, including pharmacology (primary and secondary), safety pharmacology, repeat dose, genotoxicity, and developmental and reproductive toxicology, as well as carcinogenicity studies. These studies also support the RPV LA formulation because the clinical exposure associated with oral RPV is similar to that obtained with RPV LA via IM administration. As such, studies to

support the RPV LA formulation included pivotal local tolerance studies in dogs and minipigs, as well as PK studies via IM administration. Summaries of studies conducted under NDA 202022 are provided below, as well as reviews and summaries for pivotal studies that pertain to the LA formulation. Reviews for the nonclinical safety studies summarized below for RPV LA are located in Section III.13.2. The main findings in pivotal local tolerance studies in dogs and minipigs via IM injection of RPV LA were injection site findings, which have been characterized in human subjects and are monitorable.

Pharmacology and Pharmacokinetics

The secondary pharmacodynamic effects of RPV were investigated in in vitro and in vivo studies under the original oral RPV NDA 202022. RPV did not cause in vitro inhibition of α- or β-adrenergic, dopaminergic, muscarinergic, serotonergic, opioid, interleukin, or chemokine receptors (up to 10μM, 3.7 μg/mL), or human DNA polymerase α, β, or γ (up to 1000μM, 366 μg/mL). The effects of oral RPV on a core battery of safety pharmacology parameters were evaluated in a series of in vitro and in vivo studies. For the safety pharmacology study results, please refer to the original NDA for the oral RPV formulation (NDA 202022). Briefly, no adverse effects of RPV on the cardiovascular, respiratory, or central nervous systems were noted during initial safety pharmacology studies.

Absorption was examined in rabbits and minipigs. Limited distribution studies were conducted in rabbits and rats. Excretion studies and in vivo and in vitro metabolism studies with RPV, as well as the enzymes involved in the metabolism of RPV in the human hepatocytes and enzyme induction and inhibition studies, have been described in detail in the original NDA for oral RPV under NDA 202022. In minipigs and rabbits, after a single IM administration of RPV LA as the final P338-containing formulation (G001), RPV release was fast—with a C_{max} reached within 24 h in minipigs and slower in rabbits, after which mean plasma concentrations declined, remained fairly constant thereafter, and were still quantifiable after 3 months.

Protein binding and distribution in blood cells has been described in detail in the original NDA 202022 for oral RPV. In short, serum protein binding of RPV was above 99% for all species tested (including humans) over a wide range of concentrations. In a rat distribution study with RPV LA, the highest exposures were measured in left popliteal and medial iliac lymph nodes, adjacent to injection site with tissue/plasma $AUC_{0\text{-day}42}$ ratios of 12,203 and 2,256, respectively. The tissue/plasma $AUC_{0\text{-day}42}$ ratios were lower than 1 in brain, heart, spleen and thymus.

General Toxicology Studies

Pivotal studies evaluating the final G001 clinical formulation (TMC-LA or RPV LA at 300 mg/mL in P338 at 50 mg/mL) with IM administration were conducted in dogs (4-week bridging study) and minipigs (6-week and 9-month studies). There were no nonclinical safety issues of significant concern. The main findings in these studies were injection site findings (swelling, erythema, inflammation, white deposits) that in some cases persisted during the study. However, injection site findings have been observed and characterized in human subjects and are monitorable.

Testicular immaturity in the 9-month minipig study with the LA formulation (IM administration) was also observed in the oral dog toxicology study under NDA 202022 and was associated with an inhibitory effect on steroidogenesis. Steroidogenesis effects have not been observed in humans. The phase 3 clinical data for oral RPV (NDA 202022) indicated that 21-hydroxylase was not affected by treatment with RPV. However, there was a small mean decrease in basal cortisol levels, and the cortisol response to ACTH stimulation was attenuated. Because HIV-1–infected patients are an at-risk population for adrenal insufficiency, the label includes information with regards to the potential effect of RPV on adrenal function.

Genotoxicology and Carcinogenicity

RPV genotoxicity and carcinogenicity studies were previously reviewed under NDA 202022. RPV has tested negative in the absence and presence of a metabolic activation system in the in vitro Ames reverse mutation assay and the in vitro clastogenicity mouse lymphoma assay. RPV did not induce chromosomal damage in the in vivo micronucleus test in mice.

Two-year carcinogenicity studies in mice and rats were conducted with RPV. In mice, RPV was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. At the lowest tested dose in the mouse carcinogenicity study, the systemic exposure to RPV was 21× that observed in humans at the recommended human dose (RHD). In rats, no drug-related increases in tumor incidence were observed up to RPV exposures approximately 3× higher than those in humans at the RHD.

Reproductive and Developmental Toxicology

RPV reproductive and developmental toxicology studies were previously reviewed under NDA 202022. No adverse developmental outcomes were observed when RPV was administered orally at exposures up to 15× (rats) and 70× (rabbits) the exposure in humans at the RHD. In a PPND study, RPV was administered orally up to 400 mg/kg/day through lactation. No adverse effects were noted in the offspring at maternal exposures up to 63× the exposure in humans at the RHD. Animal lactation studies with RPV have not been conducted. However, RPV was detected in the blood of nursing pups on lactation day 7 in the rat PPND study

Additional Toxicology Studies

RPV LA did not show irritating properties in vitro and was not a skin sensitizer.

Embryofetal toxicity studies were conducted in the rat and rabbit with Poloxamer 338 in order to qualify the novel excipient. No adverse developmental outcomes were observed.

Exposure Multiples

Exposure multiples, based on a proposed human dose of either 30 mg once daily (oral) or 600 mg once monthly (IM), are presented in Table 18.

Table 18. Rilpivirine Exposure Multiples

Study	NOAEL (mg/ dose)	Adverse Findings	Nonclinical AUC (ng·hr/mL)	Exposure Multiple[a]
Repeat-dose studies (IM injection)				
4-week dog	1200	None	422,500[b]	6.4
9-month minipig	600	None	1345[c]	0.72

[a] Based on human individual post hoc estimates from the final population, PK models for subjects enrolled in phase 3 studies (IM injection; AUC_{tau} =65,603 ng·hr/mL)
[b] Day 15 gender average value AUC_{0-600h}
[c] Day 224 gender average value AUC_{0-672h}
Abbreviations: IM = intramuscular, NOAEL = no observed adverse effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The potential safety concerns for CAB were initially based on the clinical experiences with approved INSTI products. Serious adverse reactions associated with INSTIs include hypersensitivity reactions (HSRs), hepatotoxicity, depressive disorders (including suicidal ideation, attempt, behavior, or completion), anxiety, and weight gain. Dolutegravir, a structurally similar INSTI to CAB is also associated with NTDs when used at the time of conception and early in pregnancy.

Oral RPV is an approved product, and the potential risks and safety concerns are based on previously reviewed clinical trial data and postmarketing reports for EDURANT or RPV-containing products. RPV is associated with serious adverse reactions such as HSRs, depressive disorders, and hepatotoxicity. These risks are generally consistent with the NNRTI drug class.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Severe skin and HSRs have been reported during the postmarketing experience with RPV-containing regimens, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms.

7.4. FDA Approach to the Safety Review

Predefined Safety Analysis Plan and Definitions

In summary, the prespecified safety analysis plan and definitions were reviewed during the protocol development and were acceptable to the clinical review team.

Use of descriptive statistics was predefined in the protocol for summarizing the safety outcomes. The review team was in agreement with the proposed approach. Additionally, the use of incidence (cumulative risk calculation based on proportion) to compare differences between the treatment group and the control groups was found acceptable. Calculating events incidence rate were not necessary because the exposure duration (patient-time) was similar between the two trials and across the treatment arms. Weighted safety analysis was not necessary because the two trials were similar in design and similar in sample size.

The Applicant translated verbatim terms to Medical Dictionary for Regulatory Activities preferred terms (PTs) for the events reported in both trials. The translations were reviewed and found acceptable.

The protocol specified use of the Division of Acquired Immunodeficiency Syndrome (DAIDS) toxicity scales for grading AEs.[8]

An IDMC was used to evaluate the safety and tolerability; and was used to identify unexpected safety issues early in the trial. Additionally, an adjudication committee was established to assess liver-related AEs.

AEs were protocol-defined as: "An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product."

Treatment-emergent AEs (TEAEs) were defined in the Applicant's analysis, and for the purpose of this review, as any AE that occurred on or after the day of treatment initiation.

Adverse drug reactions (ADRs) were defined for the purpose of this review as any TEAE considered by the investigator as related to the study drug within reasonable possibility.

AESI were determined for CAB and RPV based on preclinical and clinical experience, along with information for the INSTI and NNRTI drug classes.

Serious AEs (SAEs) were protocol-defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization (except for elective treatment of a pre-existing condition that did not worsen at baseline)
- Results in disability/incapacity
- Is a congenital anomaly/birth defect
- Other situations, including medical/scientific judgement or events that require invasive treatment (e.g., convulsions) that do not result in hospitalization
- Is associated with liver injury and impaired liver function defined as:
  - ALT ≥3× ULN and total bilirubin ≥2× ULN (>35% direct), or
  - ALT ≥3× ULN and international normalized ratio >1.5.

Data Used for Clinical Safety Assessment

Data from the two phase 3 trials (up to the week 48 window period) were utilized as the primary safety source during the review.

The Applicant submitted a 60-day SUR on 27 June 2019. The SUR included a summary for new deaths, SAEs, AEs leading to withdrawal, discontinuations due to liver events, and pregnancies. The SUR includes data received up to and including the submission date of this original NDAs (29 April 2019).

As part of the safety assessment for CAB+RPV, prescribing information for RPV-containing products were reviewed. Additionally, to assess the unique safety profile of CAB when co-administered without RPV, the safety of oral CAB was evaluated from the phase 2 clinical trials—LATTE and LATTE-2. The following sources of safety data were also reviewed.

- Blinded IND safety reports from ongoing phase 3 HIV-1 prevention trials (HPTN 083, HPTN 084) in HIV uninfected subjects
- Safety reports from the ongoing HPTN 083 trial describing seizure-like events. The cases were unblinded to help discern CAB exposure and risk of seizure events.
- Safety reports from an ongoing phase 3b trial (ATLAS-2M) in treatment-experienced but virologically suppressed HIV-1–infected subjects.

Reviewer's Approach to Safety Evaluation

Data from the two phase 3 trials (up to the week 48 window period) were analyzed both individually and pooled to describe and support the safety of CAB+RPV in HIV-1–infected subjects. Except for HIV treatment history at the time of enrollment, the two trials were otherwise nearly identical, conducted concurrently, and had similar patient demographic and baseline characteristics, allowing for pooling of the trials. Thus, the safety analyses are presented with pooled data for CAB+RPV treatment group and compared to the individual control groups. The pooled results for the control groups are also be highlighted in text when necessary.

The data from FLAIR and ATLAS control groups were evaluated individually (and pooled) to highlight differences in AE reporting incidence between the two control groups. The control groups were also analyzed individually and compared to CAB+RPV treatment groups. Historically, in HIV-1 switch design trials, AEs are reported more frequently in the treatment (or investigational) group compared to the control group because subjects in the treatment group are exposed to a new drug regimen while subjects in the control group continue on their current ARV regimen with the benefits of established tolerance. The ATLAS trial-enrolled subjects were on their current stable regimen for months or years prior to enrollment and are randomized to continue on CAR or switch to CAB+RPV. Subjects in the CAR treatment group are therefore less likely to experience new ADRs, especially in the initial weeks to months of study treatment. As described in Section 6.3.1, the FLAIR trial design—while a switch trial design— first enrolled treatment-naïve subjects into the induction phase where all subjects were treated with ABC/DTG/3TC for 20 weeks before entering the maintenance (switch) phase. Therefore, at the start of the maintenance phase, subjects in the FLAIR control group were exposed to ABC/DTG/3TC for a relatively short period (~20 weeks) compared to subjects in the ATLAS control group. Hence, the incidence of cumulative AEs in the FLAIR control group may be higher compared to the ATLAS control group.

Clinical trial data were independently analyzed in Jreview and Python v3.7. All safety assessments and conclusions are those of the clinical review team unless otherwise specified.

The review team did not identify any major data quality or integrity issues that preclude performing a safety review. No major issues were identified with respect to recording, coding, and categorizing AEs.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for comprehensive safety assessment of CAB+RPV for the proposed indication, patient population, dosage regimen, and duration. The data meets the minimum required sample size of 300 to 500, as outlined by FDA's Guidance for industry *Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* (November 2015).[2] The treatment development program includes a total of 1,590 patients dosed with oral or injectable CAB. This includes the two pivotal phase 3 trials, two phase 2 studies, and 509 subjects enrolled across the phase 1 or clinical pharmacology studies. Five hundred and ninety-one (591) subjects received at least 1 dose of CAB+RPV across the phase 3 trials, of which 283 subjects were from the FLAIR trial and 308 subjects were from the ATLAS trial. Table 19 summarizes the exposures periods for the two, phase 3 trials. The data cut-off for FLAIR and ATLAS were 30 August 2018 and 29 May 2018, respectively. Longer-term data from FLAIR are expected.

Table 19. Duration of Exposure, Safety Population- Trials FLAIR and ATLAS

	FLAIR		ATLAS		POOLED	
Parameter	CAB+RPV N=283	ABC/DTG/ 3TC N=283	CAB+RPV N=308	Current ART N=308	CAB+RPV N=591	Control N=591
Duration of treatment (weeks)						
Mean (SD)	57 (12)	58 (12)	51 (10)	51 (6)	54 (11)	54 (10)
Median (min, max)	57 (4, 73)	58 (4, 73)	53 (1, 60)	52 (6, 56)	54 (1, 73)	52 (4, 73)
Number of subjects treated, by duration, n (%)						
Any duration (at least 1 dose)	283(100%)	283 (100%)	308 (100%)	308 (100%)	591(100%)	591(100%)
<4 weeks	2(<1%)	0	2 (<1%)	0	4(<1%)	0
≥12 weeks	277 (98%)	277 (98%)	303 (98%)	306 (99%)	580 (98%)	583 (99%)
≥24 weeks	272 (96%)	270 (95%)	291 (94%)	300 (97%)	563 (95%)	570 (96%)
≥48 weeks	271 (96%)	256 (90%)	284 (92%)	294 (95%)	549 (93%)	550 (93%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADEX datasets; Phyton
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SD = standard deviation

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

The safety evaluation for CAB+RPV was adequate, and the demonstrated safety profile of CAB+RPV in the virologically suppressed HIV-1–infected population is acceptable for the indicated doses and population studied. No clear pattern with respect to the reported deaths suggests a specific safety concern. Incidence of drug discontinuation due to AEs were low without a clear pattern of association with a specific event, PT, or system organ class (SOC). The most commonly reported treatment-emergent ADRs without regard to severity, and occurring in at least 2% among CAB+RPP-treated subjects, were ISRs, pyrexia, fatigue, headache, musculoskeletal pain, rash, nausea, and sleep disorder. Our safety assessments, based on the data reviewed, are summarized in the following subsections.

7.6.1. Overall Adverse Event Summary

Summary of the TEAEs in FLAIR and ATLAS through 48 weeks is presented in Table 20. The incidences of TEAEs and ADRs were higher in the CAB+RPV treatment group compared to the controls. Overall, 561 (95%) subjects in the CAB+RPV treatment group, 225 (80%) subjects in the ABC/DTG/3TC treatment group, and 220 (71%) subjects in the CAR group experienced at least 1 TEAE. As mentioned in Section 7.4, one possible reason for the higher incidence of AEs in the CAB+RPV treatment group is due to the disproportionately shorter time on the randomized treatment.

While AEs were more commonly reported in the CAB+RPV treatment group, SAEs and discontinuation due to AEs were relatively uncommon and similar between treatment groups. No death occurred in the CAB+RPV treatment group during the maintenance period.

Exposure–response analyses conducted for certain AEs demonstrated that CAB and RPV exposures did not differ between subjects with or without anxiety, depression, pancreatitis, pyrexia, sleep disorder, and weight gain (Section III.14.2.4).

Table 20. Overview of Adverse Events,[1] Controlled Trial Safety Population, Trial Name(s), Time Studies

	FLAIR		ATLAS		Pooled	
Adverse Event	CAB+RPV (N=283)	ABC/DTG/ 3TC (N=283)	CAB+RPV (N=308)	Current ART (N=308)	CAB+RPV (N=591)	Control (N=591)
Any subject with AE	267 (94)	225 (80)	294 (95)	220 (71)	561 (95)	445 (75)
Grade 3/4	31 (11)	11 (4)	35 (11)	24 (8)	66 (11)	35 (6)
Treatment-related	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)
Treatment-interruption						
Grade 3/4 and treatment-related	14 (5)	0	14 (5)	1 (<1)	28 (5)	1 (<1)
AEs leading to withdrawal	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)
SAE	18 (6)	12 (4)	13 (4)	14 (5)	31 (5)	26 (4)
SAEs and treatment-related	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Death	0	0	0	1 (<1)	0	1 (<1)
Death related to treatment	0	0	0	0	0	0

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets
[1] Includes treatment-emergent AE as defined in Section 7.5
[2] DAIDS toxicity grades.
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, AE = adverse event, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

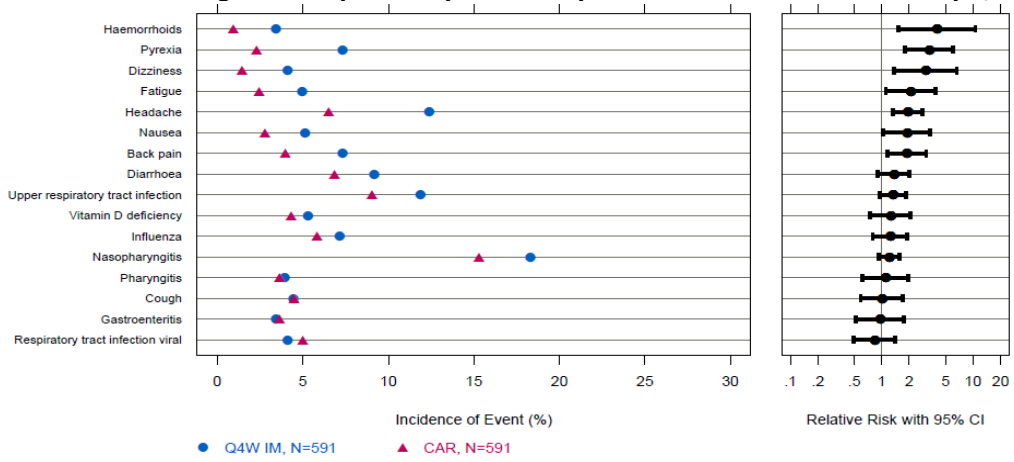
TEAEs with at least 3% incidence in the CAB+RPV treatment group (regardless of causality or severity) are summarized in Table 171 under Section III.17.5.

The Applicant conducted relative risk assessments for common AEs. As discussed in the Applicant's statistical analysis plan, safety signals were classified into a three-tier system to assess risk differences between treatment groups. Tier 2 events are those defined as commonly reported events without prespecified hypothesis. The statistical analysis plan stated that all tier 2 safety signals will be identified as those with at least 5% incidence in any of the treatment groups. Relative risk ratio was then calculated for these tier 2 events. The use of 5% cut-off is reasonable to allow noise reduction, if the purpose is to assess the relative risk differences for common AEs between treatment groups. The figure below summarizes the relative risk ratios

with 95% CI for AEs with incidence of at least 5% (i.e., cumulative or proportion risks). Note the analysis excludes ISR because the risk for ISR is not applicable to the control treatment groups.

AEs with increased risk of occurring with CAB+RPV exposure during the 48 weeks of treatment include ISR (not included in figure below), hemorrhoids, pyrexia, dizziness, fatigue, headache, nausea, back pain, diarrhea, and upper respiratory infection. Note, with the exception of hemorrhoids and upper respiratory infection, these AEs were also identified as treatment-related. These terms are captured in the United States Prescribing Information (USPI), either in the ADR table, the Injection Reactions section, or the Less Common Adverse Reactions section. The number of subjects with hemorrhoids was 20 (3%) and 5 (<1%) for the CAB+RPV and control group treatment groups, respectively. This higher incidence of hemorrhoids in the CAB+RPV treatment group was driven by the FLAIR trial. The incidence in the FLAIR and ATLAS trials for CAB+RPV and control groups were 16 (6%), 3 (1%) and 4 (1%), and 2 (<1%), respectively. The imbalance between the two trials suggests the finding is likely due to chance. While upper respiratory infection was reported more frequently in the CAB+RPV treatment group, "respiratory tract infection viral" was reported more frequently in the control group, suggesting an unlikely biological plausibility for the observed imbalance.

Figure 25. Relative Risk Summary for Treatment-Emergent Adverse Events* During Maintenance Period for Cabotegravir+Rilpivirine (CAB+RPV) and Control Treatment Groups, Pooled



Source: Applicant's analysis; ISS page 35
*Common adverse events are those reported with ≥5% in any treatment groups.
*Display excludes ISR events, since it is not applicable to CAR
Abbreviations: CAR = current antiretroviral, CI = confidence interval, IM = intramuscular, Q4W = every 4 weeks,

Lastly, for AESI, discussed in Section 7.6, exposure–safety analyses were also conducted. No relationship was established between exposure and the various AESI. Refer to Section III.14.2.4 for details on the exposure–safety analyses.

Adverse Events, Including ADRs, During the OLI Dosing Period

As previously discussed in Section 3, during the development program the Applicant included an OLI as part of CAB+RPV regimen to allow assessment of safety events (such as HSR and hepatotoxicity) prior to switching to the extended-release CAB+RPV injectables.

Overall, 187 (32%) subjects experienced at least one AE. Nasopharyngitis, headache, and vitamin D deficiency were among the most commonly reported AEs. SAEs were reported in four subjects and included enterocolitis, pyrexia, “abortion missed,” and hepatitis A. None were considered treatment-related. A total of six subjects discontinued treatment prior to switching to the extended-release formulation, but none were related to HSR or hepatotoxicity (nonviral). The events include asthenia, myalgia, ‘depression, suicide,’ and headache. Treatment-related events, or ADRs, were reported in 7% of CAB+RPV-treated subjects compared to 6% of the subjects in the comparator groups. The events in the CAB+RPV treatment group were depressive disorders; anxiety; GI events such as dyspepsia, nausea, vomiting, and diarrhea, fatigue, headache, and sleep disorders. No treatment-related hepatotoxicity or HSRs were reported. For details, refer to Section III.17.9.1

In summary, the objective of the OLI was to assess for short-term safety of CAB and RPV, particularly for hepatotoxicity and HSR, prior to the introduction of an extended-release injectable CAB+RPV. Most subjects tolerated CAB and RPV during the OLI dosing phase, and none discontinued due to HSR or drug-related hepatotoxicity. Few SAEs were reported, and no subject discontinued due to an ADR. Future dosing regimens may be considered without OLI once larger data from the ongoing ATLAS-2M is submitted by the Applicant for review. The ATLAS-2M includes a non-OLI trial design.

7.6.2. Deaths

No deaths were reported for CAB+RPV treatment group during the maintenance period. Five deaths were reported among CAB+RPV-exposed subjects across the phase 2 and 3 trials up to the original NDA data cut-off. An additional death was reported from an ongoing phase 3b trial after the original NDA data cut-off.

All deaths were considered by the investigators to be unrelated to study drug except for a case of myocardial infarction in a phase 2b trial where the investigator could not rule out the possibility of relationship to study drug.

After reviewing the case narratives, the clinical team could not rule out the possibility that three deaths were treatment-related. The deaths are due to cardiopulmonary arrest (secondary to acute pancreatitis), refractory seizure, and road traffic accident, summarized below and further discussed under Section 7.6.6 and Section III.17.9.2. For narratives on cases not highlighted here, refer to Section III.17.1.

Table 21. Summary of Deaths, Pooled Data Across Drug Development, Cabotegravir+Rilpivirine (CAB+RPV) Treatment Group

SID Age/Sex Trial	Assessment of Causality[1] (Y/N) Investigator	Applicant	Reviewer	Summary of Event
45/M Phase 3b (ATLAS-2M)	Possibly related	Not related	Possibly related	Complication from acute pancreatitis After being on treatment for approximately 74 weeks, the subject, while on travel to Japan, presented with severe abdominal pain and was diagnosed with acute severe pancreatitis. He was admitted to the ICU and experienced cardiopulmonary arrest shortly thereafter. Imaging showed bilateral cerebral infarcts and PRES; EEG showed slow waves and low brain activity; CSF was normal. He subsequently developed focal seizures and eventually succumbed to death. Concomitant medications included statin for lowering lipids. He also had past history of gallstone, requiring intervention (ERCP). At the time of the ERCP procedure, he experienced pancreatitis. Comment: *While the statin could be a contributing factor leading to acute pancreatitis, the subject had been on statin longer than CAB+RPV. Therefore, one could argue that CAB+RPV is just as likely related to the event. Additionally, the history of pancreatitis appears to be procedure-related, hence patient lacks a true history of medical pancreatitis.*
37/M Phase 2 (200056; LATTE-2)	Not related	Unlikely related	Unlikely related but cannot exclude causality	Refractory epilepsy Subject had been on the study for ~48 weeks without significant AEs. Approximately 48 weeks after the initial CAB dose and 32 weeks after initial RPV dose, he developed acute onset status epilepticus lasting for ~6 hours while alone in his home, leading to anoxic brain injury and death. Neighbors heard a 'weird' noise from the apartment of the subject starting at noon on the date of the event. Because the noises were continuing, they called the fire department at 6:30PM. EMT found the subject unconscious, Glasgow score at 3, with generalized tonic-clonic seizures and hypoxia. There was no evidence of trauma or suggestion of drug intoxication. Of note, while social history suggested recreational drug use, the only drug detected on urine and serum toxicology screening was papaverine. No autopsy was conducted. Comment: *The narrative does not provide evidence for alternative cause of seizure. Therefore, drug-related event cannot be ruled out.*

SID Age/Sex Trial	Assessment of Causality[1] (Y/N) Investigator	Applicant	Reviewer	Summary of Event
33/M Phase 2 (200056; LATTE-2)	Not related	Not related	Unlikely related but cannot exclude causality	Road traffic accident The subject died of fatal car accident 54 days after the first dose of oral CAB (in combination with ABC/3TC). The subject died at the scene of the car accident; no autopsy was conducted. There were no ongoing AEs at the time of the event. Comment: *Though theoretical, mental status change (e.g., due to seizure) could have led to the event. Therefore, drug-related event cannot be ruled out.*

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets
[1] As assessed by the investigator, Applicant, Reviewer
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, CSF = cerebrospinal fluid, DTG = dolutegravir, EEG = Electroencephalogram, EMT = emergency medical technician, ERCP = endoscopic retrograde cholangiopancreatography, ICU = intensive care unit. PRES = posterior reversible encephalopathy syndrome, SID = subject ID

7.6.3. Serious Adverse Events

The definition of SAEs is described in Section 7.2. Overall, the incidence of SAEs was similar between the CAB+RPV treatment group (5%) and the pooled control group (4%). Grade 3 and 4 SAEs were reported more frequently in the CAB+RPV treatment group. One SAE ("arthritis") was considered as related to CAB+RPV by the investigator. "Hepatitis A" is the only term reported in more than one subject. No SOC or PT was disproportionally reported as SAEs to suggest a pattern. Hence, details of the SAEs analysis are not included in this section. Refer to Section III.17.2 for further information.

Table 22. Summary of SAEs During the Maintenance Period

Serious Adverse Event	CAB+RPV N=591	ABC/DIG/3TC N=283	Current ART N=308
Any subject with SAE	31 (5%)	12 (4%)	14 (5%)
Severity of SAEs			
Grade 1	5 (1%)	2 (1%)	0 (0%)
Grade 2	9 (2%)	6 (2%)	4 (1.0%)
Grade 3	11 (2%)	4 (1%)	9 (3%)
Grade 4	8(1%)	1 (<1%)	1 (<1%)
SAE leading to discontinuation	6 (1%)	1 (<1%)	3 (1%)
SAE leading to treatment interruptions	0 (0.0%)	1 (<1%)	1 (<1%)
Treatment-related SAE	1 (<1%)	0	1 (<1%)
Ongoing SAE	5 (1%)	2 (1%)	0 (0%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets
See Section 7.4. for definition of SAE
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, SAE = serious adverse event, RPV = rilpivirine

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

Incidence of AEs leading to discontinuation were low in the FLAIR and ATLAS trials. Overall, 22 (4%) subjects in the CAB+RPV treatment group and 9 (2%) subjects in the pooled comparator group experienced AEs leading to discontinuation during the maintenance phase (Table 23).

The most common reason for discontinuing CAB+RPV was ISRs 8 (1%). The ISRs include injection site pain (n=8), swelling (n=1), nodule (n=1), discomfort (n=1), and unspecified intolerance (n=2). All were considered treatment-related.

The other common SOCs associated with discontinuation in the CAB+RPV treatment group were Infections and Infestations and Nervous System Disorders. The AEs include acute viral hepatitis (n=8), acute hepatitis A with secondary syphilis (n=1), headache (n=2), and memory impairment (n=1).

In summary, except for ISRs, other PTs infrequently led to discontinuations. The label adequately discusses ISRs as ADRs associated with CAB+RPV administration. See Section 7.7.4 for details.

Table 23 summarizes selected AEs leading to discontinuation during the maintenance period. Frequency and type of AE (e.g., falls within the prespecified AESI category) were considered while selecting the AEs for inclusion in the table.

Table 23. Selected Adverse Events Leading to Discontinuation, Safety Population, ATLAS, FLAIR Maintenance Period

Preferred Terms (PT)	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Any subject who discontinued treatment due to an AE	22 (4%)	4 (1%)	5 (2%)
Injection site pain	6 (1%)	0 (0%)	0 (0%)
Diarrhoea	2 (<1%)	0 (0%)	0 (0%)
Headache	2 (<1%)	0 (0%)	0 (0%)
Nausea	1 (<1%)	1 (<1%)	0 (0%)
Vomiting	1 (<1%)	0 (0%)	0 (0%)
Hepatocellular injury*	1 (<1%)	0 (0%)	0 (0%)
Hyperbilirubinaemia*	1 (<1%)	0 (0%)	0 (0%)
Liver function test abnormal#	1 (<1%)	0 (0%)	0 (0%)
Transaminases increased^	1 (<1%)	0 (0%)	0 (0%)
Injection site swelling	1 (<1%)	0 (0%)	0 (0%)
Injection site nodule	1 (<1%)	0 (0%)	0 (0%)
Memory impairment	1 (<1%)	0 (0%)	0 (0%)
Anxiety	1 (<1%)	0 (0%)	0 (0%)
Asthenia	1 (<1%)	0 (0%)	0 (0%)
Depression suicidal	1 (<1%)	0 (0%)	0 (0%)
Discomfort	1 (<1%)	0 (0%)	0 (0%)
Myalgia	1 (<1%)	0 (0%)	0 (0%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) AEAD datasets (212887, Jreview)
[1] Coded as MedDRA preferred terms
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

7.6.5. Treatment-Emergent Adverse Events

Please refer to Section III.17.5 for incidence of TEAEs. In this section, TEAEs considered possibly related to study drug (ADR) are discussed.

The investigators established causality of AE to the study drug. The incidence of ADRs (regardless of severity) was higher in the CAB+RPV treatment group compared with the control treatment groups — 491 (83%) subjects and 36 (6%) subjects, respectively. The most common PTs in the CAB+RPV treatment group were headache, pyrexia, nausea, fatigue, asthenia, temperature increased, dizziness, and myalgia. Among ISRs, the most commonly reported terms were pain, nodule, induration, and swelling. ADRs with at least grade 2 severity were also more commonly reported in the CAB+RPV treatment group. The most frequently reported ADRs with at least grade 2 severity in the CAB+RPV treatment group include headache (n=5), diarrhea (n=5), pyrexia (n=4), and fatigue (n=4).

The Applicant's original proposal for section 6 of the USPI is to include ADRs with incidence of at least 2% (b) (4)

(b) (4)

Refer to the footnotes in Table 24 for the group terms. The label now reflects ADRs with at least 2% incidence in the CAB+RPV treatment group, (b) (4) (Table 24). The Applicant proposed to modify the table to provide grading of the included AEs to highlight the majority of events were grade 1 in severity. The proposal was accepted by the review team.

Table 24. ADR* Regardless of Severity and Reported in at Least 2% of Subjects in the Cabotegravir+Rilpivirine (CAB+RPV) Treatment Group

Adverse Drug Reaction	CAB+RPV (N=591)	CAR (N=591)
Injection site reactions[a]	83%	0
Pyrexia[b]	8%	0
Fatigue[c]	5%	<1%
Headache	4%	<1%
Musculoskeletal pain[d]	3%	<1%
Nausea	3%	1%
Sleep disorders[e]	2%	<1%
Dizziness	2%	<1%
Rash	2%	<1%

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) AEAD datasets (212887, Jreview)
*Adverse reactions defined as "treatment-related" as assessed by the investigator.
[a] See below for additional information on injection site reactions.
[b] Pyrexia: includes pyrexia, feeling hot, chills, influenza-like illness, body temperature increased.
[c] Fatigue: includes fatigue, malaise, asthenia.
[d] Musculoskeletal pain: includes musculoskeletal pain, musculoskeletal discomfort, back pain, myalgia, pain in extremity.
[e] Sleep disorders: includes insomnia, poor quality sleep, somnolence.
[f] rash: erythema, pruritis, pruritis generalized, rash, rash—erythematous, generalized, macular, vesicular
Abbreviations: ADR = adverse drug reaction, CAR = current antiretroviral

7.6.6. Adverse Events of Special Interest (AESI)

The following AEs were recognized as potential safety-related review issues because signals were observed early in the development program for CAB, the events are associated with RPV use, or the events are associated with use of other approved INSTI agents (e.g., BIC, DTG, EVG, or RAL):

- Injection reactions
- Hypersensitivity reactions and rash
- Hepatobiliary events
- Psychiatric events (including depressive disorders)
- Neurologic events (including seizure)
- GI events (including pancreatitis)
- Musculoskeletal events related to injection or rhabdomyolysis
- Weight gain
- Pregnancy and embryo-fetal toxicity

Additionally, pyrexia was recognized as a potential safety issue early in the review of this NDA.

While most of the risks listed above were important and included in labeling, injection reaction was considered potentially unfamiliar to HIV care providers and patients. This issue is therefore unique and important and warrants discussion under Section 7.7. Additionally, several recent publications indicate risk of weight increase with INSTI use.[9] While the clinical significance of the weight increase is still under investigation, the team considered the issue relevant for discussion under Section 7.7. AESI not discussed in Section 7.7 are discussed here.

Pyrexia

Pyrexia was recognized as a potential safety issue early in the review of this NDA. “Pyrexia” (regardless of severity, causality), as defined by the Applicant, occurred more frequently in the CAB+RPV treatment group (7%) in comparison to the pooled control groups (2%). Given this imbalance, we conducted further analyses using broader pooled terms than what the Applicant used to define “pyrexia.” The following terms were identified by the review team: “chills,” “feeling of body temperature change,” “feeling hot,” “body temperature increased,” “pyrexia,” and “influenza-like illness.” We also conducted patient profile analyses to exclude infectious causes for “pyrexia.” Except for two subjects, no concurrent viral or bacterial infections were identified among subjects with “influenza-like illness.” In our analysis using expanded pooled terms, more subjects experienced “pyrexia” compared to the Applicant’s original analysis: 15% in the CAB+RPV treatment group and 7% in the pooled control group. Pyrexia is included in the ADR table under section 6 of the USPI. Of note, “pyrexia” was not documented or measured by healthcare providers. These AEs were subjective reporting by subjects enrolled in the trials.

Furthermore, due to the concern that “pyrexia” may also be associated with an underlying/ongoing systemic medical event, we also analyzed the data to evaluate for a temporal relationship between “pyrexia” and HSR or ISR (or injection). In summary, no temporal relationship was observed between pyrexia and HSRs. However, temporal relationships were

observed between pyrexia and ISRs. Please see Section 7.7.4 for further discussion on injection reactions.

Injection Reaction

As discussed previously, ISRs were common. The team noted systemic/general AEs occurring in association with injection of the drug products or ISRs. Refer to Section 7.7.4 for assessment and risk mitigation recommendations.

HSR and Rash

Many ARV products are associated with HSRs or rash. Drugs in both INSTI and NNRTI classes have a WARNINGS and PRECAUTIONS for severe rash events or HSR, including erythema multiforme, Stevens-Johnson syndrome, and Drug Reaction with Eosinophilia and Systemic Symptoms. The RPV label contains a WARNINGS and PRECAUTIONS for severe rash and Drug Reaction with Eosinophilia and Systemic Symptoms. Therefore, we assessed for the incidence of rash and HSR with CAB+RPV administration. Our evaluation also included review of the phase 2 data to assess the association of CAB with HSR in the absence of RPV.

HSR

The analysis approach considered the knowledge that HSRs may or may not be limited to skin reaction. For example, type I HSRs include anaphylaxis reaction; type II HSRs can manifest as hemolytic anemia; whereas type III HSR events can include vasculitis, glomerulonephritis, and arthritis. For the purposes of this analysis, potentially severe or serious skin reactions, including urticaria and drug eruption were categorized under HSRs, whereas rash without systemic symptoms or lacking severity/seriousness was reviewed under the category of "Rash."

Table 25 provides general characteristics of the AEs suggestive of potential HSRs during the phase 3 clinical trials. The AE terms are summarized in Table 26.

Table 25. Summary of "Hypersensitivity" Reactions Maintenance Period

Outcome	CAB+RPV N=591	ABC/DTG/3TC N=283	CAR N=308
Any subject with 'hypersensitivity' reactions	38 (6%)	13 (5%)	10 (3%)
SAE	0	0	0
Treatment discontinuation	0	0	0
Treatment related	6* (1%)	2 (<1%)	0
Severity			
Grade 1	30 (5%)	13 (5%)	9 (3%)
Grade 2	12 (2%)	0	0
Grade 3	1**(<1%)	0	0
Grade 4	0	0	0

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) AEAD datasets (212887, Jreview)
*Conjunctivitis, eosinophilia, lip swelling, swelling, arthritis, myositis
**Arthritis
Abbreviations: 3TC = lamivudine, ABC = abacavir, CAB = cabotegravir, CAR = current antiretroviral, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Table 26. Description of "Hypersensitivity" Reactions During Maintenance Period

Adverse Event	CAB+RPV N=591	ABC/DTG/3TC N=283	CAR N=308
Any subject with HSR	38(6%)	13(5%)	10(3%)
Conjunctivitis	17(3%)	5(2%)	3(1%)
Drug eruption/urticaria	5(<1%)	0	1(<1%)
Drug hypersensitivity/hypersensitivity	4(<1%)	1(<1%)	0
Hypersensitivity vasculitis	1(<1%)	0	0
Eosinophilia	4(<1%)	3(<1%)	1(<1%)
Eosinophilic esophagitis	1(<1%)	0	0
Swelling (NOS, eye, joint, lips)	5(<1%)	1(<1%)	3(<1%)
Mouth ulceration/stomatitis	0	2(<1%)	1(<1%)
Myositis	1(<1%)	0	1(<1%)
Arthritis	1(<1%)	0	0

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) AEAD datasets (212887, Jreview)
Abbreviations: CAB = cabotegravir, HSR = hypersensitivity reactions, NOS = not otherwise specified

In summary, neither the pivotal EDURANT clinical trials nor the current CAB+RPV phase 3 trials identified patterns consistent with serious or severe HSRs. In fact, the EDURANT USPI was updated to include a WARNINGS and PRECAUTIONS based on cases from postmarketing experience.

No cases of SJS or toxic epidermal necrolysis were observed during the CAB+RPV phase 3 trial. No subjects discontinued treatment due to HSRs. No temporal associations were noted between events potentially representing HSRs and systemic symptoms such as "pyrexia." Few subjects (n=6) experienced ADRs that could potentially represent a form of HSR. The events include myositis, arthritis, conjunctivitis, eosinophilia, swelling, and lip swelling. One event (arthritis) was serious with grade 3 severity. Importantly, none led to treatment discontinuation.

Similarly, during the phase 2 trials, terms such as drug hypersensitivity, hypersensitivity, angioedema, uveitis, and "swelling face" were also reported, though most were mild and nonserious and none led to treatment discontinuation.

However, review of the phase 2 data and safety reports from the ongoing phase 3b trial revealed potentially serious or severe HSRs. Examples include anaphylaxis (type 1 HSR), eosinophilic granulomatosis with polyangiitis (vasculitis, type III HSR) and Immune Thrombocytopenia (type II HSR), although the Immune Thrombocytopenia case remains blinded and causality cannot be attributed. Upon closer investigation, the anaphylaxis-type reaction was a result of an erroneous RPV drug administration, where the injection punctured a blood vessel and the drug was essentially partially administered intravenously. This was confirmed through PK analysis. For this case, the C_{max} was significantly higher than the average C_{max}. The subject who experienced the vasculitis in the phase 2 trial discontinued treatment and responded to steroid therapy. However, the investigator did not consider the event to be related to HSR because the event lacked systemic symptoms.

The phase 2 data were also evaluated to identify HSR in association with CAB-only (i.e., in the absence of RPV). Events reported during the induction phases and the oral CAB comparator arm in maintenance phase of the LATTE-2 trial were evaluated. Terms (regardless of causality, severity) such as joint swelling (n=3), conjunctivitis (n=5), eye swelling (n=1), and hypersensitivity (n=1) were identified as potential HSRs.

Considering the totality of the information from phase 2, 3, and 3b trials, the known risk with RPV and other INSTIs, the review team recommends the following for the WARNINGS and PRECAUTIONS section: 1) change the subtitle to "Severe Hypersensitivity Reactions"; 2) include the postmarketing experience for EDURANT; 3) reference the association of HSR with other INSTIs and state the potential for HSR to occur with exposure to CAB; 4) include cross reference to section 6.2 "Less Common Adverse Reactions." Inclusion of HSR in section 6.2 (as opposed to section 5) is supported because, with very few exceptions, most of the events did not lead to treatment discontinuation and resolved while continuing CAB+RPV. One would anticipate the severity and seriousness of HSR to worsen with continued exposure to the drug products. The clinical team recommends routine pharmacovigilance, and if additional terms are recognized, or if the seriousness of the events change with future data or postmarketing reports, the CABENUVA label will be updated to expand the WARNINGS and PRECAUTIONS language.

Rash

Rash events were reported frequently across the ATLAS and FLAIR trials. As summarized in Table 27, the incidence of rash (regardless of severity) was numerically higher in the CAB+RPV treatment group compared to the control groups (2% versus 0.2%). The cases in the CAB+RPV treatment group were mild or moderate in severity. No serious event was reported, and no subject discontinued treatment due to rash. (b) (4) .

Table 27. Treatment-Related "Rash" During Maintenance Period, FLAIR, ATLAS

Adverse Event	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=309
Any subject with selected treatment-related AE	11(2%)	1(<1%)	0 (0%)
Erythema	2 (<1%)	0 (0%)	0 (0%)
Pruritus	1 (<1%)	0 (0%)	0 (0%)
Pruritus generalized	1 (<1%)	0 (0%)	0 (0%)
Rash	5 (1%)	0 (0%)	0 (0%)
Rash erythematous	1 (<1%)	0 (0%)	0 (0%)
Rash generalized	1 (<1%)	0 (0%)	0 (0%)
Rash macular	1 (<1%)	0 (0%)	0 (0%)
Rash vesicular	0 (0%)	1 (<1%)	0 (0%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) AEAD datasets (212887, Jreview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

Hepatobiliary Adverse Events

Hepatotoxicity (significant but asymptomatic elevation of ALT/aspartate aminotransferase [AST]) was identified as a potential safety issue early in the development program for CAB. Among subjects enrolled in the phase 2 or DDI trials who met the protocol-defined liver-stopping criteria, no alternative etiology was identified for hepatotoxicity; hence the review team considered CAB to be potentially hepatotoxic. The Division requested quarterly summary reports for liver-related adverse to enhance the safety monitoring during the IND phase. After several quarterly safety summary reports, and based on the review of the findings, the team

recommended the quarterly safety reports were no longer necessary. Refer to Section III.17.6.4 for summary of the phase 2b data.

The phase 3 protocols included "Liver Stopping Criteria (LSC)." The stopping criteria were conservative, and dosing was discontinued in subjects with specific serum biochemistries elevation, regardless of the etiology. Applicant included an independent hepatic adjudication committee to review the data from the phase 3 trials to further mitigate the risk of hepatotoxicity. Table 28 and Table 29 summarizes the clinical AEs and laboratory abnormalities reported during the maintenance period FLAIR and ATLAS. While no imbalance was noted with respect to serum liver biochemistry abnormalities among the treatment groups, the incidence of hepatic AEs was higher in the CAB+RPV-treatment group compared to the control groups—nine subjects versus one subject, respectively. The majority of the AEs were mild, and none were considered treatment-related. One subject had an SAE of hepatocellular injury/hyperbilirubinemia due to acute Hepatitis A infection and discontinued treatment.

Per the independent hepatic adjudication committee, no cases of drug-induced liver injury (DILI) were identified from the phase 3 trials. The clinical team agreed with the hepatic adjudication committee's assessment. However, the few cases identified early in the development program warrant a risk communication that CAB may be associated with hepatotoxicity. Therefore, the WARNINGS and PRECAUTIONS section will be revised to clarify the risk can be attributed to either component of CABENUVA. Hepatic laboratory abnormalities are also included in section 6 of the USPI.

Table 28. Summary of Hepato-Biliary Events During Maintenance Period

Outcome	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Any hepatic AE	9 (2%)	1 (<1%)	0
SAE[%]	3 (1%)	0	0
Treatment discontinuation[*]	1 (<1%)	0	0
Treatment interruption	0	0	0
Treatment related	0	0	0
Hospitalization[#]	2 (<1%)	0	0
Severity			
Grade 1	4 (1%)	0	0
Grade 2	5 (1%)	0	0
Grade 3[&]	1 (<1%)	1 (<1%)	0
Grade 4[^]	1 (<1%)	0	0

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) AEAD datasets (212887, Jreview)
% bile duct stone, cholecystitis, cholecystitis acute; hepatocellular injury hyperbilirubinemia; hydrocholecystis
* hepatocellular injury/hyperbilirubinemia
# bile duct stone, cholecystitis, cholecystitis acute, hydrocholecystis
& bile duct stone/cholecystitis (CAB/RPV); hepatic cirrhosis (ABC/DTG/3TC)
^ hepatocellular injury/hyperbilirubinemia
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Table 29. Maximum Postbaseline Serum Liver Biochemistry Abnormalities During Maintenance Period

Type of Abnormality	CAB+RPV N=591	ABC/DTG/3TC N=283	CAR N=308
ALT			
Grade 1 (<3× ULN)	50 (8%)	22 (8%)	28 (9%)
Grade 2 (≥3–<5× ULN)	8 (1%)	4 (1%)	4 (1%)
Grade 3 (≥5–<10× ULN)	1 (<1%)	1 (<1)	0
Grade 4 (≥10× ULN)	3 (<1%)	2 (<1)	1 (<1)
AST			
Grade 1 (<3× ULN)	51 (9%)	25 (9%)	26 (8%)
Grade 2 (≥3–<5× ULN)	11 (2%)	6(2%)	5 (2%)
Grade 3 (≥5–<10× ULN)	2 (<1%)	2 (<1%)	0
Grade 4 (≥10× ULN)	2 (<1%)	2 (<1%)	0
Total Bilirubin			
Grade 1	21 (4%)	12 (4%)	9 (3%)
Grade 2	7 (1%)	1 (<1%)	6 (2%)
Grade 3	0	0	0
Grade 4	3 (<1%)	1 (<1%)	2 (<1%)

Grading based on NIH DAIDS Toxicity Table
Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADLB datasets (212887, Jreview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CAB = cabotegravir, CAR = current antiretroviral, DTG = dolutegravir, RPV = rilpivirine, ULN = upper limit of normal

Psychiatric Adverse Events

Depressive disorders, including suicidal ideation or attempt, are labeled events for INSTIs and NNRTIs, including RPV. Psychiatric AE analyses were performed for two reasons: 1) to explore for class-related toxicity with either drug; and 2) to establish or discern if psychiatric events (especially depressive disorders) occur with CAB in the absence of RPV exposure.

The incidence of psychiatric AEs was similar between the treatment groups. No SAE was reported in the CAB+RPV treatment group, but two subjects discontinued due to anxiety (n=1) and "depression, suicidal" (n=1). All AEs in the CAB+RPV treatment group were mild or moderate.

Excluding depressive disorders, psychiatric AEs reported in the CAB+RPV treatment group during the phase 3 clinical trials include anxiety disorders (n=27), sleep disorders (n=31), and abnormal dreams (n=8). Treatment-related sleep disorders occurred with incidence of at least 2% and are included in the ADR table of the USPI. Please refer to Section III.17.6.2 for details of the full analysis. Note, sleep disorders were reported in either psychiatric or neurologic SOC. The terms were pooled from both SOCs for analysis.

The incidence of depressive disorders, including suicidal ideation or attempt, were similar between the treatment groups. SAEs were not reported in the CAB+RPV treatment group, but one subject discontinued CAB+RPV treatment due to "depression, suicidal." Review of the phase 2 and 3b safety data and the safety reports from the ongoing CAB PrEP trials suggest association of depressive disorders with CAB exposure in the absence of RPV. Therefore, despite infrequent serious or severe depressive disorders during the phase 3 trials, the USPI for CABENUVA will include the risk of depressive disorders because 1) RPV is associated with depressive disorders, and 2) the data suggest events occur with CAB+RPV or CAB alone. The

Applicant proposes (b) (4) The clinical team recommends revision of the label to communicate risk with either component of CABENUVA.

Neurologic Adverse Events

Neuropsychiatric events are associated with INSTIs and NNRTIs. For example, headache, sleep disorders, and dizziness are well described with INSTI and NNRTI use.

At least two seizure-like events were submitted as IND safety reports early in the course of CAB development program. This led to include seizure as a potential risk associated with CAB. Seizure is not an ADR described in other INSTI labelings. However, (b) (4) Older NNRTIs such as EFV are associated with convulsion in adult and pediatric patients receiving EFV, generally in the presence of known medical history of seizures.

Seizure

The occurrence of two seizure-like events early in the course of the CAB development program led to the Division's request that the Applicant submit any future seizure-like events as safety reports. Additionally, to minimize risk, the protocol was amended to assess and exclude subjects with high risk of seizures. Specifically, "Participants determined by the Investigator to have a high risk of seizures, including participants with an unstable or poorly controlled seizure disorder were to be excluded, and "Participant with a prior history of seizure may be considered for enrolment if the Investigator believes the risk of seizure recurrence is low." All subjects with a prior seizure history were to be discussed with the Medical Monitor prior to enrollment.

To date, 13 cases of seizures across the CAB development program have been reported. While some cases are clearly confounded, others lack sufficient information to determine association between events and drug exposure. Furthermore, the cases from the ongoing CAB PrEP trials were initially blinded, limiting our ability to assess for causality.

The assessment and interpretation of the reported cases considered the following background information: 1) the ability for INSTIs and NNRTIs to penetrate the CSF; 2) the association of neuropsychiatric AEs with exposure to NNRTIs and INSTIs; 3) and the lack of nonclinical neurotoxicity signal for either CAB or RPV. Even still, assessing for possible association between CAB exposure and seizures was difficult. The review team requested input from the Division of Neurology Products (DNP) to review the cases across the development program and provide risk assessment. As part of the assessment, the Division also requested for unblinding of the case reports from the ongoing CAB PrEP trials. This was accomplished without unblinding the trial sponsors, ViiV and NIH. Please refer to Section III.17.6.3 for details on the DNP evaluation.

In the phase 3 trials, no seizures were reported during the maintenance period in the CAB+RPV treatment group; one case of epilepsy was reported in the control arm during the maintenance period. One subject who withdrew from the study due to ISR had a seizure approximately 2 months after the last dose of CAB+RPV. The event was attributed to influenza meningoencephalitis.

Overall, six seizure cases were identified from the phase 1 to 3b HIV or treatment trials. Two of the six cases were assessed by the team as possibly related to CAB exposure because no alternative causative agent was identified. In addition, seven cases were identified from the ongoing PrEP trials: one from the open-label phase 2 trial (HTPN077) and six from the phase 3 PrEP trials (HPTN083 and HPTN084), though not all subjects were exposed to CAB. For additional details, refer to III.17.6.3 (neurologic review).

- HPTN077: n=1 (open-label; received CAB)
- HPTN084: n=2; these cases remains blinded. Note, this trial is relatively early in enrollment. The total target enrollment is 3,200 subjects, 1,600 subjects in the CAB treatment arm.
- HPTN083: n=4; after unblinding, 1/4 received CAB. Note, this trial is nearly complete in enrollment. The estimated enrollment in the CAB treatment arm is 2,200; total number of subjects in the trial will be ~4,200.

Based on the latest available data, the total number of subjects exposed to CAB is 5,694 (N=2,635 from phase 1, 2, 3, 3b HIV-treatment trials: 509 from phase 1 studies, 490 from phase 2b, 591 from phase 3, 1,045 from phase 3b; N=199 from HPTN077 PrEP trial; N=2,860 from HPTN083+084 PrEP trials). The incidence for possibly treatment-related seizure is (b) (4)% (b) (4); the incidence would increase to (b) (4)% ((b) (4)) if all cases are considered as treatment-related. The incidence for the general U.S. population ranges from (b) (4) per year. The limitation with our crude calculation is the clinical trials excluded subjects deemed at high risk for seizure. Therefore, it is plausible that higher rates of seizures could have been observed, if CAB has a true biologic effect, including potentially lowering the seizure threshold for those with pre-existing seizure disorders/epilepsy.

In summary, based on the calculated incidence for the CAB development program in comparison to the general background rate for seizures, and acknowledging the limitation of this crude calculation, the review team does not recommend including seizure in the USPI at this time. Seizure is recognized as AESI by the Applicant. The Applicant plans to continue careful monitoring in the postmarketing setting. In addition, several clinical trials including data from the ongoing phase 3b trial (b) (4), HPTN083 PrEP trial (n=4,500), and HPTN084 PrEP trial (N=3,200) are expected for submission, and the risk for seizure can be further evaluated.

General Neurologic AEs

Overall, the incidence of neurologic AEs was higher in the CAB+RPV treatment group compared to the control groups—22% versus 11%, respectively. Most were mild or moderate; only one subject in the control group experienced an SAE (epilepsy) during the maintenance period. Nine subjects in the CAB+RPV treatment group experienced treatment-related AEs, including headache (n=5), dizziness (n=1), poor quality sleep (n=1), somnolence (n=1), and lethargy (n=1). Two subjects discontinued due to memory impairment (n=1) and headache (n=1). The ADR table in the USPI includes headache, dizziness, and sleep disorders because the events are risks associated with CAB+RPV exposure and occurred with incidence of at least 2%. Please refer to Section III.17.6.3 for additional analysis.

Gastrointestinal Adverse Events

GI toxicities were observed in nonclinical safety studies. In the pivotal 26-week study in rats, minimal mixed cell inflammation, and minimal to slight increased apoptosis in the squamous mucosa, were observed at approximately 27× higher than human exposure at the RHD. As these were predominantly minimal findings with no associated changes in body weight or food consumption, these changes were considered nonadverse. In monkeys, however, emesis; decreased food consumption with associated weight loss; and histopathology findings in the stomach, colon, and small intestines (minimal to moderate degeneration/regeneration, inflammation and villous atrophy) were observed at 1,000 mg/kg/day in the 1- and 2-week toxicology studies. Three males at this dose in the 2-week monkey study were also euthanized prematurely due, in part, to these findings. These effects, including the deaths, occurred at approximately 7× higher than human exposure at the RHD. In the pivotal 39-week monkey study, however, no drug-related GI effects were observed up to 500 mg/kg/dose (approximately 4× higher than human exposure). Please refer to Section 7.1 for more information on the nonclinical safety studies. Additionally, a fatal GI hemorrhage was reported in the phase 2 clinical trial. Given the adverse nonclinical findings in a single species and the fatal clinical case, we carefully reviewed the GI AEs reported during the phase 3 clinical trials.

A fatal acute pancreatitis case led to concerns that CAB may be associated with pancreatitis.

In this section, the following assessments are summarized: 1) select AEs potentially representing GI toxicity, including bleeding, ulceration, or inflammation; 2) analysis of hemoglobin changes from baseline to explore potential subclinical GI bleeding; and 3) pancreatitis.

GI Ulceration or Inflammation

Potential gastric ulcer events were evaluated by searching for the following preferred AE terms: gastritis, nausea, vomiting, upper abdominal pain, epigastric pain, dyspepsia, gastric hemorrhage, hematemesis, duodenitis, gastric mucosal lesion, heartburn, gastroesophageal reflux disease, and frank GI bleed. An analysis of mean hemoglobin change from baseline during the phase 3 treatment period was also conducted to assess for subclinical GI bleed. Events potentially suggestive of GI tract inflammatory processes were assessed by searching for noninfectious “naïve” terms.

The incidence of selected AE potentially related to GI intolerance, inflammation, or ulcer was comparable between the CAB+RPV treatment group (29%) and pooled control group (24%) (Table 30). The terms in the CAB+RPV treatment group included colitis (n=2), diarrhea haemorrhagic (n=2), dyspepsia (n=13), enteritis (n=2), enterocolitis (n=1), epigastric discomfort (n=1), gastritis (n=7), gastroduodenitis (n=7), and gastroesophageal reflux disease (n=6). One event (colitis) was grade 3; none were grade 4 or led to treatment discontinuation. Three events were considered treatment-related (diarrhea hemorrhagic, gastritis, dyspepsia). Two subjects experienced SAE and included colitis and enterocolitis, requiring hospitalization. Assessment of hematological data (decrease in hemoglobin reported as AE, and mean change in Hgb from baseline) did not reveal increased incidence of anemia in the CAB+RPV treatment group (see Section III.17.7.1).

Table 30. Summary of Select GI Adverse Events in ATLAS, FLAIR Trials, Maintenance Period

Selected GI Adverse Events	CAB+RPV (N=591)	ABC/DTG/3TC (N=283)	CAR (N=308)
Subjects with any selected GI AE	174 (29%)	105 (37%)	34(11%)
Abdominal discomfort	2 (<1%)	1 (<1%)	1 (<1%)
Abdominal distension	2 (<1%)	1 (<1%)	0
Abdominal pain	17 (3%)	8 (3%)	1 (<1%)
Abdominal pain lower	4 (1%)	1 (<1%)	0
Abdominal pain upper	7 (1%)	2 (1%)	0
Colitis	1 (<1%)	0	2 (1%)
Colitis microscopic	1 (<1%)	0	0
Diarrhoea	54 (9%)	25 (9%)	15 (5%)
Diarrhoea haemorrhagic	2 (<1%)	0	0
Dyspepsia	13 (2%)	3 (1%)	2 (1%)
Enteritis	2 (<1%)	0	1 (<1%)
Enterocolitis	1 (<1%)	0	0
Eosinophilic oesophagitis	1 (<1%)	0	0
Epigastric discomfort	1 (<1%)	0	1 (<1%)
Gastritis	7 (1%)	3 (1%)	0
Gastroduodenitis	1 (<1%)	1 (<1%)	0
Gastroesophageal reflux disease	6 (1%)	3 (1%)	2 (1%)
Nausea	30 (5%)	11 (4%)	5 (2%)
Vomiting	14 (2%)	3 (1%)	4 (1%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) AEAD datasets (212887, Jreview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, CAB = cabotegravir, CAR = current antiretroviral, DTG = dolutegravir, GI = gastrointestinal, RPV = rilpivirine

With regards to the fatality case from phase 2, considering the length of treatment prior to event and given the subject's past and current medical history, the review team agrees with the investigator's assessment that the event is unlikely related to the study drug. Below is a brief case summary:

> The subject, a 54 year-old male, was treated with oral CAB in combination with other ARV for at least 168 weeks. His medical history include peptic ulcer disease, gastroesophageal reflux disease, H. Pylori, Hep C Ab positive, hepatobiliary disorder, depression, anxiety, insomnia, hypertension and smoking. He discontinued from the study to initiate treatment for Hep C. The subject had reported anorexia and weight loss in recent years. An abdominal CT scan revealed noncancerous liver lesion. Approximately 2 months after exiting the study, the subject was found deceased in his home. As the participant did not receive medical care, there are no additional medical records surrounding the event. A coroner reported gastrointestinal bleed as the cause of death, with no antecedent cause. Per the report, significant conditions contributing to death are listed as peptic ulcer disease and prior tobacco use. Both the investigator and Applicant did not believe the event was related to study drug.

In conclusion, the majority of the selected GI-related AEs were mild and nonserious, and the incidence in the CAB+RPV treatment group was comparable to the pooled control group. Note, although "naïve"-related events were noted more frequently in the CAB+RPV treatment group, few subjects experienced similarly grouped terms. While the clinical data are reassuring, given the nonclinical signal—albeit from a single species—we recommend inclusion of the most

frequently reported terms under “Less Common Adverse Reactions.” The following language is proposed for the USPI:

> *Gastrointestinal Disorders:* Abdominal pain (including upper abdominal pain), gastritis, dyspepsia, vomiting, diarrhea, flatulence.

Pancreatitis

The fatal acute pancreatitis case from the phase 3b trial triggered the concern about pancreatitis with exposure to CAB+RPV. The event was not considered treatment related by the Applicant. While other alternative etiologies are possible, the review team could not exclude with confidence causality to study drug(s). Therefore, a more detailed analysis was conducted to assess for association between CAB+RPV exposure and pancreatitis.

In brief, below is the summary of the fatal pancreatitis case from the phase 3b trial. For details, refer to Section 7.6.2:

> The subject is a 43-year-old male enrolled in ATLAS-2M. His past medical history is significant for hyperlipidemia (on statin) and hospitalization in (b) (6) for acute lithiasic cholecystitis. While on a trip to Japan and after dinner, he developed abdominal pain and was admitted to a local hospital. He was diagnosed with acute pancreatitis, confirmed by contrast CT scan. Due to hemodynamic instability, he was transferred to an ICU but continued to deteriorate. He eventually succumbed to cardio-pulmonary arrest.

Table 31 and Table 32 summarize AEs suggestive of pancreatitis and laboratory lipase elevation, respectively. The AEs are further characterized to provide seriousness, severity, discontinuation and causality. As summarized below, the incidence of treatment-related or severe (grade 2 or higher) events were similar between CAB+RPV treatment group and the pooled control group.

Acknowledging asymptomatic lipase elevations occur in HIV-infected patients, we also analyzed the phase 3 data to assess for temporal relationship between elevated lipase (regardless of severity) and AEs suggestive of pancreatitis, such as abdominal pain, abdominal pain upper, abdominal discomfort, nausea, and pancreatitis.

In summary, while recognizing the fatal pancreatitis case, the complete data from the phase 3 trial do not suggest an increased risk of pancreatitis for subjects treated with CAB+RPV. No temporal association was established between serum lipase elevation and AEs suggestive of subclinical pancreatitis. This analysis suggests the low likelihood of pancreatitis as a safety issue with CAB+RPV exposure. Therefore, no labeling is recommended for risk communication at this time; routine pharmacovigilance is recommended.

Table 31. Summary of AEs Potentially Related to Pancreatitis During the Maintenance Period

Parameter	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Terms suggestive of 'pancreas-related' AEs			
SAE Acute pancreatitis	1 (<1%)	0	0
Hospitalization	1 (<1%)	0	0
Discontinuation Nausea	1 (<1%)	1 (<1%)	0
Treatment-interruption Abdominal pain upper	1 (<1%)	0	0
Treatment-related Abdominal discomfort Abdominal pain Abdominal pain upper Nausea	45 (8%)	30 (10%)	3 (1%)
Severity			
Grade 2 Abdominal pain Abdominal pain upper Nausea Pancreatitis Chronic pancreatitis	18 (3.0%)	4 (1.4%)	6 (1.9%)
Grade 3 Abdominal pain Nausea Acute pancreatitis	3 (0.5%)	0 (0.0%)	0 (0.0%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) AEAD datasets (212887, Jreview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Table 32. Maximum Postbaseline Lipase Measurement During the Maintenance Period

Severity	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Grade 1 (1.1–<2.0× ULN)	50 (8%)	24 (8%)	25 (8%)
Grade 2 (1.5–<3.0× ULN)	46 (8%)	23 (8%)	20 (6%)
Grade 3 (3.0–<5.0× ULN)	23 (4%)	7 (2%)	3 (<1%)
Grade 4 (≥5.0× ULN)	10 (2%)	1 (<1%)	5 (2%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADLB datasets (212887, Jreview)
Grading based on NIH DAIDS Toxicity Table
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, ULN = upper limit of normal

Musculoskeletal Adverse Events

We reviewed musculoskeletal-related AEs to evaluate for temporal relationships between the musculoskeletal events and injections. This analysis is discussed in Section 7.7.4.

Additionally, as myositis and creatine kinase (CK) elevation are reported with other drugs in the INSTI class, the review also focused on evaluation of rhabdomyolysis in association with CAB+RPV exposure. Pooled terms to represent potential rhabdomyolysis events included myositis, myalgia, and rhabdomyolysis. Grade 3 to 4 CK elevations were also reviewed to assess for trends suggesting muscular toxicity.

In summary, the overall incidence of general musculoskeletal events (i.e., broader than rhabdomyolysis) was higher in the CAB+RPV treatment group compared to the control groups (23% versus 15%, respectively). However, most events were mild or moderate and rarely led to treatment discontinuation. Two SAEs (arthritis and back pain) were reported in the CAB+RPV treatment group. These events required hospitalization. Refer to Section III.17.2 for details. Pooled terms of ADRs, regardless of severity, suggestive of musculoskeletal pain are included in the ADR table of the USPI as "musculoskeletal pain."

The term "rhabdomyolysis" was not reported during the 48-week period of the clinical trial. However, AEs potentially associated with rhabdomyolysis were reported in 25 (4%) subjects in the CAB+RPV treatment group and in 9 (2%) subjects in the pooled comparator group. None were serious, and none in the CAB+RPV treatment group were grade 3 or higher. One subject in the CAB+RPV treatment group discontinued due to myalgia. Myalgia (regardless of severity or causality) was reported more frequently in the CAB+RPV treatment group: 24 (4%) subjects compared to 8 (1%) subjects in the comparator group. Treatment-related events suggestive of rhabdomyolysis (e.g., myositis, myalgia, back pain, muscle spasm, musculoskeletal discomfort, pain in extremity, musculoskeletal pain) were reported in 20 (3%) of subjects in the CAB+RPV treatment group. These terms are also captured as "musculoskeletal pain" in the ADR table of the USPI.

Overall, more subjects in the CAB+RPV treatment group experienced CK elevations in comparison to the control groups. Additionally, the incidences of grade 3 or 4 CK elevation were also higher in the CAB+RPV treatment group: 47 (8%) compared with 26 (4%) subjects in the pooled control group. The CK elevations were asymptomatic and not associated with serious clinical events.

In conclusion, while the reported events potentially representing rhabdomyolysis were neither serious nor severe, treatment-related muscular inflammation or pain (e.g., myositis, musculoskeletal pain, myositis) were reported with at least 2% incidence in the CAB+RPV treatment group. Additionally, as CK elevation was more common in the CAB+RPV treatment group, the review team recommends inclusion of "musculoskeletal pain" in the common ADR table and inclusion of CK laboratory abnormalities in the USPI for CABENUVA.

Table 33. Summary of Musculoskeletal Events During the Maintenance Period

Musculoskeletal Events	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Any subject with MS AE	133 (23%)	44 (16%)	43 (14%)
Severity			
Grade 1	110 (19%)	37 (13%)	31 (10%)
Grade 2	39 (7%)	10 (3.5%)	15 (5%)
Grade 3	3 (1%)	0 (0.0%)	1 (<1%)
Grade 4	0 (0%)	0 (0.0%)	0 (0%)
Serious*	2 (<1%)	0 (0.0%)	0 (0%)
Hospitalization[&]	2 (<1%)	0 (0.0%)	0 (0%)
Led to treatment discontinuation[^]	1 (<1%)	0 (0.0%)	0 (0%)
Led to treatment interruption	0 (0%)	0 (0.0%)	0 (0%)
Unresolved/ongoing AE[#]	25 (4%)	5 (2%)	12 (4%)
Treatment-related AEs	21 (4%)	2 (1%)	0 (0%)
Myalgia	10 (2%)	1 (<1%)	0 (0%)

Musculoskeletal Events	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Pain in extremity	3 (1%)	0 (0%)	0 (0%)
Muscle spasms	2 (<1%)	1 (<1%)	0 (0%)
Back pain	2 (<1%)	0 (0%)	0 (0%)
Arthralgia	1 (<1%)	0 (0%)	0 (0%)
Musculoskeletal discomfort	1 (<1%)	0 (0%)	0 (0%)
Musculoskeletal pain	1 (<1%)	0 (0%)	0 (0%)
Myositis	1 (<1%)	0 (0%)	0 (0%)
Musculoskeletal chest pain	1 (<1%)	0 (0%)	0 (0%)
Arthritis	1 (<1%)	0 (0%)	0 (0%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) AEAD datasets (212887, Jreview)
*Arthritis; back pain
& arthritis; back pain
^myalgia
#of the unresolved or ongoing AEs, 50% (n=10) of the subjects in the CAB/RPV treatment group had AEs related to backpain; 2 had AEs related to myalgia
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, MS = musculoskeletal, RPV = rilpivirine

CK Laboratory Events

Table 34. Maximum Postbaseline Emergent Creatine Kinase Abnormalities

Severity	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Grade 1	60(10%)	19(7%)	18(6%)
Grade 2	15(3%)	19(7%)	12(4%)
Grade 3	22(4%)	4(1%)	9(3%)
Grade 4	25(4%)	10(4%)	3 (1%)
Grade 3 or 4	47(8%)	14(5%)	12(4%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADLB datasets (212887, Jreview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

Weight Increase

Weight increase is an important risk recently identified in association with certain INSTI use. Therefore, this was considered a review issue. Please refer to Section 7.7.5 for assessments and recommendations.

7.6.7. Laboratory Findings

Liver biochemistries, CK, and lipase elevations are presented in the respective risk issues under Section 7.6. The laboratory findings in those sections are discussed in the context of the associated clinical events to help with interpretation of the significance of the clinical events. Please refer to Section III.17.7 for other laboratory results, including hematologic, lipid profiles, glucose (serum and urine), and renal. In summary, the laboratory abnormalities found during the analyses were not significant and were generally comparable to the pooled control group.

7.7. Review Issues Relevant to the Evaluation of Risk

As previously discussed, before the review process began, several potential multidisciplinary risks were identified for CABENUVA based on prior knowledge of the characteristics of the individual drug products. At the conclusion of this NDA review, the team identified the following issues that remained significant or potentially significant and important in informing the decision process to use or prescribe CABENUVA. These risks are outlined below and further discussed in this section.

1) Resistance
   - Development of resistance to CAB and RPV in virologic failures
   - Virologic failure associated with the IN L74I polymorphism in subtype A1
   - Cross-resistance with INSTI and NNRTI drug classes in virologic failures
2) Risks associated with nonadherence in the setting of residual CAB and RPV concentrations
   - Failure to adhere to the dosing schedule or initiate suppressive regimen within 30 days after last dose
   - Importance of patient selection and counseling
3) Potential risk of embryo-fetal toxicity—during treatment or post-discontinuation
   - Structural similarity to DTG and risk of NTD
4) Risks of local and systemic reaction in association with CAB+RPV injection
5) Risk of weight increase in association with INSTI exposure, including CAB

7.7.1. Resistance

7.7.1.1. Development of Resistance to CAB and RPV in Virologic Failures

Issue

The assessment of emergence of resistance to CAB and RPV in the virologic failures of FLAIR and ATLAS is critical to interpreting the overall benefit-risk and durability of the dual regimen, CAB+RPV.

Conclusion

Emergence of resistance to both CAB and RPV occurred frequently in virologic failures from both the FLAIR and ATLAS trials based on the following:

- In FLAIR, three of the four virologic failures had postbaseline resistance data showing emergence of CAB resistance (both genotypic and phenotypic evidence). All three virologic failures with resistance data had both emergent CAB and RPV resistance.

- In ATLAS, all three virologic failures had emergent RPV resistance, and one also had emergent CAB resistance.
- The INSTI resistance substitutions selected by CAB in the trials were G140R, Q148R, and N155H conferring 2.7- to 9.4-fold decreased susceptibility to CAB.
- There was no emergence of Q146L, S153Y, or T124A/S153Y substitutions, which were selected in cell culture resistance experiments.
- The NNRTI resistance substitutions selected by RPV in FLAIR and ATLAS were K101E, V108I, E138A or K, and H221L conferring 2.4- to 7-fold decreased susceptibility to RPV, consistent with resistance data from other clinical trials with RPV treatment.

Assessments

The virologic failure rate in the CAB/RPV arm for clinical trials FLAIR and ATLAS was 1.4% and 1%, respectively, and was similar to the comparative treatment arms (Table 35). In FLAIR, there were four virologic failures in the CAB arm (1.4%), and three of them had postbaseline data (See also Section III.19, Table 216). There were three virologic failures in the comparative CAR arm (1.1%), and all of them had postbaseline data.

In ATLAS, there were three virologic failures in the CAB arm (1%) and four virologic failures in the CAR group (1.3%), and all seven had postbaseline data (Table 35; Section III.19, Table 217).

Table 35. Virologic Failure Overview in FLAIR and ATLAS (FDA Analysis)

	FLAIR	ATLAS
CAB/RPV Arm	**(n=283)**	**(n=308)**
Virologic failures	4/283 (1.4%)	3/308 (1%)
With postbaseline data	¾ (75%)	3/3 (100%)
With emergent resistance to CAB	3/3 (100%)	1/3 (33%)
With emergent resistance to RPV	3/3 (100%)	3/3 (100%)
CAR Arm	(n=283)	(n=308)
Virologic failures	3/283 (1.1%)	4/308 (1.3%)
With postbaseline data	3/3 (100%)	4/4 (100%)
With emergent resistance to CAR	0/3 (0%)	2/4 (50%)

Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

Virologic Failures in Study 201584 (FLAIR) and Study 201585 ATLAS

Three of the four virologic failures in the CAB arm of FLAIR had postbaseline genotypic and phenotypic data as indicated below (see Section III.19; Table 216).

- **Subject** (b) (6) From Russia with subtype A1 and baseline IN L74I; had emergent INSTI RAS G140R with CAB phenotypic resistance of 6.7-fold and emergent NNRTI RAS K1013E with 2.6-fold decrease in RPV susceptibility.
- **Subject** (b) (6) From Russia with subtype A1 and baseline IN L74I; had emergent INSTI RAS Q148R with corresponding 5.2-fold decrease in CAB susceptibility and emergent NNRTI RAS E138A/K/T mixture with 7.1-fold decrease in RPV susceptibility.
- **Subject** (b) (6) From Russia with subtype A1 and baseline IN L74I; had emergent INSTI RAS Q148R with CAB phenotypic resistance of 9.4-fold and emergent NNRTI RAS E138K, H221L mixture, and G231E mixture with no change in RPV susceptibility.
- **Subject** (b) (6) From Russia with subtype AG; discontinued at week 8 with HIV-1 RNA of 1,259 copies/mL, but had no postbaseline resistance data.

All three virologic failures in the CAB arm of FLAIR had postbaseline genotypic and phenotypic data as indicated below.

- **Subject** (b) (6) From Russia with subtype A1 and baseline IN L74I; had no emergent INSTI RAS or phenotypic change to CAB, but had emergent NNRTI RAS E138A with 2.4-fold decrease in RPV susceptibility.
- **Subject** (b) (6): From Russia with subtype A1 and baseline IN L74I; had emergent INSTI RAS N155H with CAB phenotypic resistance of 2.7-fold and emergent NNRTI RAS E138K with 6.5-fold decrease in RPV susceptibility.
- **Subject** (b) (6): From Russia with subtype A1 and baseline IN L74I; had emergent INSTI RAS N155H with CAB phenotypic resistance of 2.7-fold and emergent NNRTI RAS E138K with 6.5-fold decrease in RPV susceptibility.
- **Subject** (b) (6): From France with subtype AG; had no emergent INSTI RAS or change in CAB phenotypic resistance, but had emergent NNRTI RAS V108I with 3.7-fold decrease in RPV susceptibility.

Four of the six (67%) virologic failure subjects with postbaseline resistance data had emergence of both CAB and RPV resistance. The emergent CAB resistance substitutions included Q148R (n=2), which conferred 5-fold and 9-fold decreased susceptibility to CAB; G140R (n=1), which conferred 7-fold decreased susceptibility to CAB; and N155H (n=1), which conferred 3-fold reduced susceptibility to CAB (Section III.19; Table 216 and Table 217). The emergent NNRTI resistance substitutions included K101E, V108I, E138A or K, and H221L, which conferred 2.4-fold to 7-fold reduced susceptibility to RPV.

In comparison, in the CAR arm, 2 of the 7 (29%) virologic failures with postbaseline resistance data had emergent resistance substitutions or phenotypic resistance to their ARV drugs (see Section III.19; Table 216 and Table 217). Two virologic failures had emergent NRTI substitutions, M184V and M184I, which conferred resistance to 3TC or emtricitabine (FTC) in

their regimen and one of them also had the emergent NNRTI resistance substitution G190S conferring resistance to EFV in their regimen.

In summary, six of the seven virologic failures from the CAB arms of FLAIR and ATLAS had postbaseline resistance data. All six had evidence of emergent RPV genotypic and phenotypic resistance, four of whom also had emergent CAB genotypic and phenotypic resistance. Thus, resistance emergence to both CAB and RPV is a concern for virologic failure with the CAB+RPV dual regimen. Resistance to RPV will certainly limit use with other NNRTI drug options because of cross-resistance among the NNRTI class. Likewise, substitutions that confer CAB resistance can confer cross-resistance to other INSTIs, although DTG may still be an option in many cases (See Cross-Resistance with INSTI and NNRTI drug classes in virologic failures).

We note that six of the seven virologic failures in CAB arm were from Russia, of whom five were infected with HIV-1 subtype A1 and had the IN L74I substitution at baseline (see 7.7.1.2 below for analyses of subtype A1 and baseline IN L74I). The other two CAB virologic failures had subtype AG without baseline IN L74I (one from Russia, one from France). In comparison, in the CAR arm, two of the seven virologic failures were from Russia and had subtype A1 virus with baseline IN L74I.

Additional Resistance Data From Trial 207966 and LATTE (LAI116482)

In Trial 207966, CVF criteria were met in nine subjects (seven on Q8W dosing and two on Q4W dosing). Eight of the virologic failures had 0 to <24 weeks of prior exposure to CAB+RPV at the time of virologic failure, with three of these subjects transitioning from the CAR arm in ATLAS Trial 201585 to Trial 207966.

INSTI RAS emerged in the viral isolates from six of the eight subjects (IN genotype and phenotype assays failed for one subject). These emergent INSTI resistance substitutions were N155H, N155N/H, Q148R, Q148R+E138E/K, and Q148Q/R+N155N/H, which were also observed in CAB+RPV trials 200056, FLAIR, and ATLAS. It was noted that two of these subjects had prior ART that contained RAL, and N155H substitutions emerged in the virus of these two subjects.

Isolates from seven of the nine virologic failure subjects had emergent NNRTI RAS, including K101E, K101E+M230L, G190Q, V179V/I, and V189I conferring reduced susceptibility to RPV of up to >119-fold.

Of interest in this trial, subtypes of the virologic failures were diverse and included A1, A, B, and C, which is somewhat different from the FLAIR and ATLAS trials, where most of the virologic failures had subtype A1.

In LATTE, there were two subjects with protocol-defined virologic failure at the week 144 analysis. Subject (b) (6) originally randomized to oral 10 mg CAB+RPV, had suspected virologic failure at week 132 (294 copies/mL HIV-1 RNA), week 144 (270 copies/mL HIV-1 RNA), and week 180 (243 copies/mL HIV-1 RNA), which was confirmed at week 192 with 1,748 copies/mL HIV-1 RNA. Genotype and phenotype were determined at weeks 132, 144, 180, and 192. This subject—who is from the United States—had subtype B virus, selected for INSTI resistance substitutions E138K and Q148R by week 132, which conferred 7- to 8-fold decreased

susceptibility to CAB, and NNRTI substitution K101E, which conferred 17- to 21-fold decreased susceptibility to RPV. At week 180, IN substitution G140A also emerged, which was maintained at week 192 and conferred >100-fold decreased susceptibility to CAB.

Subject (b) (6) with subtype B virus, was originally randomized to oral 60 mg CAB+RPV and then had suspected virologic failure at week 264 (656 copies/mL HIV-1 RNA) that was confirmed at week 276 (304 copies/mL HIV-1 RNA). Resistance testing showed that the week 264 isolate had INSTI resistance substitutions G140S and Q148R with 9.8-fold decreased susceptibility to CAB and had NNRTI substitutions K101K/E and E138E/K with a 2-fold change in susceptibility to RPV.

Importantly, in Trials 207966 and LATTE, there were virologic failures with subtypes other than A and A1, namely subtype B and subtype C, who had emergent INSTI resistance substitutions E138K, G140S, Q148R, and N155H, as well as CAB phenotypic resistance.

Analysis of CAB+RPV Virologic Failures for the INSTI and NNRTI Substitutions Selected in Cell Culture

Selection and characterization of resistant virus in cell culture provides a potential list of substitutions to monitor in clinical studies and helps provide a mechanistic understanding of CAB resistance and potential for cross-resistance with other approved INSTIs. However, substitutions that are selected in cell culture do not necessarily reflect those that will arise during therapy in the clinic.

Integrase substitutions Q146L, S153Y, and T124A/S153Y were selected in cell culture passage studies by day 56 (see Section III.18.3) and conferred fold changes in CAB susceptibility of 3.3-, 4.7- and 6.4-fold respectively. In the FLAIR and ATLAS trials, no T124A, Q146L, or S153Y substitutions emerged in the virologic failures. However, the T124 site is highly polymorphic, and there were multiple subjects with T124 polymorphisms present at baseline in the FLAIR trial. The T124A polymorphism was present at baseline in 125 subjects (22%; 125/566) and T124N, S, G, D, or Q polymorphisms were present at baseline in 188 subjects (33%; 188/566). In the CAB arm, there was 1 virologic failure (1/58; 2%) who had T124A at baseline and 4 virologic failures who had T124S at baseline (4/100; 4%). In the CAR arm, 6 virologic failures (6/88; 7%) had T124S or N at baseline. In ATLAS, three virologic failures in the CAB arm had the T124S polymorphism at baseline and two virologic failures in the CAR arm had T124S or T124N at baseline. Given that T124 amino acid position is polymorphic and present in a high proportion of subjects at baseline in FLAIR with only a 2% to 4% virologic failure rate, we conclude the presence of IN T124 polymorphisms at baseline is not associated with virologic failure. Furthermore, the phenotypic fold-change to CAB at baseline for the virologic failures was less than 1-fold (range 0.62 to 0.95). Thus, there was no phenotypic resistance to CAB for the virologic failure subjects with the IN T124S or N polymorphisms at baseline.

Additionally, resistance selection experiments with HIV-1_{NL432} harboring INSTI RAS Q148H, K, or R passaged in the presence of CAB showed selection of additional IN substitutions including G56S, V72I, L74M, V75A, T122N, E138K, G140S, G149A, and M154I. The selection of these additional INSTI substitutions reduced the susceptibility to CAB 2.0- to 410-fold. Since the INSTI resistance substitution Q148R emerged in CAB/RPV virologic failures in the clinical trials, the results from the Q148H/K/R viruses cell culture selection experiment indicate that

continued CAB exposure following virologic failure on CAB/RPV will likely result in the emergence of additional INSTI resistance substitutions and further reductions in CAB susceptibility.

The emergence of NNRTI resistance substitutions, K101E, V108I, E138A or K, and H221L, on CAB+RPV treatment in clinical trials is consistent with the NNRTI substitutions selected in RPV cell culture selection experiments (see Section III.18.3.1). Combinations of two or three NNRTI RAS conferred decreased susceptibility to RPV ranging from 3.7- to 554-fold. Thus, just as continued CAB exposure following virologic failure increases CAB resistance, continued RPV exposure can result in the emergence of additional NNRTI resistance substitutions and increased RPV resistance.

7.7.1.2. Virologic Failure Associated With IN L74I Polymorphism in Subtype A1

Issue

In the virologic failures of the FLAIR and ATLAS trials, there was an association of subtype A1 and presence of baseline IN L74I polymorphism with virologic failure. We performed analyses to determine:

- If CAB has equivalent antiviral activity against all subtypes, in particular to subtype A1
- If the presence of baseline IN L74I polymorphism is specific to subtype A1
- If there is an increased prevalence of subtype A1 in subjects from Russia.
- Whether baseline IN L74I confers decreased susceptibility to CAB

Conclusion

- The rate of CAB+RPV virologic failure was higher in subjects with subtype A1 who also had the IN L74I polymorphism. Five of the seven CAB+RPV virologic failures in FLAIR and ATLAS had HIV 1 subtype A1 and the IN L74I polymorphism detected at baseline and failure time points.
- CAB has similar antiviral activity against isolates of subtype A1 as isolates of other subtypes. CAB had a median EC_{50} value of 0.31nM (range 0.09 to 0.71nM) against subtype A1 isolates, which overlaps with the EC_{50} value ranges of other subtypes.
- In the FLAIR trial, there is a high prevalence of IN L74I in subjects with subtype A1 and A. However, from published reports, we found that IN L74I polymorphism is not specific to subtype A1 or A.
- In the FLAIR trial, there is a high prevalence of subtype A1 and polymorphic IN L74I in subjects from Russia. Subjects with subtype A1 infection whose virus did not have IN L74I at baseline did not experience virologic failure.
- The phenotypic fold-change to CAB at baseline for the virologic failures was less than 1-fold (range 0.62 to 0.95), including subjects with IN L74I at baseline. Thus, there was no detectable phenotypic resistance to CAB conferred by the IN L74I substitution at baseline.

Assessment

Association of Subtype A1 and Baseline IN L74I in Virologic Failures From FLAIR and ATLAS

In the CAB arm of the FLAIR and ATLAS trial, six of the seven virologic failures were from Russia, and of them five were infected with subtype A1 virus with baseline IN L74I (Table 36). The other two virologic failures had the AG subtype. In addition, two of the seven virologic failures in the CAR arm was from Russia and had subtype A1 virus with IN L74I at baseline. These data indicate that there may be an association of subtype A1 and the presence of IN L74I at baseline with virologic failure.

Table 36. Characteristics of Virologic Failure in FLAIR and ATLAS (FDA Analysis)

Characteristic of Virologic Failure	FLAIR	ATLAS
CAB arm	(n=283)	(n=308)
Virologic failures	4/283	3/308
From Russia	4/4	2/3
A1 subtype	¾	2/3
AG subtype	¼	1/3
IN L74I at baseline	¾	2/3
Subtype A1 and IN L74I	¾	2/3
CAR arm	(n=283)	(n=308)
Virologic failure	3/283	4/308
From Russia	1/3	¼
A1 subtype	1/3	¼
L74I at baseline	1/3	¼
Subtype A1 and IN L74I	1/3	¼

Abbreviations: CAB = cabotegravir, CAR = current antiretroviral

In FLAIR, the virologic failure rate for CAB+RPV was highest in subjects with subtype A1 (38%) followed by subtype AG (10%) (Table 37). The virologic failure rate for subjects with subtype A1 was also highest in the CAR arm (25%). The other two virologic failures in the CAR arm had subtype B.

Table 37. Virologic Failure Rate by Subtype in FLAIR (FDA Analysis)

Subtype	CAB	CAR
All	4/277 (1.4%)	3/278 (1.1%)
A	0/46 (0%)	0/26 (0%)
A1	**3/8 (38%)**	**1/4 (25%)**
AG	1/10 (10%)	0/16 (0%)
B	0/174 (0%)	2/173 (1.2%)
C	0/18 (0%)	0/20 (0%)
Other*	0/20 (0%)	0/27 (0%)

Highest rate is bolded

Abbreviations: CAB = cabotegravir, CAR = current antiretroviral

Antiviral Activity of CAB Against HIV-1 Subtypes in Cell Culture

We reviewed the CAB antiviral activity data against multiple HIV subtypes in cell culture PBMCs to determine if CAB had decreased activity against any specific subtypes or Clades, in particular subtype A1. The EC_{50} values against 24 HIV-1 isolates (including group M subtypes

A, B, C, D, E, F, G and group O (3 isolates for each)) ranged from 0.02 to 1.06nM. The EC_{50} values against just the three subtype B isolates ranged from 0.02 to 0.50nM, similar to EC_{50} values against the three subtype A1 isolates ranging from 0.09 to 0.71nM (Table 38; See also Section III.18, Table 211). Thus, the EC_{50} value ranges for the analyzed subtype A1 and subtype B isolates overlapped and were similar to the other subtypes. Therefore, the cell culture antiviral activity shows CAB has similar antiviral activity against the different subtypes and does not exhibit decreased antiviral activity against subtype A1 isolates.

We note that the amino acid at position 74 in IN was leucine for two of the subtype A1 isolates and unknown for the third isolate. For group O isolates, isoleucine was the amino acid at position 74 in IN, and the EC_{50} values for these isolates ranged from 0.3nM to 1.06nM, overlapping the EC_{50} value range of subtype B and A1 isolates. Therefore, from the data we have, we cannot conclude that the presence of IN L74I decreases CAB antiviral activity in cell culture.

Furthermore, there was no detectable phenotypic resistance to CAB conferred by the IN L74I polymorphism at baseline for FLAIR virologic failure subjects. The phenotypic fold-change to CAB at baseline for the virologic failures was less than 1-fold (range 0.62 to 0.95), including the subjects with IN L74I at baseline (See Table 216).

Table 38. Antiviral Activity against Subtype A1, B, and Clade O Isolates in Cell Culture With Leucine or Isoleucine at Position L74 in Integrase

HIV-1 Isolate	Envelope Subtype	Amino Acid Position 74	EC_{50} Value (nM) [b]	Mean EC_{50} Value of Subtype	EC_{90} Value (nM)
92RW009	A1	Leucine	0.13		0.85
92UG037	A1	Leucine	0.09	0.31	0.67
92UG029	A1	No data	0.71		2.48
92BR014	B	Leucine	0.50		0.95
JR-CSF	B	No data	0.05	0.19	0.16
92TH026	B	No data	0.02		0.26
BCF01	O	Isoleucine	0.30		2.57
BCF02	O	Isoleucine	0.55	0.64	2.50
BCF03	O	Isoleucine	1.06		3.05

Abbreviations: EC_{50} = half maximal effective concentration, EC_{90}=90% maximal effective concentration

Prevalence of Subtype A1 by Country

Subtype A1 HIV-1 is distributed globally in geographical clusters. The spread of subtype A1 from Africa to Europe was probably associated with migration from Africa, while viral mobility within Eastern Europe is probably due to transmission networks among injection drug users. After its origin in East Africa, subtype A1 migrated in Central Africa, and both variants from East and Central Africa likely originated the epidemic in Europe. The spread among Eastern European countries started from 1982, corresponding to the identification of the first outbreaks in countries formerly part of Soviet Union.[10]

The prevalence of subtype A is approximately 2% in Western and Central Europe; however, this variant has established extensive epidemics in some Mediterranean countries, such as Albania, Cyprus, and Greece. In Greece, subtype A1 is the most common non-B subtype (20.6%), rising

from a 6% prevalence in 1984 to 42% in 2004. Similarly, the subtype A epidemic in Albania probably arose from Greece, given that Albanian and Greek sequences are more related to African ones than to Eastern European ones.[10]

Consistent with literature reports, in the FLAIR trial, the prevalence of subtypes A and A1 was high in subjects from Russia. Of the 93 subjects from Russia, 73% had subtype A virus (n=68), 11% had subtype A1 virus (n=10), 2% had subtype AG virus (n=2), 12% had subtype B virus (n=11), 1% had subtype G virus (n=1), and 1% had Complex virus (n=1) (Table 39). Thus, subtype A was most prevalent subtype of HIV-1 in the subjects from Russia followed by subtype A1. The most prevalent subtype in the United States was subtype B, and there was only one subject with subtype A and no one with subtype A1 in the FLAIR study.

Table 39. Most Prevalent Subtypes in Each Country in FLAIR (FDA Analysis)

Country	Subtype B	Subtype A	Subtype A1	Subtype AG
Canada	15/21 (71%)	1/21 (5%)	0 (0%)	3/21 (14%)
France	18/39 (46%)	0 (0%)	1/39 (3%)	8/39 (21%)
Germany	30/45 (67%)	5/45 (11%)	0 (0%)	2/45 (4%)
Italy	27/37 (73%)	0 (0%)	1/37 (3%)	5/37 (14%)
Japan	18/20 (90%)	-	-	-
Netherlands	6/6 (100%)	-	-	-
Russia	**11/93 (12%)**	**68/93 (73%)**	**10/93 (11%)**	**2/93 (2%)**
Spain	124/152 (82%)	6/152 (4%)	0 (0%)	1/152 (1%)
UK	17/23 (74%)	1/23 (4%)	0 (0%)	1/23 (4%)
US	81/84 (96%)	1/84 (1%)	0 (0%)	0 (0%)

We note that of the 12 subjects from the FLAIR trial who had subtype A1 HIV-1 and were randomized into the maintenance phase, 10 subjects were from Russia, one was from France and one was from Italy (Table 40). Thus, the high prevalence of subtype A and its sub-subtypes A1 and AG in Russia provides an explanation for why most of the CAB+RPV virologic failures were from Russia, given that most of the virologic failures were infected with subtypes A1 or AG.

Table 40. Prevalence of Subtype A1 by Country in FLAIR (FDA Analysis)

	Number of Subjects With Subtype A1 (n=12)	
Country	**CAB+RPV**	**CAR**
Russia	7/8 (88%)	3/4 (75%)
France	-	1/4 (25%)
Italy	1/8 (12%)	-

Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

Prevalence of IN L74I in HIV-1 Subtypes

We further explored the relationship of subtype A1 and IN L74I. From a literature search, we found that polymorphisms such as L74I/M occur with a frequency of greater than 12% in certain subtypes such as subtypes A, AG, D, G, and O.[11] The prevalence of L74A or I in subtype A1 was found to be 10% to 50% (n=206 isolates).[12] From the same reference, the prevalence of L74A or I in subtype B was <10% (n=2,641 isolates); whereas in group O isolates, the prevalence was >90% (n=24 isolates). The authors note that L74A or I can be considered natural polymorphisms in a large number of non-B group M variants.

We examined the prevalence of IN L74I in each subtype of the subjects in the FLAIR trial. The prevalence of IN L74I was highest in subtype A and A1 with 71% (58/82) prevalence in subtype A and 67% (8/12) in subtype A1. The prevalence of IN L74I was comparable between the CAB and CAR arms (Table 41). Although more prevalent in subtypes A and A1, the L74I IN substitution was not specific to these subtypes. L74I was present in 7% (23/347) of subjects with subtype B, 23% (6/26) of subjects with subtype AG, and 9% (4/47) of subjects with other subtypes (AE, A/B, B/C, BC, BF, BG, Complex, CPX, D, F, F2, and G).

Table 41. Prevalence of L74I at Baseline by Subtype in FLAIR (FDA Analysis)

Subtype	CAB	CAR
All	54/277 (19%)	47/278 (17%)
A	32/46 (70%)	26/36 (72%)
A1	5/8 (63%)	3/4 (75%)
AG	3/10 (30%)	3/16 (19%)
B	12/174 (7%)	11/173 (6%)
C	0/18 (0%)	0/20 (0%)
Other*	2/20 (10%)	2/27 (7%)

*AE, A/B, B/C, BC, BF, BG, Complex, CPX, D, F, F2, G
A1 subtype dominates in Armenia (92% followed by subtype B)
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral

We assessed the prevalence of the IN L74I polymorphism at baseline in the FLAIR trial by country. The prevalence of IN L74I was by far the most prevalent in Russia with 69% of the subjects from Russia having IN L74I in their HIV-1, distributed similarly between the two arms (Table 42).

Table 42. Prevalence of Baseline IN L74I by Country in FLAIR (FDA Analysis)

Country	Overall	CAB	CAR
Canada	4/21 (19%)	2/9 (22%)	2/12 (17%)
France	6/39 (15%)	1/19 (5%)	5/20 (25%)
Germany	4/43 (9%)	1/22 (5%)	3/21 (14%)
Italy	3/39 (8%)	2/15 (13%)	1/24 (4%)
Japan	1/20 (5%)	0/8 (0%)	1/12 (8%)
Netherlands	0/6 (0%)	0/2 (0%)	0/4 (0%)
Russia	**63/93 (68%)**	**35/54 (65%)**	**28/39 (72%)**
South Africa	0/32 (0%)	0/15 (0%)	0/17 (0%)
Spain	12/154 (8%)	8/80 (10%)	4/74 (5%)
UK	1/23 (4%)	1/15 (7%)	0/8 (0%)
US	4/83 (5%)	3/36 (8%)	1/47 (2%)

Highest prevalence is bolded.
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral

Finally, we assessed virologic failure rates by country, subtype A1, and presence of L74I in IN at baseline. From these assessments using a denominator of the number of subjects with baseline data, the overall rate of virologic failure in FLAIR was 1.2% (n=7 virologic failures).

There was a higher proportion of virologic failures with the baseline IN L74I substitution in the CAB and CAR arms (6%; 3/53 and 2%; 1/45, respectively), whereas 0.4% (1/224) of virologic failures in the CAB arm and 0.9% (2/234) in the CAR arm had no baseline IN L74I polymorphism (Table 43). Additionally, a high proportion of the virologic failures were from Russia and had the IN L74I polymorphism.

Of note, a high proportion of subjects with both subtype A1 and the IN L74I were virologic failures: 60% (3/5) in the CAB arm compared to 33% (1/3) in the CAR arm (Table 43).

More subtype A1 subjects who also had baseline IN L74I experienced virologic failure (60%) (Table 43). The subtype A1 subjects without L74I did not experience virologic failure. Most of the subjects with subtype B did not have IN L74I at baseline. However, there were 11 subtype B subjects in the CAB arm who had IN L74I, but none of these subjects experienced virologic failure. Thus, the mere presence of IN L74I in other subtypes did not correlate with virologic failure.

Table 43. Rate of Virologic Failure in FLAIR Trial: Baseline Analysis (Russia, Subtype A1 and B. and Presence of IN L74I) (FDA Analysis)

Subgroup	All	CAB	CAR
Overall	7/566 (1.2%)	4/277 (1.4%)	3/279 (1.1%)
Presence of IN L74I at baseline	4/98 (4%)	3/53 (6%)	1/45 (2%)
IN L74I+IN T124S	4/63 (6%)	3/35 (9%)	1/28 (4%)
No L74I at baseline	3/458 (0.7%)	1/224 (0.4%)	2/234 (0.9%)
Subtype A1	4/12 (33%)	3/8 (38%)	1/4 (25%)
+IN L74I	4/8 (50%)	3/5 (60%)	1/3 (33%)
IN L74I	0/4 (0%)	0/3 (0%)	0/1 (0%)
Subtype B	2/348 (1%)	0/174 (0%)	2/174 (1%)
+IN L74I	0/22 (0%)	0/12 (0%)	0/11 (0%)
IN L74I	2/324 (0.6%)	0/153 (0%)	2/150 (1%)
Missing data	0/22	0/9	0/13
Russia	5/93 (5%)	4/54 (7%)	1/39 (3%)
+IN L74I	4/64 (6%)	3/35 (9%)	1/29 (3%)
-IN L74I	1/19 (5%)	1/12 (8%)	0/7 (0%)
Missing data	0/10	0/7	0/3

Abbreviations: CAB = cabotegravir, CAR = current antiretroviral

In summary, the rate of CAB+RPV virologic failure was higher in subjects with subtype A1 who also had the IN L74I polymorphism. Five of the seven CAB+RPV virologic failures in FLAIR and ATLAS had HIV-1 subtype A1 and the IN L74I polymorphism detected at baseline and failure time points. Subjects with subtype A1 infection whose virus did not have IN L74I at baseline did not experience virologic failure. In addition, there was no detectable phenotypic resistance to CAB conferred by the presence of IN L74I at baseline.

The other two virologic failures had subtype AG and did not have the IN L74I polymorphism. Six of the virologic failures with subtype A1 and AG were from Russia, where the prevalence of subtypes A, A1, and AG are high. Subtypes A, A1, and AG are uncommon in the United States. The presence of the IN L74I substitution in other subtypes, such as subtype B commonly seen in the United States, was not associated with virologic failure.

7.7.1.3. Cross-Resistance With INSTI and NNRTI Drug Classes in Virologic Failures

Issue

The CAB and RPV resistance substitutions selected in clinical studies confer cross-resistance to other INSTIs and NNRTIs, respectively. Thus, future treatment options with other INSTIs and NNRTIs for CAB+RPV virologic failures may be compromised.

Conclusion

The CAB resistance substitutions selected in FLAIR and ATLAS clinical trials (i.e., G140R, Q148R and N155H) confer cross-resistance to other INSTIs. However, in some cases, the INSTI DTG may still be an option for CAB-resistant virologic failures. RPV resistance substitutions selected in the clinical trials (i.e., K101E, V108I, E138A or K, and H22L) confer cross-resistance to the other NNRTIs and will limit future options for this drug class.

Additionally, based on the prolonged residual exposures for both CAB and RPV, there is a concern about resistance emergence to RPV and/or CAB after patients stop treatment and if they do not start a new suppressive ARV treatment regimen. If they develop resistance to RPV and/or CAB, the patients will have limited available treatment options because of cross-resistance with other drugs in the INSTI and NNRTI classes (see Section 7.7.2).

Assessment

In cell culture assessments, the single INSTI resistance substitutions G118R, Q148K, Q148R, and combinations of INSTI resistance substitutions T66K+L74M, E92Q+N155H, E138A+Q148R, E138K+Q148K/R, G140C+Q148R, G140S+Q148H/K/R, Y143H+N155H, and Q148+N155H had >5-fold reduced susceptibility to CAB. All of these substitutions except G140S+Q148K were cross-resistant to RAL (>5-fold reduced susceptibility). Only substitutions G118R, G140S+Q148R, and Q148R+N155H conferred cross-resistance to DTG with 10-fold, 8-fold, and 10-fold reduced susceptibility, respectively (See Section III.18.3.2, Table 215). As expected, viruses harboring RT or PI RAS retained susceptibility to CAB in cell culture. In summary, the cell culture experiments show CAB resistance substitutions can confer cross-resistance to the other INSTIs but retain susceptibility to other ARV classes (NNRTIs, NRTIs, and PIs).

In the FLAIR and ATLAS clinical trials, INSTI resistance substitutions G140R, Q148R, and N155H emerged on CAB+RPV treatment (Table 44). The IN G140R substitution emerged in 1 virologic failure with 6.7-fold reduced susceptibility to CAB. IN Q148R emerged in 2 virologic failures and conferred 5.2-fold and 9.4-fold reduced susceptibility to CAB. The IN N155H substitution emerged in 1 virologic failure and conferred 2.7-fold reduced CAB susceptibility. These emergent substitutions conferred cross-resistance to BIC, EVG, and RAL, but retained susceptibility to DTG (0.95- to 2.2-fold change).

The NNRTI resistance substitutions that emerged on CAB+RPV treatment were E138A or K (n=4), V108I (n=1), K101E (n=1), and H221H/L (n=1) (Table 44). In addition to resistance to RPV, virologic failure isolates with RT E138A or K substitutions were cross-resistant to ETR. Virologic failure isolates with K101E or V108I were resistant to EFV, etravirine (ETR), and nevirapine, as well as RPV. In one virologic failure, the H221L substitution emerged as a mixture along with the E138K but had no detectable RPV phenotypic resistance. However, this substitution is listed as an RPV resistance substitution in the IAS-USA 2019 Update of the Drug Resistance Mutations in HIV-1.[13] In summary, resistance analyses from the clinical trials show that emergent substitutions in CAB+RPV virologic failures can confer cross-resistance to other INSTIs and NNRTIs. However, each of the virologic failures still had DTG available as an INSTI option based on phenotypic data.

Table 44. Phenotype and Cross-Resistance of Emergent Substitutions in Cabotegravir (CAB) Arms of FLAIR and ATLAS (FDA Analysis)

CAB Resistance Substitutions	# Subjects	CAB Phenotypic Fold-Change at Virologic Failure	DTG Phenotypic Fold-Change at Virologic Failure	INSTI Cross-Resistance
G140R	1	6.7	2.2	BIC, RAL-resistant; DTG sensitive
Q148R	2	5.2, 9.4	0.95, 1.1	BIC, EVG, RAL-resistant; DTG sensitive
N155H	1	2.7	1.2	RAL, EVG-resistant; DTG sensitive
RPV Resistance Substitutions		**RPV Phenotypic FC at VF**		**NNRTI Cross-Resistance**
E138A/K/T	4	0.97, 2.4, 6.5, 7.1		ETR, RPV-resistant
V108I	1	3.7		EFV, NVP, RPV-resistant
K101E	1	2.6		EFV, ETR, NVP, RPV-resistant
H221H/L	1	0.97		RPV-resistant

Abbreviations: BIC = bictegravir, DTG = dolutegravir, EFV = efavirenz, ETR = etravirine, EVG = elvitegravir, FC = fold change, INSTI = integrase strand transfer inhibitor, NNRTI = nonnucleoside reverse transcriptase inhibitor, NVP = nevirapine, RAL = raltegravir, RPV = rilpivirine, VF = virologic failure

7.7.2. Risks Associated With Nonadherence in the Setting of Residual CAB and RPV Concentrations

Issue

There is the potential for development of resistance following nonadherence to monthly injection visits or not initiating suppressive regimen within 30 days after the last CAB+RPB injection.

The prolonged residual concentrations of both CAB and RPV are concerns for the potential development of resistance to RPV and CAB and cross-resistance to other drugs in the INSTI and NNRTI class during the period of treatment interruption or following treatment discontinuation.

Conclusion

As shown in the "Assessment" section below, after CAB+RPV discontinuation, the time to reach suboptimal concentrations varies among subjects. Regardless, in every individual, the residual concentrations of CAB and RPV will eventually reach an ineffective concentration while remaining high enough to provide selective pressure for resistance development to CAB or RPV. Even after 18 months post discontinuation, the residual CAB and RPV concentrations could still result in the development of resistance to CAB and RPV. This underscores the importance of initiating another suppressive regimen within 30 days after the last IM injection of CAB+RPV and the importance of patient selection and adherence counseling in order to minimize the development of resistance. As shown above in Section 7.7.1.3 resistance to CAB and RPV confers cross-resistance to other INSTIs and NNRTIs; therefore, patients will have limited treatment options after developing resistance to the CAB+RPV regimen.

To minimize the potential risk for developing resistance to CAB or RPV, careful selection of patients is important to identify those who agree to and will follow the required monthly dosing schedule. For planned missed injections, the proposed labeling for use of oral dosing and the strategy to reinitiate IM dosing is adequate to minimize the potential risk of resistance (section 5;

Residual CAB and RPV Concentrations After Discontinuation). Additionally, to minimize development of resistance patients should initiate an alternative, fully suppressive ARV regimen no later than 1 month after the final injection of CABENUVA. Additional labeling as proposed by the review team in sections 2 and 5 are adequate to convey these strategies.

Assessment

The following calculations were done to illustrate the variability in the range of residual CAB and RPV concentrations after discontinuation. The residual concentrations of CAB and RPV will eventually not be sufficient for efficacy and may result in development of resistance to CAB and RPV as well as the INSTI and NNRTI drug class.

The Applicant provided a PA-EC_{90} value of 0.166 μg/mL (411nM) for CAB and a PA-EC_{90} value of 12 ng/mL for RPV in the clinical pharmacology summary using an EC_{50} value for CAB of 0.25nM generated in HIV-1 Ba-L–infected PBMCs and EC_{90} value of 1.8nM (0.66 ng/mL) determined in human MT4 T-cells.

In the FDA assessment, using the lowest and highest PA-EC_{90} values of 25nM and 2,039nM, respectively, the trough plasma concentration (Cτ) for CAB would range between 0.03 μg/mL and 0.826 μg/mL. Thus, using the median EC_{90} value from Table 211 of 0.85nM with a serum binding value of 660-fold, the FDA calculated PA-EC_{90} for CAB equals 561nM or 0.227 μg/mL. Similar to the Applicant's calculations, the FDA calculated PA-EC_{90} values for RPV using EC_{90} values of 1.12nM to 1.79nM and the protein binding ratio of 18.5, which gave values between 21nM and 33nM (7.7 ng/mL to 12 ng/mL).

At 6 to <12 months, the range in concentrations of the detectable sample for both sexes is below or near the PA-EC_{90} (using either FDA calculated PA-median EC_{90} value of 0.227 μg/mL or Applicant's value of 0.166 μg/mL) (Table 45). At 12 to <18 months, the detectable concentrations are below the PA-EC_{90} in both males and females. Given the variability in the range of residual CAB concentrations after discontinuing the CAB+RPV regimen, the concentrations of CAB will eventually not be sufficient for efficacy but may be high enough to provide selective pressure and select for resistance to CAB. Thus, resistance to CAB and cross-resistance to INSTIs (see Section 7.7.1.3) can occur and are a concern if patients do not start another active ARV regimen after discontinuing treatment with CAB+RPV or are lost to follow-up and do not return to the clinic for treatment.

Table 45. Cabotegravir (CAB) Detectable and BQL Samples by Sampling Time and Sex in the PopPK Dataset (n=16 Pooled Studies)

Sex	Time Since Last Dose (Months)	N Detectable Samples	N BQL Samples	Percentage Detectable Samples (%)	Median (Range) Concentration of Detectable Samples (µg/mL)
Male	<6	17575	78	99.6%	2.47 (0.0104, 33.2)
Female	<6	5423	6	99.9%	2.83 (0.0120, 21.1)
Male	6–<12	97	191	33.7%	0.109 (0.0264, 1.69)
Female	6–<12	156	31	83.4%	0.269 (0.0259, 2.11)
Male	12–<18	31	143	17.8%	0.0693 (0.0279, 0.346)
Female	12–<18	95	85	52.8%	0.105 (0.0260, 0.509)
Male	>18	3	8	27.3%	0.0756 (0.0675, 0.0905)
Female	>18	9	12	42.9%	0.0733 (0.0320, 0.270)

Source: Reviewer's analysis of the CAB popPK dataset.
In the CAB popPK dataset, 26% of subjects were female and 24% of samples were contributed by females.
BQL = 0.010 µg/mL or 0.025 µg/mL in CAB studies
Target trough concentration for CAB: range 0.01 – 0.826 µg/mL [mean 0.43 µg/mL or median 0.23 µg/mL]
Abbreviations: BQL = below the limit of quantification

Likewise, the detectable concentrations of RPV are below the PA-EC_{90} 12 ng/mL after 6 months (Table 46). Therefore, RPV concentrations can also be below the PA-EC_{90} after discontinuing the CAB+RPV regimen. The RPV concentration may not be high enough to provide efficacy but able to provide selective pressure resulting in RPV resistance. As with CAB, there is a concern that resistance to RPV and cross-resistance to the NNRTI class can occur in patients (see Section 7.7.1.3) who do not start another active ARV regimen after discontinuing treatment with CAB+RPV or are lost to follow-up and do not return to the clinic for treatment.

Table 46. Rilpivirine (RPV) Observed Concentrations by Sampling Time and Sex in the PopPK Dataset (n=7 Pooled Studies)

Sex	Time Since Last Dose (Months)	N Samples	Median (Range) Concentration (ng/mL)
Male	<6	13702	68.9 (1.00, 830)
Female	<6	4346	62.9 (1.00, 388)
Male	6-<12	103	5.01 (2.07, 24.9)
Female	6-<12	97	6.05 (2.34, 17.9)

Source: Reviewer's analysis of the RPV popPK dataset.
In the RPV popPK dataset, 25% of subjects were female and 24% of samples were contributed by females.
All samples were above the BQL of 1 ng/mL.
Target trough concentration for RPV: 12 ng/mL

7.7.3. Potential Risk of Embryo-Fetal Toxicity: Structural Similarity With DTG and Risk of Neural Tube Defects

Issue

The structural similarity between DTG and CAB concerned the review team due to potential embryo-fetal risk with CAB exposure. DTG is an INSTI associated with NTD, identified in a prospective observational trial in Botswana (the Tsepamo study). The similarity index value (Tanimoto Coefficient) for CAB (relative to DTG) is 0.93. Though too premature for a definitive conclusion, at least one in vitro study suggests DTG and CAB may be a partial antagonist of the folate receptor α.[14] The Applicant, ViiV, also conducted in vitro study to assess for interaction

between INSTIs and folate receptors, as described in Section III.13.1. Additional nonclinical studies are currently ongoing. Given this information, the review team questioned what level of risk communication would be appropriate for labeling.

Conclusion

Labeling based on structural similarity should be included in Section 8.1 (Risk Summary), of the USPI as described below. This approach is consistent with the labeling approach for BIC, another INSTI also structurally similar to DTG, with a Tanimoto Coefficient of 0.90. As additional nonclinical studies are currently ongoing to support/refute the interactions between various INSTIs and folate receptors, the Division plans to evaluate the totality of the data, then make informed recommendations regarding the extent of the labeling for INSTIs, including INSTIs with structural similarity to DTG. The following text is included in CABENUVA USPI.

> While there are insufficient human data to assess the risk of neural tube defects (NTDs) with exposure to CABENUVA during pregnancy, NTDs were associated with dolutegravir, another integrase inhibitor.
>
> Discuss the benefit-risk of using CABENUVA with individuals of childbearing potential or during pregnancy
>
> Cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of CABENUVA; therefore, consideration should be given to the potential for fetal exposure during pregnancy

Assessment

Previously, the Division considered two labeling approaches for NTD risk communication: broad, INSTIs class-labeling; or selective labeling based on degree of structural similarities to DTG. The approaches were presented and discussed before the Medical Policy Council. The Division of Antiviral (DAV) concluded the available evidence did not supported class labeling. Specifically, NTD labeling for RAL or ELV was not warranted because neither is structurally similar to DTG. RAL and ELV lacked nonclinical evidence of embryo-fetal toxicity signal, and both have supportive postmarketing clinical information in WOCBP or pregnant women. Moreover, broad class labeling would negatively impact public health by unnecessarily limiting treatment options for WOCBP or pregnant women. The Medical Policy Council supported the DAVs decision to include labeling for NTD risk based on structural similarity.

At the time of the Medical Policy Council discussion, BIC was the only approved INSTI structurally similar to DTG. While DAVP considered updating BIC labeling to reflect the language that is included in the DTG USPI (with respect to sections 2 and 5), the Division became aware of several ongoing nonclinical (animal models and in vitro) studies. The objectives of these studies are to further elucidate the potential mechanism of action for causing NTD. As mentioned above, these studies will hopefully support or refute the interactions between various INSTIs and folate receptors. Therefore, the Division prefers evaluating all the data to help make informed recommendations regarding the extent of the labeling for other INSTIs. Until then, to communicate risk, the DAV recommends including a statement cross-referencing DTG in section 8 of CAB and BIC USPIs.

7.7.4. Injection Reactions

Issue

As discussed previously, ISRs were common, and the proposed label adequately describes the risk. ISRs were also observed following both IM and subcutaneous dosing in the 3-month bridging study in rats (see Section 7.1 for more information). During review of the phase 3 data, the team also noted systemic/general AEs occurring in association with injection administration, with or without ISRs. Therefore, the review was broadened to evaluate: 1) isolated, local ISRs and 2) systemic reactions in association with injection (with or without ISRs). Another risk is administration errors, including injuries to adjacent tissues such as sciatic nerve or penetrating blood vessels and administering medication partially intravenously.

Conclusion

Local ISRs were frequently reported during the maintenance period and are adequately labeled. Importantly, CAB+RPV administration is also associated with systemic reactions, including pyrexia, sciatica, and musculoskeletal pain, as evident by the temporal relationships between the systemic events and the injections/ISRs. The local and systemic risks are equally important and are now included in product labeling. Rare but serious postinjection events such as vasovagal reactions and other reactions including a constellation of symptoms (dyspnea, hypotension, nausea, sweating) were also reported. The constellation of symptoms noted were likely related to inadvertent intravenous administration of drug. The WARNINGS and PRECAUTION section includes language to communicate this risk.

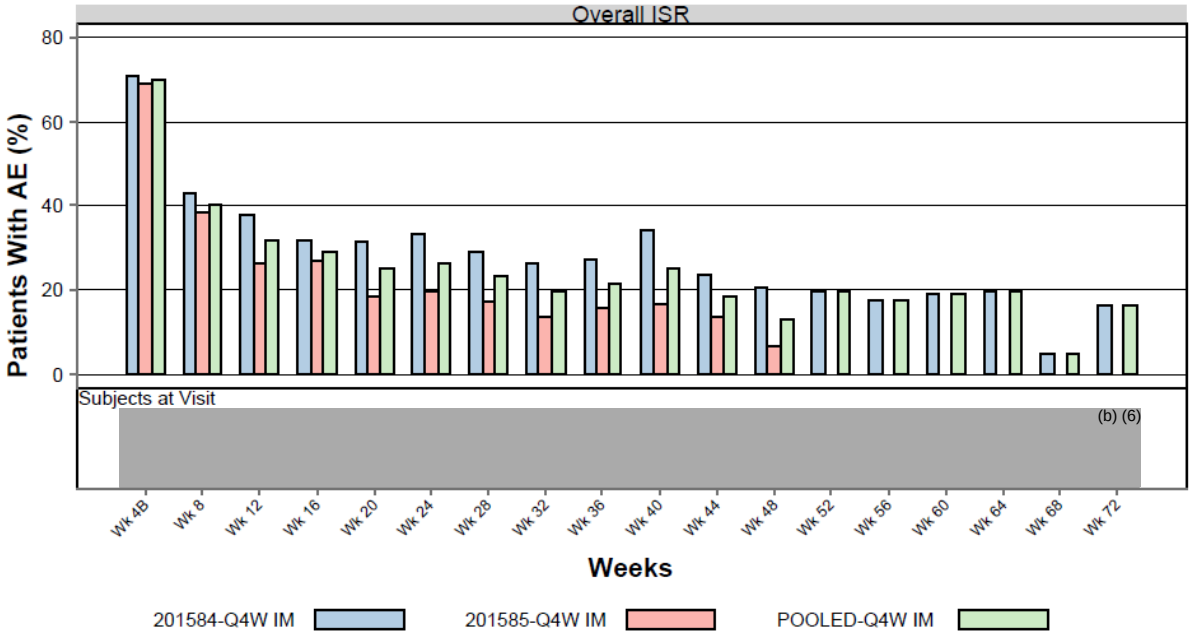
Assessments

Local ISRs

Local ISRs were frequently reported during the maintenance period. Overall, 83% of subjects had at least 1 local ISR (all cause, all grade). Most ISRs were grade 1(75%) or grade 2 (36%). Grade 3 events were reported in 4% of subjects; no grade 4 ISRs were reported. Six subjects (1%) discontinued treatment due to ISRs. Pain was the most common ISR. Abscess and cellulitis at the injection site were rarely reported during the clinical trial. Refer to Section III.17.6.2 for additional details.

The Applicant also conducted an analysis to assess frequency of ISR reporting as a function of time. As summarized in the figure below (Figure 26), the number of reported ISRs appears to decrease over the course of the maintenance period. While this finding is reassuring, one cannot confidently conclude the reason for the decreased reporting is due to absence of events. It is conceivable that subjects stopped reporting ISRs because of increased tolerance and not due to lack of events. (b) (4)

Figure 26. Incidence of Overall ISR AEs During Mainentance Period, FLAIR and ATLAS



Source: Applicant's CSR ISS NDA 212888, page 54
Abbreviations: AE = adverse event, IM = intramuscular, ISR = injection site reaction, Q4W = every 4 weeks

Systemic Reaction in Association With Injection or ISRs

As mentioned in Section 7.6.6, due to the concern that "pyrexia" may also be associated with systemic medical events, the temporal relationship between "pyrexia" and HSR was assessed. As part of the HSR spectrum, drug allergic reaction was also evaluated. Timing of the injection administration (and ISRs) therefore became part of the analysis for systemic events in association with pyrexia. The analyses identified that injection and/or ISRs was temporally associated with a) pyrexia, b) musculoskeletal events, c) sciatica, and d) other systemic events.

Pyrexia

We conducted analyses to evaluate for evidence of a temporal relationship (i.e., within 7 days) between "pyrexia" and ISRs or injection of the drug products. For reference of pooled terms defining "pyrexia," please see Section III.17.6.1.

A temporal association was observed between "pyrexia" and ISRs, as evident by the higher occurrence of "pyrexia" within ≤7 days after an ISR compared to >7 days: 79 events out of 3,663 ISRs (2%), and 47 events out of 3,663 ISRs (1%), respectively.

Similarly, there were more "pyrexia" events occurring within ≤7 days after the injection visit (i.e., irrespective of the presence of ISR). Within 7 days postinjection visit, a "pyrexia" event was reported in 107 out of 136 occurrences, (79%), compared to "pyrexia" occurring after 7 days postinjection (25 out of 136 occurrences [18%]). This finding also suggests a likely temporal association between "pyrexia" and injection.

Additional analyses were conducted to evaluate the incidence of "pyrexia" among subjects with higher than average CAB or RPV C_{max} values (>10 or 400 µg/mL, respectively). Among the 26

subjects with high CAB or RPV C_{max} values, 8 (31%) reported "pyrexia" at the time of the elevated C_{max}. Refer to Section III.17.6.4 for details. One subject also experienced "orthostatic hypotension" (see "Other Postinjection Systemic Reactions" below).

Musculoskeletal Events

The incidence of musculoskeletal events (grouped terms back pain, myalgia, and pain in extremity) was higher in the CAB+RPV treatment group compared to the control group: 74 subjects (13%, 91 events) and 36 subjects (<6%, 45 events), respectively. Additionally, of the 91 events, at least 40% occurred within 7 days after administration of injection.

Sciatica

The incidence of sciatica was higher in the CAB+RPV treatment group compared to the control groups: 10 (2%) and 3 (<1%), respectively. While the events were not treatment-related or led to treatment discontinuation, the observed imbalance in the number of subjects with sciatica is concerning, considering the mode and site of administration—injections in the gluteal muscle. An analysis was therefore conducted to assess for temporal association. Of the 10 subjects with sciatica (11 events), approximately 55% reported sciatica within 7 days of an injection.

Other Post-injection Systemic Reactions, Including Vasovagal Reactions

Presyncopal or vasovagal reactions were reported in <1% of subjects. For additional assessment of exposure-events analysis of the phase 3 data, refer to Section III.17.6.4.

During the development program, at least two serious cases suggestive of vasovagal reaction were reported. These cases were in the setting of inadvertent intravenous or partial intravenous administration of study drugs. The cases are summarized below:

> Case 1 (b) (6)): The subject is a 42-year-old female from South Africa enrolled in ATLAS-2M trial who experienced a grade 3 presyncope approximately 40 weeks after initiation of intramuscular treatment with CAB+RPV IM. The event occurred within 3 minutes of IM injections. The subject developed a sudden drop in blood pressure (from baseline of 123/79 mmHg to 68/22 mmHg) and heart rate (from 71 bpm to 65 bpm) with dizziness, heavy sensation on the chest, a strange sense of smell, numbness of the face, and abdominal cramps. No loss of consciousness or nausea were reported. During the event the lungs were clear. No medications were administered for her symptoms. The subject had history of cocaine use, but no history of atopy or asthma. Blood chemistry, including troponins were normal. Electrocardiograms (ECG) revealed normal sinus rhythm with heart rate of 73 bpm and QTcB interval of 430 ms to 431 ms. RPV concentration (C_{max}) was higher than expected. She was transferred to the unit of the hospital for observation but she discharged herself without having been assessed by a clinician. CAB+RPV were continued.
>
> Given the onset of symptoms of shortness of breath and the chest pain immediately after administration of the study drugs and full recovery without treatment within 15 minutes, suggests the plausibility of a vasovagal reaction.

Case 2 ([redacted]): The subject is a 44-year-old female from Sweden enrolled in ATLAS-2M. She had received CAB+RPV for at least 56 days at the time of the serious, grade 3 "allergic reaction." The subject began to experience the symptoms while the needle was in situ. Within minutes, she started feeling tingling in the throat, shortness of breath, nausea, and sweating. Auscultation of the lungs was clear and pulse was regular. ECG showed no change from earlier ECG, P-Troponin was <5; CK and CK-muscle/brain were negative. Within ten minutes after onset of the symptoms and prior to the administration of any treatment, the subject began to recover. Tryptase level was normal. The RPV plasma concentration measured 3 hours after study drug administration was 1490 ng/mL, which was higher than expected from an intramuscular injection, and consistent with (partial) intravenous administration of RPV. Per the investigator after the initial report, his opinion was "that the reaction was caused by the injection, the very rapid onset of nausea, dyspnea and sweating leads me to think of not allergic but rather a reaction to a temporary high concentration of the injected substances." The subject was treated with steroid and epinephrine; event resolved and CAB+RPV were discontinued. The diagnosis of 'allergic reaction' was revised to reflect it was likely related to inadvertent intravenous administration of RPV.

7.7.5. Weight Increase

Issue

Weight increase is as an important risk recently identified in association with certain INSTI use. Potential interaction with concomitant use of tenofovir alafenamide was also identified as a potential risk for weight increase. Furthermore, baseline covariates such as gender (female) and race (black) appear to increase the risk of weight gain.[9] The clinical significance of the weight increase in association with INSTIs exposure is still under investigation. Given this recent finding, change in weight was an important review issue for consideration.

Conclusion

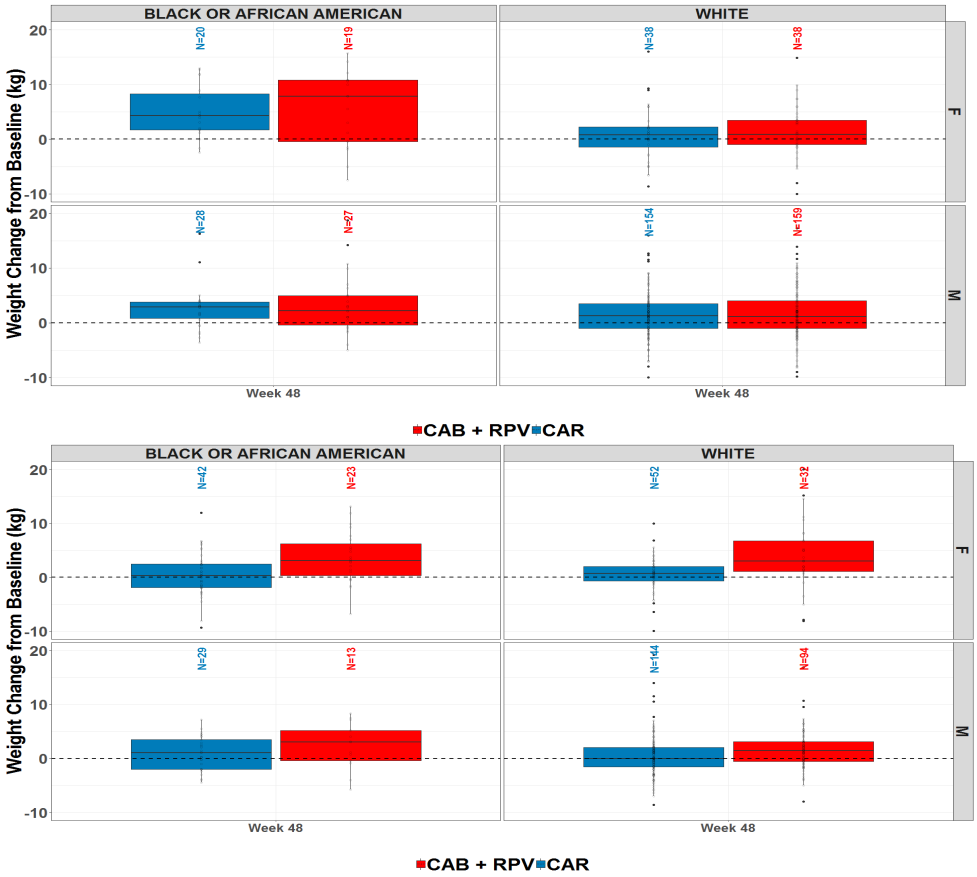
In summary, weight gain was observed in the CAB+RPV treatment group and in the control groups. The median weight increases in the CAB+RPV treatment group and the ABC/DTG/3TC treatment group were higher than the CAR treatment group, likely due to lower proportion of INSTI use as part of the regimen in the CAR group. The observed weight increase was also most pronounced in women and black subjects. The proposed labeling adequately describes the observation from the clinical trials. While the observed weight gain is likely associated with INSTI exposure, the clinical implication of the observed weight gain such as cardiovascular or other metabolic risks will require more data and longer follow-up data. If weight gain results in cardiovascular or other metabolic risks, then additional labeling may be warranted in the WARNINGS and PRECAUTIONS section.

Assessment

In the FLAIR trial, the median weight increase at week 48 was 1.3 kg for CAB+RPV-treated subjects compared with 1.5 kg in ABC/DTG/3TC-treated subjects. In the ATLAS trial, CAB+RPV-treated subjects had a median weight increase of 1.8 kg, compared with a 0.3 kg weight gain in the CAR-treated subjects.

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)
The following figures summarize the effect of race and gender on weight gain in the two phase 3 clinical trials. The findings are consistent with previous reports.

Figure 27. Weight Gain by Race, Gender for FLAIR, ATLAS Trial, Maintenance Period



Source: Clinical Reviewer's and ADS analysis of integrated summary of safety (ISS) ADSL, ADVS datasets (Python)
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

To assess for increased cardiovascular and metabolic risks (e.g., elevated total cholesterol, LDL, hyperglycemia) in association with weight increase, the review team reviewed the laboratory data, including total cholesterol, HDL, LDL, elevated serum glucose, and glucose urine dipstick. During the maintenance period, no meaningful differences with respect to the aforementioned laboratory data were observed between the CAB+RPV treatment group and the control groups or between subjects who experienced at least a 1 kg weight increase compared to subjects who relatively maintained their baseline weight. This analysis has limited value in assessing the long-term cardiovascular or metabolic risks because the duration of treatment was for only 48 weeks. Longer data are necessary to determine if the observed weight increase leads to increased cardiovascular or metabolic risks.

8. Therapeutic Individualization

8.1. Intrinsic and Extrinsic Factors

Human clinical pharmacology studies (food effect, renal impairment, hepatic impairment, QT study, and DDI studies) were conducted with oral CAB 30 mg or oral RPV 25 mg, 75 mg, or 150 mg. C_{max} and AUC from oral CAB 30 mg exceeds C_{max} and AUC from CAB 400 mg IM. C_{max} and AUC from oral RPV 25 mg are similar to C_{max} and AUC from CAB 600 mg IM. Therefore, we agree the data from studies with oral CAB or RPV are applicable to IM administration.

8.1.1. Age, Body Weight, Body Mass Index, Needle Gauge and Length, Sex, Smoking Status, Split Injection

In population PK (popPK) analyses of the pivotal studies, intrinsic and extrinsic factors were evaluated for associations with CAB exposure (Section III.14.2.1.1). Statistically significant covariates included age, BMI, body weight, needle gauge and length, sex, smoking status, and split injection. Note split injections were only used in certain phase 1-2 studies, for example, 400 mg given as two 200 mg injections. Simulations were conducted to evaluate the clinical significance of these covariates. Due to a high efficacy rate (>90%) regardless of CAB or RPV exposure quartile in phase 3 studies, the 5th percentile of AUC and C_{min} values in pivotal studies were used as target concentrations for efficacy (714 µg·h/mL for AUC and 0.65 µg/mL for C_{min}).

Regarding CAB efficacy, the only subgroups with a significantly >5% of subjects below the efficacy target were females and obese subjects. After the first injection, significantly >5% of females and subjects with BMI ≥30 kg/m^2 had CAB exposures below the target for efficacy. At week 48, exposures were not lower in females versus males, and there was less of an effect of BMI ≥30 kg/m^2 versus BMI <30 kg/m^2 on the PK of CAB as compared to the initial injection. In the phase 3 studies, there was also a trend toward lower efficacy in women with BMI ≥30 kg/m^2 (Section 6.5.2). Due to the very low failure rate of 1.5% in phase 3 studies and the fact that exposures were relatively low only after the first injection, no CAB dose adjustment is warranted for female or obese patients.

Regarding CAB safety, target concentrations for safety were identified as the median C_{max} at an oral CAB dose of 60 mg (13.1 µg/mL). No AEs of interest were found to be related to CAB exposure, and <5% of subjects exceeded target concentrations for safety regardless of subgroup.

We do not recommend CAB dose adjustment based on any of the aforementioned subgroups.

In popPK analyses of the pivotal studies, intrinsic and extrinsic factors were evaluated for associations with RPV exposure (Section III.14.2.2.1).

The 5th percentile of AUC and C_{min} values in pivotal studies were used as target concentrations for efficacy (20,062 ng·h/mL for AUC and 17.3 ng/mL for C_{min}). Target concentrations for safety were identified as the highest RPV concentration that does not prolong the QT interval (551 ng/mL). Statistically significant covariates were age and study phase. The fraction of subjects with RPV exposures outside the efficacy or safety targets was not found to vary significantly with age category. We do not recommend RPV dose adjustment based on age.

8.1.2. Food Effect

The effect of food on the PK of oral CAB was evaluated in studies LAI117020 (moderate fat) and 205,696 (high fat). When administered with a moderate fat meal (30% fat, 670 calories) versus fasted, the CAB AUC ratio (90% CI) was 1.08 (0.98, 1.20). When administered with a high fat meal (53% fat, 870 calories) versus fasted, the CAB AUC ratio (90% CI) was 1.14 (1.02, 1.28). Because the phase 3 tablet formulation was not used in study LAI117020, results for the effect of a moderate-fat meal are not described in labeling. As oral RPV is to be taken with a meal (per the approved prescribing information of EDURANT), the phase 3 study protocols stated that recommended intake of oral CAB was with food at the same time as oral RPV.

Proposed labeling for oral CAB states it can be taken with or without food, and that when taken at the same time as oral RPV to take with a meal. We think the most common scenario is that patients would take CAB at the same time as RPV. Thus we proposed that labeling should state that oral CAB should be taken at the same time as RPV with a meal and the Applicant agreed.

8.1.3. Renal Impairment

Mild, Moderate, and Severe Renal Impairment

CAB renal impairment study 201,480 was conducted in subjects with severe renal impairment (creatinine clearance <30 mL/min based on 24-hour urine collection) and healthy matched control subjects. Subjects received a single oral dose of CAB 30 mg. In subjects with severe renal impairment versus those with normal renal function, the total CAB AUC ratio (90% CI) was 0.97 (0.84, 1.14). Unbound CAB concentration ratios (90% CI) measured at 2 hours and 24 hours postdose were 1.32 (0.81 to 2.12) and 1.67 (1.33 to 2.09).

As CAB is >99% bound and renal impairment can affect protein binding, unbound concentrations are of more interest than total concentrations. At 2 hours postdose, the mean 32% increased unbound concentration in severe renal impairment was not statistically significant. However, at 24 hours postdose, the mean 67% increased unbound concentration in severe renal impairment was statistically significant. However, from a safety perspective, concentrations closer to C_{max} (i.e., 2 hours postdose) would be of more relevance than concentrations measured 24 hours postdose.

Note, no CAB-related AEs were found to be associated with CAB C_{max}, AUC, or C_{min} and that the difference between the 5^{th} and 95^{th} percentiles and geometric means of PK parameters in phase 3 was ≥34%.

Oral RPV labeling states that for patients with mild or moderate renal impairment, no dose adjustment is necessary. For patients with severe renal impairment, increased monitoring for AEs is recommended.

We agree with proposed labeling, which states that for patients on CAB and RPV with mild or moderate renal impairment no dose adjustment is necessary, and for patients with severe renal impairment, increased monitoring for AEs is recommended. The Applicant agreed with this proposal.

End-Stage Renal Disease (ESRD)

No data are available for CAB or RPV in patients with ESRD, on or off dialysis. However, oral RPV labeling states that for patients with ESRD, increased monitoring for AEs is recommended. Due to the lack of data for either CAB or RPV, we propose that CABENUVA labeling should state that for patients with ESRD and not on dialysis, effects on the PK of CAB and RPV are unknown. As both CAB and RPV are highly protein bound (>99%), we proposed to state in labeling that for patients with ESRD on dialysis, no effect on the PK of CAB or RPV is expected. The Applicant agreed with these proposals.

8.1.4. Hepatic Impairment

The effect of hepatic impairment on the PK of CAB in subjects with hepatic impairment was evaluated in study 201479. Subjects with moderate hepatic impairment (Child-Pugh score of 7 to 9) and matched healthy control subjects received a single dose of CAB 30 mg. In subjects with moderate hepatic impairment versus healthy controls, the total CAB AUC ratio (90% CI) was 0.73 (0.50 to 1.06). In subjects with moderate hepatic impairment versus healthy controls, 2 and 24 hour CAB unbound concentration ratios (90% CI) were 1.40 (0.80 to 2.46) and 1.55 (0.82 to 2.94). Of note, none of the mean differences in total or unbound CAB exposure were statistically significant. Note, no CAB-related AEs were found to be associated with CAB C_{max}, AUC, or C_{min} and that the difference between the 5^{th} and 95^{th} percentiles and geometric means of PK parameters in phase 3 was ≥34%. Thus, the increases in CAB unbound concentration ratios are not clinically significant.

Oral RPV labeling states that no dose adjustment is necessary for patients with mild or moderate hepatic impairment, and RPV has not been studied in patients with severe hepatic impairment.

We agree with proposed labeling, which states that for patients with mild or moderate hepatic impairment, no dose adjustment of CAB or RPV is necessary, and that the effect of severe hepatic impairment on the PK of CAB or RPV is unknown.

8.1.5. UGT1A1 Polymorphisms

The effect of UGT1A1 polymorphisms on the PK of CAB was evaluated via a retrospective, noninterventional pharmacogenomics (PGx) analysis. For the PK PGx analysis, the data were derived from four phase 1 and two phase 2 studies (ITZ111839, LAI116181, LAI115428, LAI116815, LAI116482, and 200056) and included subjects who received oral CAB 30 mg once daily administration for at least 8 days. The PGx analysis population (N=347) was genotyped for the variants rs4148323 (*6 allele) and rs8175347 (*1/*28/*36/*37 alleles) via either (b) (4) UGT1A1 reduced function (47%), and low function (16%) subjects had increased CAB C_{tau} (117% and 150%, respectively) as compared to normal function (37%) subjects.

The Applicant defined their normal, reduced, and low function phenotypes as subjects having 0, 1, or 2 copies of reduced function alleles (*6/*28/*36/*37), respectively. We agree with the Applicant's genotype to phenotype assignments. We agree with proposed labeling, which states that for patients on CAB and RPV, no clinically significant differences in the PK of CAB were observed based on UGT1A1 polymorphisms.

8.2. Drug Interactions

Note, no RPV DDI studies were conducted for these NDAs. With the exception of rifabutin, proposed labeling regarding DDIs with RPV are consistent with EDURANT labeling.

Effects of Other Drugs on CAB and RPV

CAB is primarily eliminated by UGT1A1 (major) and UGT1A9 (minor)-mediated metabolism. In vitro, CAB is a substrate of transporters P-gp and breast cancer resistance protein (BCRP); however, due to its high permeability, no interaction with P-gp or BCRP inhibitors is expected.

DDI studies evaluating effects on the PK of CAB were conducted with etravirine, RPV, and antimycobacterials rifabutin and rifampin. These studies were likely conducted because frequent concomitant use is anticipated (RPV) or because the other drug is an enzyme and/or transporter inducer that could affect the PK of CAB (etravirine, rifabutin, and rifampin). No significant changes in CAB PK parameters (geometric mean ratios of PK parameters were within 1.00 and 1.14) were observed when coadministered with etravirine or RPV. DDIs with antimycobacterials are described below.

RPV is primarily eliminated by cytochrome P450 (CYP) 3A-mediated metabolism.

Use of certain CYP3A and/or UGT1A1 inducers with CAB or RPV is contraindicated (see below).

PBPK modeling was conducted in lieu of clinical studies to evaluate the effect of UGT1A1 and UGT1A9 inhibitors on the PK of CAB. UGT1A1/9 inhibitors were predicted to have no significant effect on the PK of CAB. We agree with proposed labeling, which states that UGT1A1 inhibitors are not expected to interact with CAB. Because a selective UGT1A9 inhibitor was not used in the PBPK analyses, the predicted effect of a UGT1A9 inhibitor on CAB is not described in labeling (Section III.14.3).

Contraindications With Inducers of UGT1A1 and/or CYP3A

We agree with proposed labeling, which contraindicates use of CAB or RPV with following drugs due to induction of UGT1A1 and/or CYP3A: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, systemic dexamethasone (more than a single-dose treatment), and St John's wort. With the exception of rifabutin, due to CYP3A induction oral RPV labeling contains contraindications for the same drugs.

In separate DDI studies with rifabutin, the CAB and RPV PK parameter most affected was C_{24}. The CAB C_{24} (90% CI) ratio was 0.74 (0.70 to 0.78). Two RPV–rifabutin DDI studies were conducted. For RPV C_{24} after administration of RPV 25 mg with/without rifabutin, the RPV C_{24} ratio (90% CI) was 0.52 (0.46 to 0.59). For RPV C_{24} after administration of RPV 50 mg with rifabutin in comparison to RPV 25 mg alone, the RPV C_{24} ratio (90% CI) was 0.93 (0.85 to 1.01). Oral RPV labeling states that RPV 50 mg daily should be taken with rifabutin.

Using the 5th percentile of CAB and RPV C_{24} values from phase 3 studies as target concentrations for efficacy, the Applicant conducted simulations to evaluate the impact of rifabutin on CAB and RPV (30% increase in clearance for CAB, 72% increase in clearance for

RPV). After CAB 600 mg IM on week 1 followed by 400 mg Q4W IM, ~85% of subjects taking rifabutin were expected to reach the CAB target at week 4 and >95% of subjects by week 8. After RPV 900 mg IM on week 1 then 600 mg Q4W IM, ~75% of subjects taking rifabutin were expected to reach the RPV target at week 4 and >95% of subjects by week 8.

Without CAB or RPV dose adjustment, the majority of subjects on concomitant rifabutin are expected to maintain therapeutic CAB and RPV concentrations. Because HIV/TB co-infected patients are a very vulnerable population where the impact of lower CAB and RPV exposures is unknown, we agree with contraindication of rifabutin.

Antacids

No DDI study with CAB and an antacid was conducted. In phase 3 studies, antacids were to be taken at least 2 hours before or 4 hours after taking oral CAB (for consistency with labeling recommendations for oral RPV). Only eight subjects enrolled in phase 3 studies took antacids during the OLI or oral bridging to replace injections and PK sampling was insufficient to characterize the magnitude of a potential interaction of CAB with antacids.

Chelation to antacids is a class effect of INSTIs. The applicant assessed the potential for CAB to chelate in vitro and the results suggested that CAB chelated to a similar extent as DTG. PK data from DDI trials are available from other INSTIs where an antacid was given 2 hours before or within 4 hours after taking oral INSTI. Greatest exposure reductions were observed with bictegravir (mean C_{max} decreased by 58%) and RAL (mean C_{min} decreased by 62%). Considering that oral CAB 10 mg demonstrated induction and maintenance of virologic suppression in study LAI116482 (CAB C_{max} and AUC were approximately dose-proportional between 10 mg and 30 mg in this study) and antacids will be used on an intermittent basis during the OLI or oral bridging, the proposed staggering approach (antacids can be taken at least 2 hours before or 4 hours after taking oral CAB) is expected to circumvent the potential for significant decrease in CAB exposure when given with antacids.

Macrolides

According to prescribing information, QT prolongation has been reported in patients using azithromycin, clarithromycin, erythromycin, (b) (4) and the class of macrolides appears to be associated with Torsades de Pointes. Because RPV only prolongs the QT interval at doses ≥75 mg (RPV IM results in exposures similar to approved 25 mg PO), the approved oral RPV label states that due to azithromycin being a weak CYP3A inhibitor, consider use of azithromycin as an alternative to clarithromycin (strong inhibitor) or erythromycin (moderate inhibitor) to mitigate the risk of QT prolongation associated with elevated RPV exposures.

The language proposed by the Applicant in the Warning section of the CABENUVA label (CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes) seems to suggest the risk of QT prolongation regardless of whether RPV exposures are therapeutic or elevated.

To clarify that the macrolide-RPV interaction has a PK and pharmacodynamic component, the clinical comment was modified to the following: “Macrolides are expected to increase concentrations of rilpivirine and are associated with a risk of Torsade de Pointes [Warnings and

Precautions (5.5)]. Where possible, consider alternatives, such as azithromycin, which increases rilpivirine concentrations less than other macrolides."

Effects of CAB and RPV on Other Drugs

In vitro, CAB is an inhibitor of transporters OAT1 and OAT3. PBPK modeling was conducted in lieu of clinical studies to evaluate the effect of CAB on the PK of substrates of OAT1 or OAT3. We disagreed with proposed labeling, which stated (b) (4) . Based on sensitivity analyses accounting for uncertainty in the potency of OAT1/3 inhibition by CAB, final labeling in section 12.3 states "cabotegravir may increase the AUC of OAT1/3 substrates up to approximately 80%" (see Section III.14.3).

When coadministered with CAB in clinical DDI studies, no significant changes in PK parameters of ethinyl estradiol, levonorgestrel, midazolam, or RPV were observed (geometric mean ratios of PK parameters ranged from 0.92 to 1.12).

Potential effects of RPV on other drugs are not discussed in EDURANT labeling but are discussed in the Clinical Pharmacology review of NDA 202022. However, the clinical significance of these potential interactions has not been demonstrated. Specifically, based on in vitro data, RPV is a possible inhibitor of CYP 2C8, 2C9; and 2D6 and is a possible inducer of CYP1A2. Based on in vitro data and a DDI study with methadone, RPV is a weak inducer of CYP2B6.

Methadone

In a drug interaction study with RPV, geometric mean ratios of methadone PK parameters ranged from 0.78 to 0.87, and RPV exposure was unchanged. Methadone is a substrate of CYP 2B6 and 3A. As CAB is not an in vitro inhibitor or inducer of CYP3A4 or 2B6, no further interaction is expected when methadone is coadministered with CAB and RPV. We agree with proposed labeling stating that "monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients."

8.3. Pediatric Labeling/Plans for Pediatric Drug Development

Under the Pediatric Research Equity Act (PREA), the Applicant is required to conduct pediatric studies because this product contains a new molecular entity. Pursuant to this requirement, the Applicant has an agreed Pediatric Study Plan with a planned deferral of pediatric studies in subjects ≥2 years of age, and a waiver for subjects <2 years of age because studies would be highly impractical in this age group.

The Division will issue PREA postmarketing requirements (PMRs) requesting a study in pediatric subjects at least 2 years of age and weighing at least 10 kg. The three proposed PREA PMRs are:

CABENUVA

1) Conduct a study in subjects weighing 35 kg and higher (approximately 12 to less than 18 years of age) who are HIV-1–infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of CABENUVA. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.

Final protocol submission: N/A

Study completion: 7/2022

Final report submission: 1/2023

2) Conduct a study in subjects weighing 25 to less than 35 kg (approximately 6 to less than 12 years of age) who are HIV-1–infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of CABENUVA. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.

Final protocol submission:

Study completion: 6/2023

Final report submission: 12/2023

3) Conduct a study in subjects weighing 10 kg to less than 25 kg (approximately 2 to less than 6 years of age) who are HIV-1–infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, safety and tolerability, and antiviral activity of CABENUVA. Study participants must be monitored for a minimum of 24 weeks to assess safety and durability of antiviral response.

Final protocol submission:

Study completion: 02/2026

Final report submission: 08/2026

VOCABRIA

1) Conduct a study in subjects weighing 35 kg and higher (approximately 12 to less than 18 years of age) who are HIV-1–infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, tolerability, and short-term safety of VOCABRIA after 4-week administration in combination with other antiretroviral drug(s).

Final protocol submission: N/A

Study completion: 7/2022

Final report submission: 1/2023

2) Conduct a study in subjects weighing 25 kg to <35 kg (approximately 6 to less than 12 years of age) who are HIV-1–infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, tolerability, and short-term safety of VOCABRIA after 4-week administration in combination with other antiretroviral drug(s).

Final protocol submission:

Study completion: 6/2023

Final report submission: 12/2023

3) Conduct a study in subjects weighing 10 kg to <25 kg (approximately 2 to less than 6 years of age) who are HIV-1–infected, virologically suppressed (HIV-1 RNA <50 copies/mL) and on a stable antiretroviral regimen at the time of enrollment, to assess the pharmacokinetics, tolerability, and short-term safety of VOCABRIA after 4-week administration in combination with other antiretroviral drug(s).

Final protocol submission:

Study completion: 02/2026

Final report submission: 08/2026

8.4. Pregnancy and Lactation

Pregnancy

Nonclinical Data

The reproductive and developmental toxicology studies with CAB are summarized in Section 7.1. In the rat PPND study, a delay in the onset of parturition, increased stillbirths, and neonatal deaths by PND 4 were observed at 28× the human exposure at the RHD. These effects were attributed to CAB exposure during the period of gestation rather than during lactation, and were not observed at approximately 13× the human exposure at the RHD. In the combined fertility and embryo-fetal development study in rats, a minor decrease in fetal body weight was also observed at 28× the human exposure at the RHD. No drug-related effects on embryo-fetal development were observed in rabbits at exposures similar to human exposure at the RHD.

Clinical Data

Overall, during the CAB+RPV development program, 13 confirmed pregnancies were reported among subjects treated with CAB+RPV. Among these, 1 was ongoing, 5 were terminated electively, 4 resulted in spontaneous abortion/miscarriage and 3 resulted in live births. No congenital anomaly was reported with the live births. As the human pregnancy data are insufficient to make a conclusive statement about risk of congenital anomaly or pregnancy loss after exposure to CAB, the nonclinical data are key in informing risks.

Summary and Recommendation

There are insufficient human data on the use of CABENUVA during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. CABENUVA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus or the patient. The risks with CAB include fetal weight-loss/stillbirths and NTD. Risk assessment for NTD and the team's recommendation is discussed in Section 7.7.3. Risks of fetal weight-loss and stillbirths are discussed here.

CAB*:* The nonclinical data for CAB suggest embryo-fetal risks, including stillbirths and fetal weight loss. While the risks appear dose-dependent, stillbirths and fetal weight loss were observed at greater than 28× the exposure in humans at the RHD. Because of the large safety margin, the likelihood that the events will be observed in the clinical settings is minimal. Residual concentrations of CAB and RPV may remain in the systemic circulation of patients for prolonged periods (at least for 12 to 18 months) after discontinuation. Hence, even after discontinuing CAB+RPV, the theoretical embryo-fetal risk persists. However, these concentrations are expected to be exceedingly lower than the exposures observed in the nonclinical studies, increasing the safety margin. This risk is therefore considered significantly low.

RPV: No significant toxicological effects were observed in embryo-fetal toxicity studies with RPV in rats and rabbits with exposure 15× (rat) and 70× (rabbits) the exposure in humans. No adverse effects were noted in the offspring at maternal exposures up to 63× the exposure in humans at the RHD. Lower exposures with oral RPV were observed during pregnancy. Viral load should be monitored closely if the patient remains on CAB+RPV during pregnancy.

Based on the data summarized above, the team does not recommend additional labeling in sections 2 or 5 of the USPI, such as mandatory pregnancy testing or contraception before use, or restrictions for WOCBP. Such recommendation would unnecessarily deter CAB+RPV use among WOCBP, or lead to high discontinuation rate among women who become pregnant while on CAB+RPV regimen, which in turn could result in virologic failure and risk of HIV-1 transmission to the infant. A unique and attractive aspect of CAB+RPV for treatment is its long half-life, allowing for monthly dosing regimen. WOCBP should have access to CAB+RPV without creating potential limitations. Additionally, women who become pregnant while receiving CAB+RPV should consider the benefits and risk of continuing CAB+RPV against the alternative regimens. The review team, in consultation with the Division of Pediatric and Maternal Health and the Division of Bone, Reproductive, and Urologic Products, concluded that risk communication under 8.1 (risk summary) of the USPI is sufficient. The team recommends pharmacovigilance to collect pregnancy data through the Antiretroviral Pregnancy Registry.

9. Product Quality

For NDA 212888 (CABENUVA) each of the Office of Pharmaceutical Quality review teams found the product quality information acceptable from their perspectives - with the exception of the Office of Pharmaceutical Manufacturing Assessment team. Their CR recommendation is based on deficiencies observed at the GLAXO OPERATIONS UK LIMITED manufacturing facility for NDA 212888 (CABENUVA). Specifically, (b) (4)

(b) (4)

by the time of the action date. Furthermore, the Drug Master File (DMF (b) (4)) for RPV was found inadequate to support approval for NDA 212888. Therefore, from an OPQ perspective, this NDA is not recommended for approval in its present form until the above mentioned issues are satisfactorily resolved. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective

Approval—The Office of Pharmaceutical Quality review team has assessed NDA 212887 (VOCABRIA) with respect to Chemistry, Manufacturing, and Controls, and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. The Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

Although each discipline recommends approval for NDA 212877, this NDA will receive a CR action. As stated above, deficiencies were identified in the product quality information for the CABENUVA NDA. The approval of the VOCABRIA NDA is contingent on the approval of the CABENUVA NDA; therefore, the CABENUVA NDA deficiencies must be adequately addressed before the VOCABRIA NDA can be approved.

9.1. Device or Combination Product Considerations

The Center for Devices and Radiological Health (CDRH) recommends approval for the device constituent of the combination product. The Applicant used information gathered in the phase 3 clinical study to determine what devices to use in their copack. The Applicant followed the CDRH's recommendations from previous communications and used 510(k) cleared devices and a needle with a safety feature in their to-be-marketed copack kit. The device description, design controls, risk analysis, design verification, clinical validation, labeling, and quality systems/manufacturing controls were acceptable.

There are no outstanding unresolved information requests or any outstanding deficiencies. No postmarketing commitments or PMRs are recommended. See Appendix III.23 for further details.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The results of the clinical sites inspections support the conclusion that the studies were conducted adequately, and the data generated support the proposed indication. A total of four clinical investigator sites were selected for audit. The sites were chosen for inspection based primarily upon enrollment of relatively large numbers of subjects and participation in both the FLAIR and ATLAS Studies. They include: Dr. Miguel Gorgolas Hernandez-Morales (Protocol 201584/Site 225283), Dr. Maria Del Mar Masia (Protocol 201584/Site 225120 and Protocol

201585/Site 225163), Dr. Christopher Bettacchi (Protocol 201584/Site 222234 and Protocol 201585/Site 222290), and Dr. Franco Antonia Felizarta (Protocol 201584/Site 222193 and Protocol 201585/Site 222276). Please refer to Section III.21 for a summary of findings from clinical site inspections and Section III.24 for financial disclosure.

11. Advisory Committee Summary

CAB+RPV was not taken to an FDA advisory committee because no unexpected significant safety or efficacy issues were identified, and no controversial or challenging issues arose that would benefit from advisory committee discussion.

III. Appendices

12. Summary of Regulatory History

Table 47. Summary of Regulatory History

Date	Activity	Outcome
January 21, 2008	Investigational new drug application (IND) 101429 for CAB (referred to as GSK1265744 early in development) was submitted in the United States for the treatment of HIV-1 infection	
September 3, 2010	Type C meeting held with FDA to discuss early development plan for the extended-release injectable formulation of CAB.	FDA agreed with ViiV the submitted preliminary nonclinical data for the oral and injectable CAB formulations appear reasonable to support initiation of clinical trials with the extended-release formulation. The FDA also advised ViiV that the need for additional PK studies with the extended-release formulation is dependent on the results of the initial PK study, and whether the selected dose for the extended-release formulation results in similar exposure to the oral dose that was found to have antiviral activity (based on the comparison of the relevant PK parameter(s) between the two formulations).
September 17, 2010	IND 109678 for CAB extended-release, injectable suspension submitted for the treatment of HIV-1 infection	

Date	Activity	Outcome
March 27, 2012	Type C, clinical guidance, Face-to-Face meeting to discuss development plans for CAB (tablet and extended-release injectable) including use in combination with Janssen's rilpivirine tablet and RPV extended-release injectable for the treatment of HIV-1 infection	The FDA provided general advice for the planned phase 2b trials –LATTE and LATTE-2. The development proposed to first conduct LATTE trial to inform the LATTE-2 trial design. LATTE (LAI116482) is a Phase 2b, dose ranging study of oral CAB in combination with 2 NRTIs for induction of HIV-1 virologic suppression, followed by an evaluation of maintenance of virologic suppression with oral CAB combined with oral rilpivirine in HIV-1 infected, antiretroviral therapy naive adult subjects. Based on the Week 48 results of the trial, dose will be selected for oral CAB. LATTE-2 will initiate after review of LATTE trial. FDA recommended the dose selection to support dual regimen with CAB should be based on 48-week data from the maintenance phase (i.e. 72 weeks of treatment: 24 weeks induction plus 48 weeks maintenance data) to assess the durability of the dual regimen of oral CAB plus RPV. Additionally, to support dose selection for the extended-release CAB and RPV, leveraging PK, safety, and efficacy data from the oral formulations may be acceptable provided that the exposures from the doses selected for the extended-release are similar to the exposures observed with the oral tablets that were found to be generally safe with acceptable antiviral activity, as to be demonstrated by the Week 72 results from LATTE trial.
April 20, 2012	Result summary for LATTE submitted in support of initiation of LATTE-2 (200056). Study 200056 is a Phase IIb trial consisting of an Oral Induction Period to evaluate CAB 30 mg once daily plus 2 NRTIs, followed by a Maintenance Period where subjects are randomized 2:1 to receive either CAB IM + RPV IM or continue CAB 30 mg + 2NRTIs.	FDA was in general agreement and provided advice on trial deign, including dose selection and PK, safety and efficacy assessments. The protocol was subsequently amended to include evaluation of CAB IM + RPV IM administered every 4 or 8 weeks.
July 22, 2013	Summary of the safety, pharmacokinetics, and antiviral activity results from the ongoing phase 2b trials-LATTE and LATTE-2, to support initiation of the phase 3 trials.	Although ViiV initially selected the Q8W dosing frequency, ViiV revised the plan and selected the Q4W dosing frequency based on the virologic outcome after the Week 32 timepoint. The FDA suggested they continue the Q8W dosing in LATTE2 and consider adding a third arm in phase 3 trials to assess the Q8W dosing. ViiV agreed to allow the Q8W dosing in LATTE2 but declined to add a third arm in their phase 3 trial.

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Date	Activity	Outcome
August 28, 2015	Type C, CMC guidance, Teleconference meeting to discuss the development of cabotegravir injectable suspension	FDA provided feedback on ViiV's plans for the pivotal clinical and commercial drug product development, including input from OPQ's drug product, process, and biopharmaceutics teams.
September 17, 2015	Type C, Clinical guidance, Face-to-Face meeting to discuss development plans for oral and long-acting injectable formulation of GSK126574	ViiV plans to include a 48-week data from the Maintenance Phase of the phase 3 trials in the NDA submission to support use of LA CAB+RPV for maintenance of virologic suppression. ViiV clarified that oral CAB is being developed for a short-term use indication (i.e. for oral lead-in) and for use to bridge dosing when scheduled injectable doses are anticipated to be missed. The oral lead-in will allow for safety assessment prior to switching to the extended-release injectables. FDA agreed with the general proposed plan and advised ViiV to obtain feedback on feasibility and uptake of an injectable formulation for the treatment of HIV from key patients and key opinion leaders.
January 19, 2016	Draft protocols for two phase 3 studies (201584 and 201585) submitted to FDA	201584: A Phase III, Randomized, Multicenter, Parallel-Group, Open-Label Study Evaluating the Efficacy, Safety, and Tolerability of Long-Acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch from an Integrase Inhibitor Single Tablet Regimen in HIV-1 Infected Antiretroviral Therapy Naïve Adult Subjects 201585: A Phase III, Randomized, Multicenter, Parallel-group, Non-Inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Switching to Long-Acting Cabotegravir Plus Long-Acting Rilpivirine from current INI- NNRTI-, or PI-based Antiretroviral Regimen in HIV-1–infected Adults who are Virologically Suppressed
April 12, 2016	Type C, Clinical guidance, Teleconference meeting to discuss phase 3 clinical development program for cabotegravir LA in combination with rilpivirine LA for the treatment of HIV-1 infection	FDA agreed with ViiV to evaluate the proposed Q4W dosing regimen in phase 3 studies with a start date of September 2016. FDA also agreed that the two phase 3 switch studies, "Integrase Switch (201584)" and "Stable Switch (201585)," can serve as the basis for evaluation of the safety and effectiveness of CAB LA, in combination with RPV LA, to maintain virologic suppression in HIV-1–infected, virologically suppressed adults.

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Date	Activity	Outcome
August 19, 2016	Type B, End of phase 2 (Clinical), Teleconference meeting to discuss phase 3 clinical development program for cabotegravir LA in combination with rilpivirine LA for treatment of HIV-1 infection	FDA agreed with ViiV that existing phase 2b data and planned phase 3 data generated with the oral tablet can provide sufficient data to allow approval of oral CAB 30 mg for the following indications: a) Short-term oral lead-in dosing in combination with EDURANT for at least 4 weeks to assess tolerability of oral cabotegravir and rilpivirine prior to monthly maintenance administration of CAB/RPV LA for the treatment of HIV-1 infection b) Short-term oral therapy in combination with EDURANT for patients who will miss planned maintenance dosing with CAB/RPV LA.
November 15, 2016	Type B, End-of-phase 2 (CMC) Teleconference to discuss CMC topics concerning the phase 3 development program of cabotegravir oral tablets and LA formulation to support NDA submission	Guidance provided to ViiV on their proposed co-packaged kit of CAB LA+RPV LA. ViiV also confirmed plans to submit a draft human factors (HF) validation study for the FDA to review.
December 6, 2017	Type C, Teleconference meeting to discuss development of CAB LA+RPV LA co-pack	ViiV agreed with FDA's recommendations on the Instructions for Use (IFU) and indicated that the HF protocol will be submitted to the Agency in 2Q 2018.
May 1, 2018	Proposed Human Factors (HF) Validation Protocol and Interim Risk Assessment report submitted by ViiV	FDA reviewed and provided comments on the HF protocol on June 27, 2018.
July 12, 2018	Type C, Clinical guidance to discuss inclusion of Q8W clinical data in NDA.	FDA reviewed and provided comments to ViiV on September 21, 2018 that it was not in agreement with their proposal (b) (4)
January 23, 2019	Type B Correspondence, Pre-NDA Preliminary Comments (CMC)	Preliminary comments provided to Applicant were sufficient.
January 28, 2019	Type B, Face-to-Face, Pre-NDA Meeting	Proposals for the content and format of the two NDAs, one for oral CAB and the other for the co-package of CAB LA+RPV LA injectable regimen as well as the results of the phase 3 studies (ATLAS and FLAIR) was discussed.

Abbreviations: CAB = cabotegravir, CMC = Chemistry, Manufacturing, and Controls, GSK = GlaxoSmithKline, INI = integrase inhibitor, LA = long-acting, NNRTI = Nonnucleoside reverse transcriptase inh bitor, OPQ = Office of Pharmaceutical Quality, PI = protease inh bitor, PK = pharmacokinetic, PO = by mouth, PrEP = pre-exposure prophylaxis, Q4W = every 4 weeks, Q8W = every 8 weeks, RPV = rilpivirine

13. Pharmacology Toxicology Assessments and Additional Information

13.1. CAB

13.1.1. Summary Review of Studies Submitted Under IND

The oral form of CAB was originally reviewed under IND 101429, and the IM injectable form was reviewed under IND 109678. All nonclinical safety studies conducted in support of CAB were also submitted to the present NDAs and are reviewed in the following sections.

13.1.2. Pharmacology (Primary and Secondary)

The potential off-target effects of GSK1265744 were evaluated in a panel of 81 in vitro assays (study #RH2007/00209), including 16 enzymes and 65 receptors, ion channels and transporter binding sites (10µM drug), and 12 isolated tissue assays (up to 100µM drug). No drug-related effects, defined as >50% inhibition, were observed with the exception of a 53% inhibition of the melanocortin-4 receptor (MC4R). MC4R is involved in the regulation of energy homeostasis, blood pressure, glucose and lipid homeostasis, and reproductive activity; and MC4R mutations and antagonism can promote weight gain and obesity.[5,6]

13.1.3. Safety Pharmacology

Table 48. Safety Pharmacology Studies

Study Title (Study No.)	Findings
hERG Assay (Study #FD2007/00242)	hERG-transfected HEK-293 cells were treated with up to a GSK1265744 concentration of 17.61µM, or 7.14 µg/mL (limited by solubility). Potassium current was inhibited 28.5% at the highest concentration, and an IC_{50} was not identified. This was not considered to be of clinical concern.
Oral Cardiovascular Function Study in Monkeys (Study #CD2007/00707)	Heart rate, blood pressure, electrocardiography parameters, and body temperature were evaluated in cynomolgus monkeys (4 males/group) up to 76 hours after single oral gavage doses of GSK1265744 (0, 8, 25, and 1,000 mg/kg). Increases in heart rate (16-23%) and mean arterial pressure (3.7-8.6%) were observed at 1,000 mg/kg up to 2 hours postdose. NOEL =25 mg/kg.
Oral Respiratory Function Study in Rats (Study #CD2007/00268)	Respiratory parameters (respiratory rate, tidal volume, minute volume, and total pulmonary resistance) and body temperature were evaluated in Crl:CD(SD) rats (4 males/group) up to 7 days after single oral gavage doses of GSK1265744 (0, 30, 100, and 300 mg/kg). No drug-related effects were observed up to the highest dose tested. NOEL =300 mg/kg.

Abbreviations: AUC = area under the curve; IC_{50} = concentration inhibiting 50% activity; NOEL = no observed effect level

In addition, an assessment of neurobehavioral activity (functional observational battery including measurement of hind foot splay) was conducted as a part of the 14-day repeat-dose toxicology study in rats (study #RD2006/01741), and electrocardiography was performed in the 14-day (study #CD2007/00680), 4-week (study #CD2008/00632), and 39-week (study #RD2009/00027) repeat-dose toxicology studies in monkeys. No drug-related effects on these parameters were

observed in these studies. Please see the individual study reviews in Section 13.1.5 for more information.

13.1.4. Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics

The in vitro and in vivo studies designed to assess the PK of CAB are described below. In vivo studies were conducted in mice, rats, dogs, and monkeys. The systemic exposures and metabolites formed in these studies indicate that rats and monkeys are appropriate species for use in the pivotal nonclinical safety studies.

Absorption

Single-dose absorption studies were conducted in mice, rats, dogs, and monkeys using oral, subcutaneous, and IM formulations of CAB. Pharmacokinetic parameters following single oral gavage dosing in rats, dogs, and monkeys, and following single IM or subcutaneous dosing in rats and monkeys, are presented in the following tables.

Table 49. Pharmacokinetic Data Following Single Oral Doses in Rats, Dogs, and Monkeys

Species:	Rat (Male, n = 3)				Dog (Male, n = 2 or 3)						Monkey (Male, n = 2)		
Report No.:	RH2007/00168				RH2007/00170						RH2007/00171		
Test Article Form:	Free Acid				Free Acid			Sodium Salt			Free Acid		Sodium Salt
Dose Level (mg/kg):	5	50	150	500	5	30	30 *	1 *	5 *	30 *	5 *	30 *	30 *
PK Parameters													
$AUC_{0\text{-}24}$ (µg.h/mL)	234	703	982	1156	21.846	40.204	19.888	21.266	51.163	125.359	52.433	146.176	485.199
C_{max} (µg/mL)	12.8	37.9	49.2	52.8	2.235	3.627	2.000	2.925	6.285	11.050	5.360	10.650	45.400
T_{max} (h)	4	8	12	4	[2 - 2]	2	2	[1 - 1]	[1 - 1]	[1 - 2]	[2 - 2]	[2 - 2]	[2 - 4]

Additional Information:
* indicates fasted feeding condition, other dose groups are non-fasted.
Data presented are mean values (T_{max} reported as median or [range]).

Abbreviations: PK = pharmacokinetic

Table 50. Pharmacokinetic Data Following Single IM/SC Doses in Rats

Report No.:	RH2009/00012		RH2009/00013			
Gender (M/F)/Number of Animals:	M/3		M/5			
Feeding Condition:	Non-fasted		Non-fasted			
Vehicle/Formulation:	[a]		[d]			
Analyte:	GSK1265744		GSK1265744			
Assay:	HPLC-MS/MS		HPLC-MS/MS			
Sample:	Plasma		Plasma			
Sample Collection Intervals (Day):	1 [b], 3, 6, 7, 9, 13, 14, 16, 20, 22, 24, 27, 29, 36 and 106		1 [b], 2, 3, 7, 8, 10, 23, 30, 39, 45, 53, 60 and 67			
Method of Administration:	Subcutaneous	Intramuscular	Subcutaneous		Intramuscular	
Dose (mg/kg):	5	5	5	5	5	5
Test Material Particle Size (microns):	NA	NA	5.59	68.9	5.59	68.9
PK Parameters:						
$AUC_{0\text{-}t}$ (µg.h/mL)	2606 [c]	3115 [c]	4320 [e]	3322 [e]	5042 [e]	3811 [e]
$AUC_{0\text{-}24}$ (µg.h/mL)	63.3	60.3	61	42	87	51
C_{max} (µg/mL)	6.5	10.3	7.1	5	12.2	7.5
Median T_{max}	6 Days	7 Days	8 Days	8 Days	7 Days	7 Days

Additional Information:
NA = Not applicable.
a = (b) (4)
b = Samples collected at multiple times on Day 1.
c = AUC through the last sampling time on Day 36.
d = (b) (4)
e = AUC through the last sampling time on Day 67.

Abbreviations: HPLC-MS/MS = high-performance liquid chromatography with tandem mass spectrometry, IM = intramuscular, SC = subcutaneous

Table 51. Pharmacokinetic Data Following Single IM/SC Doses in Monkeys

Report No.:	CD2009/00373				CD2009/00513		CD2009/00656	
Gender (M/F)/Number of Animals:	M / 4				M / 4		M / 4	
Feeding Condition:	Non-fasted				Non-fasted		Non-fasted	
Vehicle/Formulation:	[a]				[a]		[b]	
Analyte:	GSK1265744				GSK1265744		GSK1265744	
Assay:	HPLC-MS/MS				HPLC-MS/MS		HPLC-MS/MS	
Sample:	Plasma				Plasma		Plasma	
Sample Collection Intervals (Day):	Up to 43 days after dosing				Up to 56 days after dosing		Up to 49 days after dosing	
Method of Administration:	Subcutaneous		Intramuscular		Subcutaneous	Intramuscular	Subcutaneous	Intramuscular
Dose (mg/kg):	1 [c]	5 [d]	1 [c]	5 [d]	5 [e]	5 [e]	10	10
PK Parameters (mean):								
$AUC_{0\text{-}t}$ (µg.h/mL)	61	191.1	57	156.7	119	310	505.3	682.1
$AUC_{0\text{-}24}$ (µg.h/mL)	3.3	3.7	3.1	4.6	2.3	3.2	14.2	35.0
C_{max} (µg/mL)	0.26	0.42	0.17	0.33	0.16	0.46	1.0	2.6
Median T_{max} (h)	4	5	3	5	8	18	6	5

Additional Information:
(b) (4)
c = Particle size: (b) (4) microns.
d = Particle size: microns.
e = Particle size: microns.

Abbreviations: HPLC-MS/MS = high-performance liquid chromatography with tandem mass spectrometry, IM = intramuscular, SC = subcutaneous

CAB oral bioavailability, as determined in single-dose intravenous and oral gavage studies, was 63% in dogs and 56% in monkeys under fasted conditions, and 44% in dogs under nonfasted conditions. When administered as an oral capsule in dogs and monkeys, CAB oral bioavailability was 3% to 8% in both species. As a result, all pivotal oral toxicology studies utilized the oral gavage formulation.

The serum half-life of CAB was 5.7 hours in dogs and 4.0 hours in monkeys when administered once intravenously, and was 4.3 hours in monkeys when administered once orally. In single-dose rat and monkey studies with the long-acting injections, however, the half-life was 12 to 29 days (subcutaneous) or 8 to 12 days (IM).

No clear differences in CAB exposures were observed between males and females in rats and monkeys after single doses, but exposures were generally about 20% higher in females in rats after repeat dosing (see "Toxicokinetic Data" below). CAB exposures also increased in a generally less than dose-proportional manner. In the repeat-dose studies, no meaningful accumulation was seen with oral dosing, but a roughly 2-fold increase in exposure was seen between the first and third doses in the rat subcutaneous and IM study (study #2010N104820). When co-administered with RPV, CAB exposures (both AUC and C_{max}) were slightly elevated but generally similar compared to CAB alone.

Distribution

The in vitro plasma protein binding of CAB was evaluated in rat, dog, monkey, and human plasma at concentrations up to 10µM. Protein binding was shown to be very high (≥99.3%) in all species evaluated. In a follow-up study in human plasma, plasma protein binding was generally consistent (99.4% to 99.5%) at CAB concentrations from 500 to 20,000 ng/mL. Plasma protein binding of CAB glucuronide, a metabolite of CAB, was low (≤33%) in rat and human plasma.

In in vitro transport and inhibition studies, CAB was shown to have high passive membrane permeability and to be a substrate for P-glycoprotein and BCRP. No meaningful inhibition of P-glycoprotein, BCRP, bile salt export pump, MRP2, MRP4, OATP1B1, OATP1B3, OCT1, or OCT2 were observed up to in vitro concentrations of 30µM, but CAB was shown to inhibit OAT1, OAT3, MATE1, and MATE2-K (IC_{50}=0.812µM, 0.411µM, 18.2µM, and 14.2µM, respectively). Hepatic uptake of CAB was also not mediated by OATP1B1, OATP1B3, OATP2B1, or OCT1.

Transport and inhibition studies with CAB glucuronide showed that this metabolite was a substrate for OATP1B1, OATP1B3, OAT3, MRP2, MRP3, and MRP4, but was not a substrate for P-glycoprotein, BCRP, OAT1, or OAT4. Likewise, CAB glucuronide was shown to inhibit OAT1 and OAT3 (IC_{50}=73.4 and 36.5µM, respectively), but not MDR, BCRP, bile salt export pump, MATE1, MATE2-K, MRP2, MRP4, OATP1B1, OATP1B3, or OCT2 up to concentrations of 300µM. While CAB glucuronide is a substrate for hepatic uptake transporters OATP1B1 and OATP1B3, hepatic uptake of this molecule is low, indicating it is likely not excreted by this route.

In a 28-day tissue distribution study in which Lister-Hooded rats received a single 30 mg/kg oral dose of [^{14}C]GSK1265744, CAB was shown to distribute to most tissues within 1 day of dosing. In the blood, peak concentrations were 1 day postdose and were still detectable by day 28. Drug levels were also higher in the blood than in all other tissues throughout the study, with the exception of the contents of the small and large intestines. Other than the blood, highest tissue levels were observed in the lung, bulbourethral gland, renal medulla, adrenal medulla, and pigmented skin. Drug was also detected in the brain at low levels (0.015- to 0.020-fold relative to blood) up to at least 7 days postdose, demonstrating that CAB crosses the blood–brain barrier in small amounts. No meaningful differences in drug levels in pigmented versus nonpigmented skin

were observed, indicating that CAB likely does not bind to melanin. Dedicated distribution studies in pregnant animals were not conducted, but as demonstrated in the oral investigative TK study in rats (study #2017N311115), CAB is present in fetal tissue on GD 20 in rats.

Additional distribution studies with long-acting CAB indicate that the drug is primarily isolated to depots within tissue when administered subcutaneously or intramuscularly and is associated with some degree of edema and immune cell infiltration presumably to help clear the foreign material. Intracellular CAB in these regions is primarily limited to macrophages and multinucleated giant cells. The drug depots can expand in volume as a result of this immune response, which is more predominant following subcutaneous dosing. This volume expansion via the subcutaneous route also correlates to higher drug plasma levels at earlier time points than via the IM route. The drug is also present in lymph nodes and fluid at concentrations ≤37% that of blood at least 7 days postdose in rats following a single IM dose of 40 mg/kg.

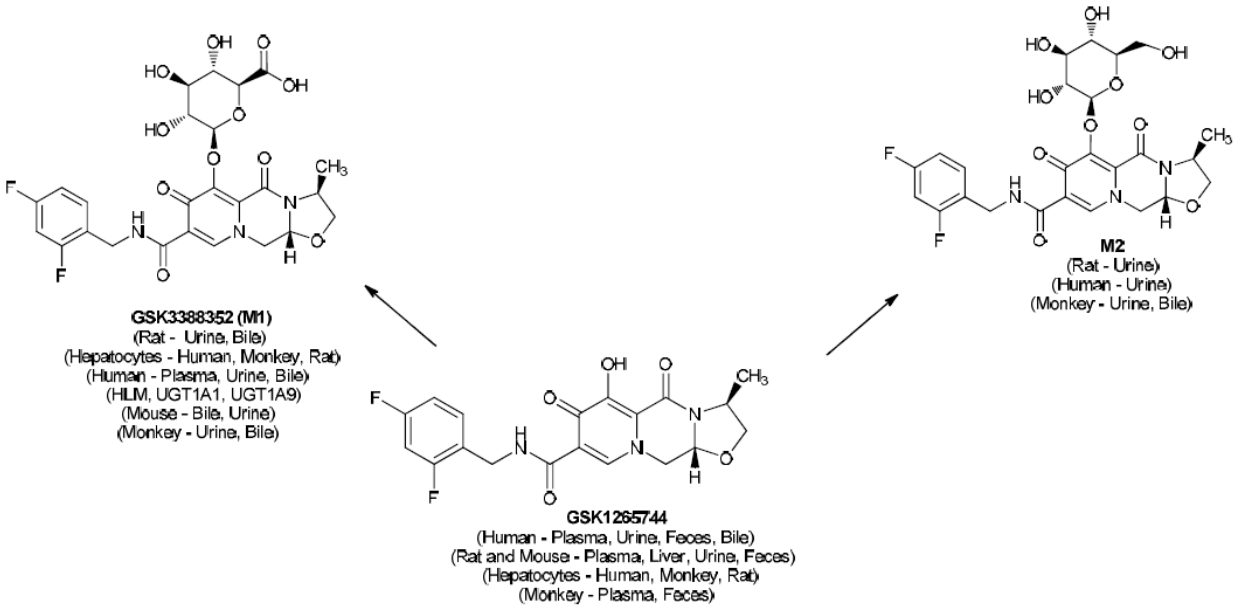
Metabolism

In vitro studies in rat, dog, monkey, and human hepatocytes and liver microsomes identified the glucuronide metabolite of CAB (CAB glucuronide, or M1) to be the primary metabolite formed in all species tested up to 50µM concentration. Human microsomes isolated from the liver, kidney, and intestines, and perfusion of CAB through rat livers, were also shown to form the CAB glucuronide. Follow-up studies with recombinant uridine 5'-diphospho-glucuronosyltransferases and human liver microsomes, and up to 100µM CAB, confirmed that formation of this metabolite in humans is primarily due to UGT1A1 and, to an extent, UGT1A9. CAB was also shown to inhibit UGT1A3 and UGT1A9 in these studies (IC_{50}=12µM and 46µM, respectively).

Additional in vitro studies identified the formation of a glutathione adduct in microsomes from rats, monkeys, and humans, but not dogs (up to 100µM CAB). No significant formation of the enantiomer, (b) (4), and the diastereomer, (b) (4), were detected in rat, dog, monkey, and human hepatocytes (up to 10µM CAB). CAB was also shown to be unlikely to induce CYP3A4 expression in vivo, as measured by pregnane X receptor activation (up to 10µM CAB). No notable increases in CYP1A2, 2B6, or 3A4 expression were detected in human hepatocytes following a 24-hour incubation with 30µM CAB. CAB was also shown to be a metabolism-dependent inhibitor of CYP3A4/5 in human liver microsomes.

In vivo metabolite studies were conducted in CD-1 mice, Sprague-Dawley rats, and cynomolgus monkeys following single oral doses of CAB (30 mg/kg in mice and rats, 10 mg/kg in monkeys). In all three species, CAB was the principle component in the plasma and liver within 1 to 7 days postdose and was primarily excreted in the feces intact. Of the roughly 2% of CAB excreted via bile and urine in mice and rats, the majority was CAB glucuronide. Products of oxidation (M6) and oxidation, defluorination, and glutathionylation (M5) were also detected in urine and bile, respectively, in mice. M6, a glucose conjugate (M2), and intact CAB (at very low levels) were also detected in rat urine. CAB glucuronide was also the primary metabolite detected in monkey urine and bile, with low levels of M2 and a cysteine conjugate (M3) also present in both urine and bile. The only quantifiable metabolite in humans was the glucuronide conjugate (M1), and M2 was present at nonquantifiable levels. As such, all human metabolites were present in the species selected for the nonclinical safety studies.

Figure 28. Metabolic Profile of Cabotegravir



M2 is the preferred structure based on metabolic precedence and comparison with M1.
M3 (+cysteine, +O, -F) and M4 (+pentose) were also detected in human urine (<1% dose).
Two other minor metabolites: M5 (+glutathione, +O, -F) and M6 (+ O) were observed that were specific to the nonclinical species.
HLM = Human liver microsomes.

Excretion

The routes of CAB excretion were evaluated in intact and bile-duct-cannulated male CD-1 mice, Sprague-Dawley rats, and cynomolgus monkeys following single oral doses of [^{14}C]GSK1265744 (30 mg/kg in mice and rats, 10 mg/kg in monkeys). In mice and rats, >90% of CAB was excreted within the first 48 hours postdose, while the remainder was slowly excreted over the next 5 days. Only about 2% of the administered dose was recovered in the bile and urine in these species, and no accumulation in the liver was observed. In intact monkeys, 78.7% and 11.1% of the administered dose was recovered in the feces and urine, respectively. In bile-duct-cannulated monkeys, 54.6%, 14.7%, and 14.5% were recovered in the feces, urine, and bile, respectively. As such, the primary route of excretion in all species evaluated was via the feces, while minor amounts were also excreted via the urine and bile in monkeys. See the "Metabolism" section for additional information on metabolite excretion.

Dedicated lactation studies were not conducted with CAB. However, TK data in F_1 pups from the pivotal PPND study (study #2015N236973) demonstrate that the drug is present in F_1 pup serum by PND 10, indicating that CAB is present in milk.

Table 52. Toxicokinetic Data

Study Title (Study No.) | **Major Findings**

General Toxicology Studies

2-Week Oral Toxicity Study in Mice (Study #RD2009/00692)

Sample collection times: 0.5, 1, 2, 4, 8, and 24 hours postdose on days 1 and 14

NOAEL=1,000 mg/kg/day ($AUC_{0\text{-}24hr}$ =2,586.5 µg·hr/mL at day 14, gender-averaged)

Exposure multiple =17.7

Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir ($AUC_{0\text{-}t}$ =146 µg·hr/mL)

Parameter	Sex	Dose of GSK1265744B (mg/kg/day)[1]					
		10		75		1000	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
$AUC_{0\text{-}24\ h}$ (µg.h/mL)	Males	427	681	1113	1430	2006	2385
	Females	494	699	1168	1610	2123	2788
C_{max} (µg/mL)	Males	27.8	38.8	66.0	84.2	118	132
	Females	35.0	38.3	58.9	99.6	125	152
T_{max} (h)	Males	2.0	2.0	2.0	8.0	2.0	2.0
	Females	1.0	2.0	1.0	2.0	0.5	1.0

1. All dose levels and toxicokinetic parameters are in terms of GSK1265744, the parent compound. Toxicokinetic parameters were derived from mean plasma concentration data (N =3/timepoint/sex/group).

13-Week Oral Toxicity Study in Mice (Study #2012N142081)

Sample collection times: 0.5, 1, 2, 4, 8, and 24 hours postdose on day 1 and weeks 4 and 13

NOAEL=75 mg/kg/day ($AUC_{0\text{-}24hr}$ =1,345 µg·hr/mL at week 13, gender-averaged)

Exposure multiple =9.2

Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir ($AUC_{0\text{-}t}$ =146 µg·hr/mL)

Parameter	Period	Males		
		Dose of GSK1265744 (mg/kg/day)		
		10	75	1000
$AUC_{0\text{-}t}$ (µg.h/mL)	Day 1	433	971	1800
	Week 4	576	1300	1710
	Week 13	552	1330	2150
C_{max} (µg /mL)	Day 1	23.6	60.2	122
	Week 4	34.7	68.8	108
	Week 13	29.8	76.4	122
T_{max} (h)	Day 1	8	8	1
	Week 4	2	8	2
	Week 13	4	8	1

Parameter	Period	Females		
		Dose of GSK1265744 (mg/kg/day)		
		10	75	1000
$AUC_{0\text{-}t}$ (µg.h/mL)	Day 1	352	915	1790
	Week 4	712	1420	2300
	Week 13	691	1360	2430
C_{max} (µg /mL)	Day 1	23.2	44.1	103
	Week 4	39.4	82.0	132
	Week 13	35.5	69.1	133
T_{max} (h)	Day 1	2	8	4
	Week 4	8	8	2
	Week 13	4	2	1

Study Title (Study No.)	Major Findings

2-Week Oral Toxicity Study in Rats (Study #RD2006/01741)

Sample collection times: Predose and 1, 2, 4, 8, 10, and 24 hours postdose on days 1 and 14

NOAEL =300 mg/kg/day ($AUC_{0\text{-}24hr}$ =2,893.7 µg·hr/mL at day 14, gender-averaged)

Exposure multiple=19.8

Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir ($AUC_{0\text{-}t}$ =146 µg·hr/mL)

Male (n = 3)

Dose (mg/kg/day)		30	100	300
Mean $AUC_{0\text{-}24}$ (ng.h/mL)	Day 1	293897 (243101 – 365188)	489819 (460757 – 522106)	707628 (668198 – 761340)
	Day 14	1849172 (1176695 – 2285193)	2222721 (2091908 – 2296856)	2510388 (2422424 – 2640178)
Mean C_{max} (ng/mL)	Day 1	14438 (12497 – 17731)	22903 (21490 – 24394)	35791 (33946 – 37937)
	Day 14	82076 (53257 – 99575)	98369 (98079 – 98845)	113659 (112396 – 115385)

Female (n = 3)

Dose (mg/kg/day)		30	100	300
Mean $AUC_{0\text{-}24}$ (ng.h/mL)	Day 1	307975 (241424 – 355934)	471582 (327632 – 701379)	798517 (759873 – 842448)
	Day 14	1605280 (1370509 – 1903713)	2435243 (2173674 – 2881754)	3276967 (2952081 – 3827720)
Mean C_{max} (ng/mL)\	Day 1	14368 (12064 – 15841)	23998 (18569 - 34728)	41016 (39590 – 43560)
	Day 14	73826 (65079 – 86379)	110864 (98487 – 134822)	147098 (130703 – 171380)

4-Week Oral Toxicity Study in Rats With a 2-Week Recovery (Study #RD2008/00448)

Sample collection times: 0.25, 0.5, 1, 2, 4, 8, and 24 hours postdose days 1 and 28

NOAEL =1,000 mg/kg/day ($AUC_{0\text{-}24hr}$=3,735 µg·hr/mL at day 28, gender-averaged)

Exposure multiple=25.6

Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir ($AUC_{0\text{-}t}$ =146 µg·hr/mL)

Parameter	Period	Male		
		Dose of GSK1265744 (mg/kg/day)		
		1	75	1000
$AUC_{0\text{-}24}$ [a] (µg.h/mL)	Day 1	70.7 [63.9 – 76.8]	1309 [1096 – 1632]	3368 [3266 – 3519]
	Day 28	739 [648 – 813]	3000 [2967 – 3040]	3345 [3214 – 3432]
C_{max} [a] (µg/mL)	Day 1	4.23 [3.73 – 4.75]	66.1 [51.5 – 82.0]	161 [150 – 180]
	Day 28	34.3 [31.8 – 36.3]	143 [140 – 146]	150 [149 – 151]
Median T_{max} [a] (h)	Day 1	4 [2 – 4]	2 [2]	4 [4 – 8]
	Day 28	4 [0.5 – 4]	2 [0.25 – 4]	2 [0.25 – 8]
Parameter	Period	Female		
		Dose of GSK1265744 (mg/kg/day)		
		1	75	1000
$AUC_{0\text{-}24}$ [a] (µg.h/mL)	Day 1	78.3 [58.8 – 93.2]	1484 [1306 – 1721]	3732 [3451 – 3993]
	Day 28	852 [792 – 930]	3832 [3064 – 4394]	4125 [3659 – 4629]
C_{max} [a] (µg/mL)	Day 1	4.48 [4.08 – 4.96]	72.8 [60.2 – 87.8]	181 [161 – 200]
	Day 28	38.8 [37.7 – 40.8]	176 [139 – 200]	193 [172 – 214]
Median T_{max} [a] (h)	Day 1	2 [2 – 4]	4 [2 – 8]	2 [2]
	Day 28	4 [0.25 – 4]	2 [0.25 – 8]	0.5 [0.25 – 1]

a. Mean [Range] for AUC and C_{max}; Median [Range] for T_{max}

Study Title (Study No.)	Major Findings
3-Month Subcutaneous and Intramuscular Toxicity Study in Rats With a 14-Day, 75-Day or 51-Day Recovery (Study #2010N104820) Sample collection times: • Groups 1-4: Predose, up to 336 hours postdose on day 1, and routinely throughout day 136. • Groups 5-8: Predose, up to 336 hours postdose on day 1, and routinely throughout day 112. • Groups 9-10: Predose each week, routinely throughout dosing, and throughout day 99. NOAEL =10 mg/kg/dose when administered once monthly intramuscularly ($AUC_{1440-2160hr}$ =25,467.5 µg·hr/mL at day 91, gender-averaged) <u>Exposure multiple =10.3</u> Based on mean steady-state exposures in healthy human volunteers receiving 400 mg monthly cabotegravir injection (AUC_{0-t} =2,461 µg·hr/mL)	Once monthly subcutaneous route (Groups 1-4, Male): **Male** **Subcutaneous Dose of GSK1265744 (mg/kg/dose)[c]** **Parameter[a,b]** **5** **30** **100** AUC_{0-720} (µg.h/mL): 4076 [3538 – 5052]; 17516 [13864 – 23636]; 31464 [22594 – 41661] $AUC_{1440-2160}$ (µg.h/mL): 11204 [8074 – 13513]; 48082 [37243 – 54532]; 70494 [59895 – 85122] C_{max} 1st Dose (µg/mL): 7.44 [5.89 – 8.34]; 33.8 [25.2 – 46.4]; 62.0 [41.1 – 85.2] C_{max} 3rd Dose (µg/mL): 19.2 [13.5 – 22.6]; 84.8 [66.8 – 96.3]; 118 [107 – 140] Overall Study C_{max} (µg/mL): 19.2 [13.5 – 22.6]; 84.8 [66.8 – 96.3]; 137 [107 – 166[d]] Median T_{max} 3rd Dose[e] (day): 15 [8 – 15]; 15 [15 – 15]; 15 [15 – 15] a. N = 3/group. Results are reported as mean unless stated otherwise and [range]. b. AUC_{0-720} = AUC from Day 1 through predose on Day 31 (during 1st dose interval). $AUC_{1440-2160}$ = AUC from predose on Day 61 through predose on Day 91 (during 3rd dose interval). c. GSK1265744 was administered on Days 1, 31, and 61. d. The overall C_{max} value for this animal (4015) occurred on Day 2 of the 2nd dose interval. e. The values represent the day of the 3rd monthly dose interval. Once monthly subcutaneous route (Groups 1-4, Female): **Female** **Subcutaneous Dose of GSK1265744 (mg/kg/dose)[c]** **Parameter[a,b]** **5** **30** **100** AUC_{0-720} (µg.h/mL): 7644 [5767 – 8775]; 22304 [17866 – 27470]; 58245 [52894 – 66040] $AUC_{1440-2160}$ (µg.h/mL): 15238 [14303 – 16045]; 55956 [41339 – 70624]; 116602 [105082 – 124604] C_{max} 1st Dose (µg/mL): 13.3 [9.34 – 16.7; 40.6 [31.3 – 51.6]; 121 [107 – 137] C_{max} 3rd Dose (µg/mL): 26.8 [26.0 – 27.9]; 96.8 [65.3 – 132]; 195 [172 – 208] Overall Study C_{max} (µg/mL): 26.8 [26.0 – 27.9]; 96.8 [65.3 – 132]; 195 [172 – 208] Median T_{max} 3rd Dose[d] (day): 15 [15 – 15]; 15 [15 – 21]; 15 [15 – 15] a. N = 3/group. Results are reported as mean unless stated otherwise and [range]. b. AUC_{0-720} = AUC from Day 1 through predose on Day 31 (during 1st dose interval). $AUC_{1440-2160}$ = AUC from predose on Day 61 through predose on Day 91 (during 3rd dose interval). c. GSK1265744 was administered on Days 1, 31, and 61. d. The values represent the day of the 3rd monthly dose interval. Once monthly intramuscular route (Groups 5-8, Male):

Study Title (Study No.)	Major Findings

Parameter[a,b]	Male		
	Intramuscular Dose of GSK1265744 (mg/kg/dose)[c]		
	2.5	10	75
AUC_{0-720} (µg.h/mL)	5588 [5386 – 5888]	18331 [16976 – 20964]	55684 [52230 – 62367]
$AUC_{1440-2160}$ (µg.h/mL)	7031 [6945 – 7078]	26001 [21538 – 28560]	78051 [74734 – 80570]
C_{max} 1st Dose (µg/mL)	12.7 [11.4 – 14.1]	37.8 [34.4 – 40.8]	106 [94.6 – 116]
C_{max} 3rd Dose (µg/mL)	16.7 [14.7 – 18.8]	49.6 [47.8 – 51.2]	120 [118 – 123]
Overall Study C_{max} (µg/mL)	16.9 [15.2[d] – 18.8]	49.6 [47.8 – 51.2]	135 [129 – 142][e]
Median T_{max} 3rd Dose[f] (day)	8 [6 – 8]	15 [6 – 15]	1 [1 – 2]

a. N = 3/group. Results are reported as mean unless stated otherwise and [range].
b. AUC_{0-720} = AUC from Day 1 through predose on Day 31 (during 1st dose interval). $AUC_{1440-2160}$ = AUC from predose on Day 61 through predose on Day 91 (during 3rd dose interval).
c. GSK1265744 was administered on Days 1, 31, and 61.
d. Observed on Day 8 of the second dose interval.
e. Observed on Day 15 of the second dose interval for each animal.
f. The values represent the day of the 3rd monthly dose interval.

Once monthly intramuscular route (Groups 5-8, Female):

Parameter[a,b]	Female		
	Intramuscular Dose of GSK1265744 (mg/kg/dose)[c]		
	2.5	10	75
AUC_{0-720} (µg.h/mL)	5230 [5049 – 5439]	18420 [16184 – 20868]	82061 [79150 – 84534]
$AUC_{1440-2160}$ (µg.h/mL)	5500 [5263 – 5622]	24934 [23435 – 27919]	107080 [92466 – 115252]
C_{max} 1st Dose (µg/mL)	15.8 [15.1 – 16.3]	44.2 [33.7 – 49.5]	151 [150 – 152]
C_{max} 3rd Dose (µg/mL)	12.4 [11.5 – 13.6][d]	55.2 [50.6 – 60.3]	170 [151 – 181]
Overall Study C_{max} (µg/mL)	15.9 [15.2 – 16.3]	55.2 [50.6 – 60.3]	181 [179 – 183][e]
Median T_{max} 3rd Dose[f] (day)	8 [8 – 8]	15 [8 – 15]	15 [8 – 15]

a. N = 3/group. Results are reported as mean unless stated otherwise and [range].
b. AUC_{0-720} = AUC from Day 1 through predose on Day 31. $AUC_{1440-2160}$ = AUC from predose on Day 61 through predose on Day 91.
c. GSK1265744 was administered on Days 1, 31, and 61.
d. Overall C_{max} values observed on Day 6 of the first dose interval (Animal No. 6515), Day 8 of the first dose interval (Animal No. 6513), and Day 8 of the second dose interval (Animal No. 6614).
e. Overall C_{max} values observed on Day 8 of the second dose interval for Animal No. 8514; the overall Cmax values for the other two animals occurred during the third dose interval.
f. The values represent the day of the 3rd monthly dose interval.

Once weekly subcutaneous route (Groups 9-10):

Parameter[a,b]	Subcutaneous Dose of GSK1265744 (mg/kg/dose)[c]	
	100	
	Male	Female
$AUC_{2016-2184}$ (µg.h/mL)	22291 [21631 – 22907]	34315 [32842 – 35565]
Week 13 C_{max} (µg/mL)	143 [141 – 144]	223 [214 – 235]
Overall Study C_{max} (µg/mL)	166 [154 – 184][d]	226 [221 – 235][e]
Median T_{max} Week 13[f] (day)	7 [7 – 8]	3 [2 – 6]

a. N = 3/group. Results are reported as mean unless stated otherwise and [range].
b. $AUC_{2016-2184}$ = AUC during Week 13 (from predose on Day 85 to Day 92).
c. GSK1265744 was administered once a week for 13 consecutive weeks.
d. The overall C_{max} value occurred 6 days after the dose was given on Week 8 for Animal No. 10015, and 14 days (last sample collected, Day 99) after the last dose was administered (Week 13; Animal No. 10014 and Animal No. 10013).
e. The overall C_{max} value occurred 14 days (last sample collected, Day 99) after the last dose was administered on Week 13 for Animal No. 10515 (the overall C_{max} value for the other two animals occurred during Week 13).
f. The values represent the day of the 13th week.

Study Title (Study No.)	Major Findings

26-Week Oral Toxicity Study in Rats With a 6-Week Recovery Period (Study #RD2009/00031)

Sample collection times: Predose and 0.25, 0.5, 1, 2, 4, 8 and 24 hours postdose on weeks 4, 13 and 26

NOAEL =1,000 mg/kg/day ($AUC_{0\text{-}24hr}$ =3,992 µg·hr/mL at week 26, gender-averaged)

Exposure multiple =27.3

Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir ($AUC_{0\text{-}t}$ =146 µg·hr/mL)

Parameter [a]	Period	Male		
		Dose of GSK1265744B (mg/kg/day)		
		0.5	5	1000
$AUC_{0\text{-}24}$ (µg.h/mL)	Week 4	329 [306 – 371]	1961 [1888 – 2064]	3753 [3656 – 3896]
	Week 13	491 [419 – 568]	1792 [1751 – 1823]	2958 [2869 – 3017]
	Week 26	451 [389 – 495]	1861 [1744 – 2011]	3203 [3005 – 3313]
C_{max} (µg/mL)	Week 4	16.2 [15.2 – 17.6]	93.2 [86.3 – 99.6]	174 [167 – 179]
	Week 13	23.1 [19.9 – 25.4]	85.6 [80.7 – 89.3]	144 [138 – 151]
	Week 26	23.1 [21.6 – 24.4]	91.4 [87.3 – 96.7]	148 [146 – 150]
T_{max} (h)	Week 4	2 [2]	1 [1]	2 [0.5 – 2]
	Week 13	2 [2]	1 [0.25 – 2]	0.5 [0.25 – 2]
	Week 26	2 [1 - 2]	1 [0.5 – 2]	0.5 [0.25 – 4]

Parameter [a]	Period	Female		
		Dose of GSK1265744B (mg/kg/day)		
		0.5	5	1000
$AUC_{0\text{-}24}$ (µg.h/mL)	Week 4	404 [327 – 469]	1672 [1588 – 1776n]	4403 [4101 – 4627]
	Week 13	659 [531 – 753]	1951 [1811 – 2181]	4079 [3944 – 4159]
	Week 26	675 [486 – 818]	2083 [1806 – 2359]	4781 [4711 – 4907]
C_{max} (µg/mL)	Week 4	19.4 [15.6 – 23.1]	85.1 [77.3 – 92.2]	210 [200 – 220]
	Week 13	30.4 [25.1 – 34.1]	94.4 [88.4 – 104]	190 [178 – 201]
	Week 26	31.6 [24.5 – 37.5]	102 [85.6 – 117]	224 [215 – 233]
T_{max} (h)	Week 4	2 [1 – 2]	1 [0.5 – 2]	0.5 [0.25 – 2]
	Week 13	2 [2]	2 [2]	1 [0.5 – 2]
	Week 26	2 [1 – 2]	1 [0.5 – 1]	0.5 [0.25 – 1]

a. Results are reported as mean ($AUC_{0\text{-}24}$ and C_{max}) or median (T_{max}) and [range].

Study Title (Study No.)	Major Findings

2-Week Oral Toxicity Study in Monkeys (Study #CD2007/00680)

Sample collection times: Predose and 0.25, 0.5, 1, 2, 4, 8, and 24 hours postdose on days 1 and 14. All high-dose males were euthanized 4 hours postdose on day 14, so 8 and 24 samples from this group were not collected.

NOAEL =25 mg/kg/day ($AUC_{0\text{-}24hr}$ =232.2 µg·hr/mL at day 14, gender-averaged)

Exposure multiple =1.6

Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir ($AUC_{0\text{-}t}$ =146 µg·hr/mL)

Parameter	Period	Male		
		Dose of GSK1265744 (mg/kg/day)		
		8	25	1000
$AUC_{0\text{-}24}$ [a] (ng.h/mL)	Day 1	128174 [80186 – 178068]	233423 [190439 – 287215]	1050958 [799988 – 1394626]
	Day 14	144252 [b] [115871 – 194823] [b]	233252 [198017 – 256532]	ND [c]
$AUC_{0\text{-}4}$ [a, c] (ng.h/mL)	Day 1	ND	ND	131873 [120843-137786]
	Day 14	ND	ND	224032 [b] [185575-286178]
C_{max} [a] (ng/mL)	Day 1	12167 [6786 – 16658]	20754 [20350 – 21472]	66974 [48219 – 91501]
	Day 14	14568 [12493 – 17584]	22699 [20086 – 24603]	ND [c]
T_{max} [a] (h)	Day 1	1 [1 – 2]	2 [2 – 4]	8 [4 – 8]
	Day 14	2 [1 – 2]	2 [2]	ND [c]

n = 3/dose group
ND = Not Determined.
a. Mean [Range] for AUC and C_{max}; Median [Range] for T_{max}
b. Emesis was observed in one animal in this dose group
c. $AUC_{0\text{-}24}$ and a definitive C_{max} or T_{max} were not determined on Day 14 for males given 1000 mg/kg/day due to their early termination; however, utilizing the available plasma concentration data, $AUC_{0\text{-}4}$ was calculated for males given 1000 mg/kg/day on Days 1 and 14 to allow for systemic exposure comparison across time.

Parameter	Period	Female		
		Dose of GSK1265744 (mg/kg/day)		
		8	25	1000
$AUC_{0\text{-}24}$ [a] (ng.h/mL)	Day 1	104228 [86590 – 137130]	233973 [b] [159152 – 321155] [b]	961322 [b] [870097 – 1113039] [b]
	Day 14	124431 [76766 – 183261]	231169 [191988 – 285507]	945723 [777889 – 1073887]
C_{max} [a] (ng/mL)	Day 1	11755 [6221 – 16361]	23573 [19205 – 30872]	59156 [49807 – 69484]
	Day 14	15517 [10164 – 20866]	22169 [15039 – 29936]	65870 [57623 – 71165]
T_{max} [a] (h)	Day 1	2 [1 – 2]	2 [2 – 4]	8 [4 – 8]
	Day 14	1 [1 – 2]	2 [1 - 2]	2 [2 - 4]

n = 3/dose group
a. Mean [Range] for AUC and C_{max}; Median [Range] for T_{max}
b. Emesis was observed in one animal in this dose group

Study Title (Study No.)	Major Findings
4-Week Oral Toxicity Study in Monkeys With a 2-Week Recovery (Study #CD2008/00632) Sample collection times: Predose and 0.25, 0.5, 1, 2, 4, 8, and 24 hours postdose on days 1 and 28. NOAEL =500 mg/kg/day ($AUC_{0\text{-}24hr}$ =902.5 µg·hr/mL at day 28, gender-averaged) <u>Exposure multiple =6.2</u> Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir ($AUC_{0\text{-}t}$ =146 µg·hr/mL)	

Parameter	Period	Male		
		Dose of GSK1265744 (mg/kg/day)		
		5	50	500
$AUC_{0\text{-}24}$ [a] (µg.h/mL)	Day 1	115 [94.4 – 149]	311 [283 – 343]	697 [616 – 773]
	Day 28	100 [56.6 – 150]	276 [270 – 281]	901 [860 – 945]
C_{max} [a] (µg/mL)	Day 1	12.6 [11.4 – 14.9]	20.8 [18.4 – 24.2]	38.2 [33.1 – 43.3]
	Day 28	10.0 [3.71 – 15.2]	17.4 [16.1 – 18.6]	58.1 [50.3 – 63.3]
Median T_{max} [a] (h)	Day 1	2 [2]	4 [1 - 8]	4 [2 – 8]
	Day 28	2 [2]	2 [2 – 8]	2 [2 – 8]

n = 3 to 5/group
a. Mean [Range] for AUC and C_{max}; Median [Range] for T_{max}

Parameter	Period	Female		
		Dose of GSK1265744 (mg/kg/day)		
		5	50	500
$AUC_{0\text{-}24}$ [a] (µg.h/mL)	Day 1	85.3 [58.3 – 114]	311 [244 – 433]	664 [577 – 732]
	Day 28	80.9 [64.5 – 113]	279 [268 – 287]	904 [792 – 1114]
C_{max} [a] (µg/mL)	Day 1	10.4 [9.76 – 11.5]	23.9 [18.0 – 29.0]	39.1 [33.3 – 43.1]
	Day 28	9.07 [6.95 – 11.4]	20.0 [18.1 – 22.8]	65.0 [53.7 – 79.1]
Median T_{max} [a] (h)	Day 1	1 [1 – 2]	2 [2 - 4]	4 [2 - 8]
	Day 28	2 [0.5 – 2]	2 [2]	2 [2]

n = 3 to 5/group
a. Mean [Range] for AUC and C_{max}; Median [Range] for T_{max}

Study Title (Study No.)	Major Findings

39-Week Oral Toxicity Study in Monkeys with a 6-Week Recovery (Study #RD2009/00027)

Sample collection times: Predose and 0.5, 1, 2, 4, 8, and 24 hours postdose on weeks 4, 26, and 39.

NOAEL =500 mg/kg/day ($AUC_{0\text{-}24hr}$ =547 µg·hr/mL at week 39, gender-averaged)

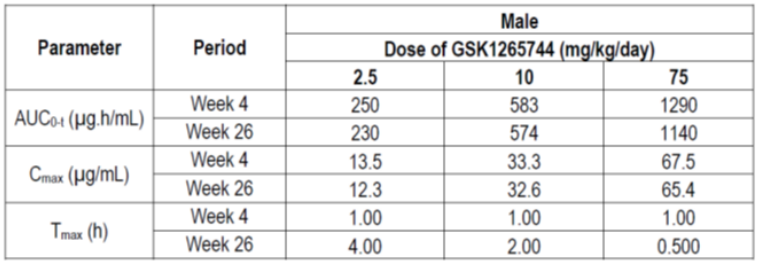
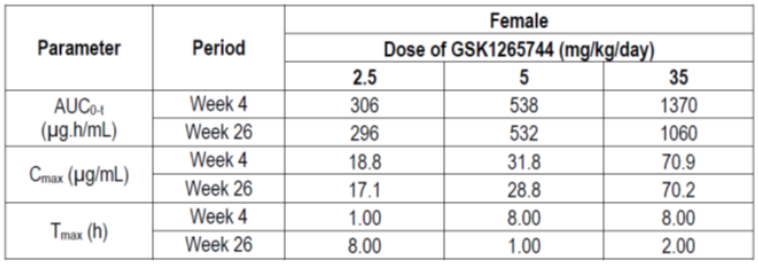
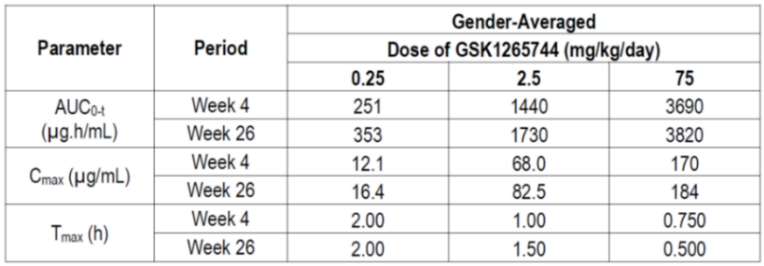
Exposure multiple =3.7

Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir ($AUC_{0\text{-}t}$ =146 µg·hr/mL)

Parameter [a]	Period	Male		
		Dose of GSK1265744B (mg/kg/day)		
		5 (n=4)	50 (n=4)	500 (n=6)
$AUC_{0\text{-}24}$ (µg.h/mL)	Week 4	62.1 [47.3 – 87.3]	251 [222 – 267]	644 [505 – 826]
	Week 26	90.4 [47.6 – 138]	296 [207 – 376]	575 [415 – 749]
	Week 39	37.7 [29.2 – 44.8]	229 [209 – 249]	542 [359 – 781]
C_{max} (µg/mL)	Week 4	7.15 [5.53 – 9.77]	22.1 [17.0 – 31.1]	45.3 [37.4 – 61.7]
	Week 26	10.3 [3.58 – 19.3]	25.1 [14.6 – 37.0]	37.3 [27.2 – 47.6]
	Week 39	3.37 [2.69 – 3.88]	21.1 [14.3 – 32.9]	36.8 [23.9 – 57.2]
T_{max} (h)	Week 4	1.25 [0.5 – 2]	1 [1 -4]	4 [2 -4]
	Week 26	1.25 [0.5 – 2]	3 [1 -4]	2 [1 -4]
	Week 39	2 [1 - 2]	3 [2 – 4]	2 [2 – 8]

Parameter [a]	Period	Female		
		Dose of GSK1265744B (mg/kg/day)		
		5 (n=4)	50 (n=4)	500 (n=6)
$AUC_{0\text{-}24}$ (µg.h/mL)	Week 4	69.6 [46.0 – 80.8]	303 [214 – 379]	807 [557 – 1008]
	Week 26	65.7 [51.8 – 73.9]	255 [162 – 340]	678 [585 – 727]
	Week 39	67.8 [50.1 – 103]	254 [220 – 305]	552 [447 – 623]
C_{max} (µg/mL)	Week 4	8.77 [4.90 – 11.0]	27.3 [22.4 – 35.4]	56.4 [43.5 – 66.7]
	Week 26	5.87 [4.03 – 7.74]	22.4 [13.8 – 41.7]	40.8 [36.8 – 45.6]
	Week 39	6.33 [2.54 – 12.7]	17.4 [14.0 – 21.3]	32.4 [29.8 – 35.1]
T_{max} (h)	Week 4	1 [1]	1 [1 – 2]	2 [2 – 4]
	Week 26	2 [2 - 4]	2 [1 – 2]	4 [2 – 8]
	Week 39	0.75 [0.5 – 4]	4 [2 – 8]	4 [4 – 8]

a. Results are reported as mean ($AUC_{0\text{-}24}$ and C_{max}) or median (T_{max}) and [range].

Study Title (Study No.)	Major Findings
Carcinogenicity Studies	
2-Year Oral Carcinogenicity Study in Mice (Study #2017N310750) Sample collection times: Predose and 0.5, 1, 2, 4, 8, and 24 hours postdose on Weeks 4 and 26. Male NOAEL=75 mg/kg/dose (AUC_{0-t} =1,140 µg·hr/mL at week 26) Female NOAEL=35 mg/kg/dose in females (AUC_{0-t} =1,060 µg·hr/mL at week 26) <u>Exposure multiple =7.8 in males, 7.3 in females</u> Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir (AUC_{0-t} =146 µg·hr/mL)	 
2-Year Oral Carcinogenicity Study in Rats (Study #2017N310751) Sample collection times: Predose and 0.25, 0.5, 1, 2, 4, 8, and 24 hours postdose on weeks 4 and 26. NOAEL=75 mg/kg/dose (AUC_{0-t} =3,820 µg·hr/mL at week 26, gender-averaged) <u>Exposure multiple =26.2</u> Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir (AUC_{0-t} =146 µg·hr/mL)	

Study Title (Study No.) | **Major Findings**

Reproductive Toxicology Studies

Oral Embryofetal Development Study in Rabbits (Study #CD2009/00842)

Sample collection times: Predose and 0.5, 1, 2, 4, 8, and 24 hours postdose on GD 11.

Embryofetal NOAEL =500 mg/kg/day (AUC_{0-t} =47.4 µg·hr/mL at GD 11)

Exposure multiple =0.3

Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir (AUC_{0-t} =146 µg·hr/mL)

Parameter	Day pc [b]	Dose Level of GSK1265744B (mg/kg/day) [a]		
		30	500	2000
AUC_{0-24} (µg.h/mL)	11	10.5	47.4	96.1
C_{max} (µg/mL)	11	0.95	3.39	7.51
T_{max} (h)	11	2.0	1.0	0.6

a. All dose levels and toxicokinetic parameters are in terms of GSK1265744, the parent compound. Toxicokinetic parameters were derived from mean plasma concentration data.
b. Dose Day 5.

Oral Pre- and Postnatal Developmental Study in Rats (Study #2015N236973)

Sample collection times: 3, 8, and 10 hours postdose on PND 10 only. Only the F_0 animals were treated. Samples were collected from the F_1 pups only.

Pre- and postnatal NOAEL=5 mg/kg/day

Parameter	Period	Male Pups		
		Dose of GSK1265744B (mg/kg/day)		
		0.5	5	1000
C_{max} (ng/mL)	Day 10 pp	15600	58400	72500

Parameter	Period	Female Pups		
		Dose of GSK1265744B (mg/kg/day)		
		0.5	5	1000
C_{max} (ng/mL)	Day 10 pp	15700	52600	78300

Oral Investigative Toxicokinetics Study in Rats (Study #2017N311115)

Sample collection times: 1, 2, 4 and 8 hours postdose on GD 20. Predose samples were not collected, and serum concentrations were assumed to be zero. As a result, the AUC_{0-8hr} values for groups 3 and 4, and the exposure multiple calculated below, were assumed to be underestimated.

Pre- and postnatal NOAEL=5 mg/kg/day (from Study #2015N236973; AUC_{0-8hr} =553 µg·hr/mL)

Exposure multiple =9.9

Based on mean steady-state exposures in healthy human volunteers receiving 30 mg QD oral cabotegravir (AUC_{0-8hr} =55.9 µg·hr/mL).

Parameter		Group			
		1	2	3	4
		Dose of GSK1265744 (mg/kg/day)			
		5[a]	1000[a]	5[b]	1000[b]
AUC_{0-t} (µg·h/mL)	**Mean**	**151**	**789**	**553**	**679**
	Min	129	642	479	584
	Max	173	967	638	788
C_{max} (µg/mL)	**Mean**	**25.5**	**118**	**81.4**	**110**
	Min	21.5	93.2	69.3	89.5
	Max	29.6	143	94.2	142
T_{max} (h)	**Median**	**1.50**	**1.00**	**1.50**	**1.00**
	Min	1.00	1.00	1.00	1.00
	Max	2.00	4.00	4.00	1.00
Fetal Tissue: Maternal Plasma[c]	**Mean**	**0.194**	**0.222**	**0.258**	**0.267**
	Min	0.167	0.164	0.195	0.200
	Max	0.237	0.314	0.328	0.326

GD: Gestation day.
a. Group 1 and 2 animals were dosed one time on GD 20.
b. Group 3 and 4 animals were dosed once daily from GD 6 through GD 20. Plasma samples used for analysis were collected from pregnant rats between approximately 1 and 8 hours post-dosing and from fetuses at approximately 9 hours post-maternal dosing on GD20.
c. Fetal Tissue to Maternal Plasma Ratios were calculated as: Mean of fetal tissue concentration (ng/g) / corresponding 8 hour maternal plasma concentration (ng/mL). AUC_{0-8} was underestimated for Groups 3 and 4 animals by assuming the pre-dose concentration to be zero.

Abbreviations: GD = gestation day, NOAEL = no observed adverse effect level, PND = postnatal day, QD = once daily

13.1.5. Toxicology

13.1.5.1. General Toxicology

Single-Dose Toxicology/Toxicokinetic Studies

Single-dose toxicology studies with CAB have been conducted in mice, rats, and monkeys. In mice (study #RD2009/00691), male Crl:CD1(ICR) mice (15/group) were treated with single doses of drug by oral gavage (10, 100, 1,000 and 2,000 mg/kg/dose). One animal given 2,000 mg/kg displayed decreased activity and irregular breathing 1.5 hours postdose. Necropsy of this animal revealed an abscess of the preputial gland, moderate single-cell hepatocellular necrosis, neutrophilia in the lung vasculature, and a swollen ventral abdomen that predated treatment, but no apparent cause of morbidity. The NOAEL for this study was 1,000 mg/kg/dose.

In Sprague-Dawley rats (study #RD2009/01359; 10/sex/group), single doses of the drug were administered either subcutaneously (0, 10, 30, and 100 mg/kg/dose) or intramuscularly (0, 2.5, 10, and 75 mg/kg/dose), and necropsies were performed on either day 76 to 77 (subcutaneous) or day 85 to 86 (IM). One high-dose subcutaneous male was found dead on day 39, but necropsy did not reveal a cause of death, and drug plasma exposures were below those of other animals at this dose level. Because this was observed in a single animal well after dosing, and because no correlation was seen with drug exposure, this was considered incidental. ISRs (erythema, edema, and granulomatous/mixed cell inflammation) were observed at ≥30 mg/kg in the subcutaneous groups and at 75 mg/kg in the IM groups. These findings were generally very slight with mild to moderate findings present in some subcutaneous mid- and high-dose animals, and were considered nonadverse. The NOAEL for this study was 100 mg/kg/dose and 75 mg/kg/dose for subcutaneous and IM administration, respectively. The IM coadministration of 10 mg/kg CAB and 60 mg/kg RPV was also evaluated in rats in a single-dose PK study (study #2011N127517). An assessment of local tolerance following administration of both drugs at the same location was not conducted as CAB and RPV were administered in separate injections at two different locations, but no clear additive or synergistic systemic toxicities were observed in this study relative to either drug on its own. The NOAEL for CAB in this study was 10 mg/kg. As mentioned in the “Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics” section above, CAB exposures were slightly elevated when co-administered with RPV but were generally similar to CAB alone.

In a dose-escalation study in monkeys (study #RD2007/01415), single oral gavage doses of the drug (150, 300, and 1,000 mg/kg/dose) were administered to two male cynomolgus monkeys with a roughly 13-day washout period between doses. No drug-related effects were observed, and the NOAEL for this study was 1,000 mg/kg/dose. In addition, up to 10 mg/kg CAB was evaluated in single subcutaneous and IM doses in cynomolgus monkeys (study #CD2009/00656), and 10 mg/kg CAB, delivered intramuscularly, was also evaluated in combination with 60 mg/kg RPV (study #2010N105579). CAB-related findings in these studies were limited to ISRs (erythema, edema, and skin thickening). A mass at the injection site was observed in a single treated animal in the subcutaneous group, and a biopsy confirmed this to be the result of subcutaneous granulomatous inflammation. As in the rat combination study described above, CAB and RPV were administered as separate injections in two different locations, and an assessment of local tolerance with both drugs administered at the same location

was not included. However, no additive or synergistic systemic toxicities were observed following coadministration of CAB and RPV. The NOAEL for CAB in these studies was 10 mg/kg/dose, and exposures were similar but generally higher via the IM, rather than subcutaneous, route.

2-Week Oral Toxicity Study in Mice (Study #RD2009/00692)

Key Study Findings

- NOAEL=1,000 mg/kg/dose ($AUC_{0\text{-}24hr}$ =2,586.5 µg·hr/mL, C_{max} =142 µg/mL on day 14). No adverse, drug-related toxicities were observed up to the highest dose tested.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 53. 2-Week Mouse Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	0, 10, 75, and 1,000 mg/kg/dose; Once daily
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Crl:CD1(ICR) mice
Number/sex/group:	10/sex/group
Age:	11-12 weeks
Satellite groups/unique design:	36/sex/dose
Deviations affecting interpretation:	None

Abbreviations: HPMC = hydroxypropyl methylcellulose

Table 54. 2-Week Mouse Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. No drug-related findings.
Body weights	Measured 2-3× weekly. No drug-related findings.
Food consumption	Measured twice weekly. No drug-related findings.
Ophthalmoscopy	Evaluated pretreatment and on day 14 predose. No drug-related findings.
Hematology	Evaluated at necropsy (day 15-16). Mean cell hemoglobin concentration was decreased 2.5-3.2% in all treated males. This was considered nonadverse due to the low magnitude of the changes and the absence of this finding in females.
Clinical chemistry	Evaluated at necropsy (day 15-16). Increased calcium (5.3-6.8%) and cholesterol (27.7-44.0%) were observed in all treated females. Increased triglycerides (36.5%) were observed in high-dose females. These were considered nonadverse due to the lack of a clear dose response and the absence of findings in males.
Gross pathology	Evaluated at necropsy (day 15-16). No drug-related findings.
Organ weights	Evaluated at necropsy (day 15-16). Brain weight was increased 5.7% in high-dose males. This was considered nonadverse because it was a minor change and was not observed in females.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy (day 15-16). Only control and high-dose samples evaluated for most organs. Minimal to moderate neutrophilic inflammation in the nasal cavity was observed in 1 male/1 female at the high dose. This was likely due to reflux of gavage material and was therefore not considered drug-related.

13-Week Oral Toxicity Study in Mice (Study #2012N142081):

Key Study Findings

- NOAEL=75 mg/kg/day ($AUC_{0\text{-}24hr}$=1,345 µg·hr/mL, C_{max}=72.8 µg/mL at week 13) due to adverse body weight decreases at the high dose.
- One main study animal and three satellite animals were either found dead or euthanized prematurely as a result of gavage-related gastric reflux or trauma. In addition, six high-dose males and three high-dose females had histopathology findings in the nasal cavity (epithelial degeneration/regeneration, neutrophilic inflammation, and exudate) at necropsy, which is consistent with gavage-related gastric reflux. All of these findings were attributed to gavage-related issues and were not considered adverse.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 55. 13-Week Mouse Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	0, 10, 75, and 1,000 mg/kg/dose; Once daily
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Crl:CD1(ICR) mice
Number/sex/group:	12/sex/group
Age:	6 weeks
Satellite groups/unique design:	9-54/sex/dose
Deviations affecting interpretation:	None

Abbreviations: HPMC = hydroxypropyl methylcellulose

Table 56. 13-Week Mouse Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	One high-dose male was euthanized in extremis about 6 hours postdose on day 68 due to labored breathing, distended abdomen, purple skin in the abdominal and lumbar regions, partly closed eyes, cold to the touch, and suspected dehydration. Dosing reflux was previously noted in this animal on the same day. Necropsy findings in this animal included dilatation of the stomach and small intestine, and marked epithelial degeneration and regeneration with pronounced inflammation and exudate in the nasal cavity. These findings are consistent with gastric reflux resulting from the gavage procedure. In the satellite groups, 1 low-dose and 1 mid-dose male were euthanized on days 18 and 37, respectively, and 1 high-dose female was found dead on day 47. The death of the low-dose satellite male was due to swallowing of the gavage needle the day prior. The mid-dose satellite male experienced breathing abnormalities and blue skin on the abdomen prior to euthanasia, but no drug-related lesions were observed during necropsy. Death of the high-dose satellite female occurred shortly after dosing on day 47, and no clinical signs or drug-related pathology findings were observed. All three satellite deaths were therefore likely attributed to gavage dosing errors rather than drug-related toxicities.
Clinical signs	Examined at least once daily. No drug-related findings.

Parameters	Major Findings
Body weights	Measured once weekly. Body weight were decreased 4.0-4.4% in high-dose males from weeks 11-13, and were decreased 3.6-8.4% in high-dose females from weeks 6-13. Body weight gain was decreased 16.2% in high-dose males, and was decreased 17.6-13.3% in mid- and high-dose females, from weeks -1 to 13. This was considered adverse at the high dose only.
Food consumption	Measured once weekly. No drug-related findings.
Ophthalmoscopy	Evaluated pretreatment and on week 13. No drug-related findings.
Hematology	Evaluated at necropsy (day 92). Decreased mean cell hemoglobin concentrations (2.0-2.9%) and increased red cell distribution width (2.3-11.0%) were observed in all treated males. Neutrophil levels were increased 71.3% in high-dose males. All changes were considered nonadverse as they were minor changes that were either not statistically significant or not dose-dependent, and were not present in females.
Clinical chemistry	Evaluated at necropsy (day 92). Glucose was decreased 20.1-23.1% in all high-dose animals. This was considered nonadverse due to the low magnitude of the change and lack of a histopathological correlate.
Gross pathology	Evaluated at necropsy (day 92). Pale discoloration of kidney was observed in 1 control female, 1 male/1 female at the low dose, 1 male/3 females at the mid-dose, and 3 males/1 female at the high dose. This was considered nonadverse due to the lack of a histopathological correlate and the presence in controls.
Organ weights	Evaluated at necropsy (day 92). Heart weight was increased 11.6% in high-dose males (15.4% relative to body weight). Kidney weight was increased 12.8% in high-dose males (16.8% relative to body weight). These were considered nonadverse due to the lack of a histopathological correlate and their absence in females.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy (day 92). Only control and high-dose samples evaluated for most organs. In the nasal cavity, minimal to severe epithelial degeneration/regeneration was observed in 6 males/3 females, minimal to mild neutrophilic inflammation was observed in 2 males/3 females, and minimal to moderate exudate was observed in 2 males/2 females, all at high dose. These findings are consistent with gastric reflux resulting from oral gavage and correspond to the gavage-related deaths (see "Mortality" section). As such, the nasal cavity findings were considered not drug-related. In addition, minimal to moderate myeloid hypercellularity in the bone marrow was observed in 2 high-dose females. This was considered nonadverse due to the low severity of the findings and their absence in males.

2-Week Oral Toxicity Study in Rats (Study #RD2006/01741)

Key Study Findings

- NOAEL=300 mg/kg/dose ($AUC_{0\text{-}24h}$r=2,893.7 µg·hr/mL, C_{max}=130.4 µg/mL on day 14). No adverse, drug-related toxicities were observed up to the highest dose tested.
- Minimal to moderate eosinophilic droplets in the kidney tubular epithelium were observed in 6 control, 6 low-dose, 4 mid-dose, and 6 high-dose males (mild to moderate findings limited to 4 high-dose males). Follow-up analyses confirmed these droplets to be positive for α2u-globulin and albumin, which is a finding specific to male rats that is not relevant to humans. The kidney finding was therefore considered nonadverse.

Conducting laboratory: (b) (4)

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)
GLP compliance: Yes

Table 57. 2-Week Rat Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	0, 30, 100, and 300 mg/kg/dose; Once daily
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Sprague-Dawley rats (b) (4)
Number/sex/group:	10/sex/group
Age:	11-12 weeks
Satellite groups/unique design:	3/sex/dose
Deviations affecting interpretation:	None

Abbreviations: HPMC = hydroxypropyl methylcellulose

Table 58. 2-Week Rat Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. No drug-related findings.
Body weights	Measured 1-3× weekly. No drug-related findings.
Food consumption	Measured twice weekly. No drug-related findings.
Ophthalmoscopy	Evaluated pretreatment and 1 hour postdose on day 14. No drug-related findings.
Neurobehavioral assessment	An FOB, including landing foot splay, was conducted pretreatment and on day 5 predose and 8 and 24-25 hours postdose. There were no drug-related findings.
Hematology/coagulation	Evaluated at necropsy (day 15-16). Hematocrit was decreased 2.5-3.3% in mid- and high-dose females. This was considered nonadverse due to the low magnitude of the change.
Clinical chemistry	Evaluated at necropsy (day 15-16). Bilirubin was decreased 11.1-39.3% in all treated animals. Phosphorus was increased 13.3% in high-dose females. Both were considered nonadverse due to the low magnitude of the changes.
Urinalysis	Evaluated at necropsy (day 15-16). Increased urine protein/creatinine ratio (48.9%) and urine total protein excretion (51.9%) were observed in high-dose males. These changes were not statistically significant and are likely incidental.
Gross pathology	Evaluated at necropsy (day 15-16). No drug-related findings.
Organ weights	Evaluated at necropsy (day 15-16). Increased heart (10.5-15.3%) and thymus weights (21.1-38.6%) were observed in mid- and high-dose males. Because these were in males only and were not associated with any histopathology or clinical pathology correlates, these were considered drug-related but nonadverse.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy (day 15-16). Only control and high-dose samples evaluated for most organs. Minimal to moderate eosinophilic droplets in the kidney tubular epithelium were observed in 6 control, 6 low-dose, 4 mid-dose and 6 high-dose males (mild to moderate findings limited to 4 high-dose males). Follow-up analyses confirmed these droplets to be positive for α2u-globulin and albumin, which is a finding specific to male rats.[15,16] The kidney finding was therefore considered nonadverse. Mild to moderate focal necrosis in the liver was observed in 1 low-dose male and 1 male/1 female at the high dose (moderate finding was in the low-dose male only, and minimal subcapsular necrosis in the liver was present in 2 control males). The liver finding was considered incidental due to the lack of dose-dependence and the presence in control animals.

Parameters	Major Findings
Liver cytochrome P450 analysis	Evaluated at necropsy (day 15-16). No drug-related increases in CYP1A1, 1A2, 2B1, 2B2, 2E1, 3A2, 3A23 or 4A1 were detected.

Abbreviations: FOB = Functional Observational Battery

4-Week Oral Toxicity Study in Rats With a 2-Week Recovery (Study #RD2008/00448)

Key Study Findings

- NOAEL=1,000 mg/kg/dose ($AUC_{0\text{-}24hr}$=3735 µg·hr/mL, C_{max}=171.5 µg/mL on day 28). No adverse, drug-related toxicities were observed up to the highest dose tested.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 59. 4-Week Rat Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	0, 1, 75, and 1,000 mg/kg/dose; Once daily
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Sprague-Dawley rats (b) (4)
Number/sex/group:	10/sex/main group (all doses) 6/sex/recovery group (control and high dose only)
Age:	11 weeks
Satellite groups/unique design:	3/sex/dose
Deviations affecting interpretation:	None

Abbreviations: HPMC = hydroxypropyl methylcellulose

Table 60. 4-Week Rat Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. No drug-related findings.
Body weights	Measured twice weekly. Body weights were decreased up to 8.7% in all treated males throughout the treatment phase relative to concurrent controls and were decreased up to 14.1% at the high dose at the end of the recovery phase. Body weights were also decreased up to 4.1% in some animals prior to treatment (day -4). As this was seen pretreatment and only in males, this was likely an incidental finding.
Food consumption	Measured twice weekly. No drug-related changes.
Ophthalmoscopy	Evaluated pretreatment and 45 minutes postdose on day 28. No drug-related findings.
Hematology/coagulation	Evaluated at necropsy (day 29-30 and 44). Decreased reticulocytes (15.6%) and APTT (9.1%) were observed in high-dose males on day 29-30. Hemoglobin was decreased 5.0% in high-dose females on day 29-30. All changes were considered nonadverse due to high variability among groups, low magnitude of the changes, and differences between sexes.

Parameters	Major Findings
Clinical chemistry	Evaluated at necropsy (day 29-30 and 44). Bilirubin was decreased 8.4-37.9% in all treated animals on day 29-30. Increased ALT (43.6%), AST (26.9%) and GLDH (3.3-fold) were observed in high-dose females on day 29-30. Decreased GLDH (46.1%), total protein (8.2%), globulin (14.3%) and cholesterol (22.5%) were observed in high-dose males on day 44. Increased glucose (7.1%) was observed in high-dose females on day 44. All changes were considered nonadverse due to the lack of histopathology correlates.
Urinalysis	Evaluated at necropsy (day 29-30 and 44). Increased urine glucose excretion (26.8-34.1%) and urine total protein volume (14.3-18.8%) in all treated females on day 29-30. These changes were considered nonadverse due to the lack of histopathology correlates.
Gross pathology	Evaluated at necropsy (day 29-30 and 44). Scabs and hair loss in assorted locations were observed in several treated animals as well as 2 control males. As noted in the "Histopathology" section, this was considered nonadverse due to the lack of a clear dose response.
Organ weights	Evaluated at necropsy (day 29-30 and 44). No drug-related changes.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy (day 29-30 and 44). Only control and high-dose samples evaluated for most organs. Minimal glandular hyperplasia was noted in the cecum in 2 high-dose males on day 29-30. As this was a minimal finding, this was considered nonadverse. In the skin on day 29-30, minimal to mild neutrophilic exudate was observed in 1 control, 2 low-dose and 6 high-dose males, minimal to moderate epidermal hyperplasia was observed in 2 control, 2 low-dose and 7 high-dose males, and 1 mid-dose female, and minimal lymphoplasmacytic inflammation in the subcutis was observed in 1 high-dose male. All skin findings corresponded to random, focal instances of hair loss and scabs that are common in this species. Because the skin findings were predominantly minimal to mild, and because the gross pathology findings lacked a clear dose response, this was considered nonadverse.

Abbreviations: ALT = alanine aminotransferase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, GLDH = glutamate dehydrogenase

3-Month Subcutaneous and Intramuscular Toxicity Study in Rats With a 14-Day, 75-Day or 51-Day Recovery (Study #2010N104820)

Key Study Findings

- NOAEL=5 mg/kg/dose when administered once monthly subcutaneously ($AUC_{1440\text{-}2160hr}$=13,221 µg·hr/mL, C_{max}=23.0 µg/mL at day 91) due to adverse ISRs observed at ≥30 mg/kg/dose.
- NOAEL=10 mg/kg/month when administered once monthly intramuscularly ($AUC_{1440\text{-}2160hr}$=25,467.5 µg·hr/mL, C_{max}=52.4 µg/mL at day 91) due to adverse ISRs observed at 75 mg/kg/dose.
- A NOAEL for once weekly subcutaneous administration was not determined due to adverse ISRs at 100 mg/kg/dose, the only dose level evaluated with this regimen.
- ISRs observed via all routes consisted of minimal to severe granulomatous and/or mixed cell inflammation and nodules/masses, which generally increased in incidence and severity with dose level and dosing frequency. These findings were generally more severe in the subcutaneous groups, particularly those which were dosed once weekly,

than in the IM groups. As all animals were euthanized at the end of their respective recovery periods, the ISRs also did not fully recover in all animals.

- Decreased thymus weight or the observation of "small thymus" was observed in many treated animals, and in some cases correlated to lymphoid depletion in this organ. These findings were likely the result of stress or were secondary to the ISRs and were therefore considered nonadverse.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 61. 3-Month Rat Subcutaneous/Intramuscular Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	Groups 1-4: 0, 5, 30, and 100 mg/kg once monthly Groups 5-8: 0, 2.5, 10, and 75 mg/kg once monthly Groups 9-10: 0 and 100 mg/kg once weekly
Route of administration:	Subcutaneous (groups 1-4 and 9-10) or Intramuscular (groups 5-8)
Formulation/vehicle:	(b) (4) polyethylene glycol 3350, and (b) (4) (b) (4) mannitol in (b) (4)
Species/strain:	Sprague-Dawley rats (b) (4)
Number/sex/group:	12/sex/main group; 3/sex/satellite group
Age:	13-15 weeks
Satellite groups/unique design:	Animals in groups 1-4 were treated subcutaneously once monthly for 3 months and had a 75-day recovery period. Animals in groups 5-8 were treated intramuscularly once monthly for 3 months and had a 51-day recovery period. Animals in groups 9-10 were treated subcutaneously once weekly for 13 weeks and had a 14-day recovery period. All animals were euthanized at the end of the recovery periods.
Deviations affecting interpretation:	None

Table 62. 3-Month Rat Subcutaneous/Intramuscular Toxicity Study Findings

Parameters	Major Findings
Mortality	One group 8 male and 1 group 4 male were found dead on day 61 and day 122, respectively. There were no adverse clinical signs and causes of death were not determined. A second group 8 male was euthanized on day 39 due to decreased activity, partly closed eyes, generalized weakness, hunched posture, decreased muscle tone, irregular breathing, incoordination, lack of feces, and suspected dehydration. No drug-related pathology findings were observed in this animal. Drug concentrations in these 3 animals were also shown to be below those of group 10, in which no deaths were observed. Since no correlation with drug exposure and no drug-related pathology correlates were observed, these deaths were likely incidental. A fourth animal (group 4 female) was euthanized on day 108 due to a large mass on the right hindlimb (malignant schwannoma) which interfered with this animal's normal bodily functions. This was also considered incidental.

Parameters	Major Findings
Clinical signs/injection site reactions	Examined at least once daily. Draize scoring performed postdose and twice weekly thereafter. Very slight to moderate/severe erythema and edema at the injection sites were observed as early as day 7. These findings were generally dose-dependent, were more severe via the subcutaneous route, and persisted into recovery particularly at the highest doses. • In groups 1-4 (subcutaneous monthly), reactions were observed at all doses and persisted into recovery at ≥30 mg/kg/dose. • In groups 5-8 (intramuscular monthly), reactions which sometimes persisted into recovery were observed at 75 mg/kg/dose only. • In groups 9-10 (subcutaneous weekly), reactions which persisted into recovery were observed at 100 mg/kg/dose. These findings correspond to the pathology findings described below. The injection site reactions were considered adverse at ≥30 mg/kg when given once monthly subcutaneously, at 75 mg/kg when given once monthly intramuscularly, and at 100 mg/kg when given once weekly subcutaneously.
Body weights	Measured once weekly. In groups 1-4 (subcutaneous monthly), body weights were increased 2-5% in males at all doses, and 4% in low-dose females only. In groups 5-8 (intramuscular monthly), body weights were decreased 5-6% in females at all doses. These changes were considered nonadverse due to the lack of a clear dose response and low magnitude of the changes.
Food consumption	Measured once weekly. No drug-related findings.
Ophthalmoscopy	Evaluated predose and during the last week of dosing. No drug-related findings.
Hematology/coagulation	Evaluated on week 8 and at necropsy. In groups 1-4 (subcutaneous monthly), lymphocytes were decreased 9.9-32.0% in males at ≥30 mg/kg/dose on weeks 8 and 19. In groups 9-10 (subcutaneous weekly), neutrophils were increased 64.9-82.0% in both sexes in the treatment group on week 8, and 53.6% in females only on week 14.
Clinical chemistry	Evaluated on week 8 and at necropsy. In groups 1-4 (subcutaneous monthly), urea was increased 13.9-17.8% in mid- and high-dose males on week 19. Decreases in bilirubin (16.7-68.6%) were also observed in groups 4, 8, and 10 relative to their respective controls on weeks 8 and at necropsy. These were considered nonadverse due to the lack of a histopathological correlate.
Urinalysis	Evaluated on week 8 and at necropsy. No drug-related findings.
Gross pathology	Evaluated at necropsy. The following were observed: • In groups 1-4 (subcutaneous monthly), pale areas, nodules and/or masses were present at the injection sites at all doses and increased in incidence and severity with dose. Small thymus was observed in 1 low-dose and 1 high-dose males, and 1 mid-dose and 2 high-dose females. • In groups 5-8 (intramuscular monthly), pale/raised areas, pale foci, masses and nodules were observed at the injection sites of most animals at the high dose. Small thymus was observed in 1 low-dose and 1 mid-dose females and 1 high-dose male. • In groups 9-10 (subcutaneous weekly), Masses and nodules were observed at the injection sites in all treated animals. Small thymus was present in 1 treated male. All injection site findings correlated to granulomatous and/or mixed cell inflammation at the injection sites (see “Histopathology” section). The small thymus correlated, in some cases, to lymphoid depletion in the thymus, but the lymphoid depletion was not dose-dependent and was present in some controls. The thymus findings were likely the result of stress or secondary to the injection site reactions, and were therefore considered nonadverse. The injection site reactions were considered adverse at ≥30 mg/kg when given

Parameters	Major Findings
	once monthly subcutaneously, at 75 mg/kg when given once monthly intramuscularly, and at 100 mg/kg when given once weekly subcutaneously.
Organ weights	Evaluated at necropsy. Decreased thymus weight was observed in group 8 animals and group 10 males (9.4-12.8%; not statistically significant). These changes corresponded to the lymphoid depletion and "small thymus" observations in the pathology sections, and were likely the result of stress or secondary to the injection site reactions. As such, they were considered nonadverse.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy. Only control and high-dose samples evaluated for some organs. The following were observed: • In groups 1-4 (subcutaneous monthly), minimal to moderate granulomatous/mixed cell inflammation at the injection sites were observed in 3 males/2 females at the low-dose and almost all mid- and high-dose animals. Mild to moderate findings were limited to the mid- and high doses (severity was highest at the high dose). Minimal lymphoid depletion in the thymus was observed in 1 mid-dose and 1 high-dose females (also 2 control males). • In groups 5-8 (intramuscular monthly), minimal to mild granulomatous/mixed cell inflammation at the injection sites were observed in 9 males/7 females at the high dose. Moderate lymphoid depletion in the thymus was observed in 1 low-dose and 1 mid-dose females and 1 high-dose male. • In groups 9-10 (subcutaneous weekly), moderate to severe granulomatous/mixed cell inflammation at the injection sites were observed in all treated animals. Lymphoid atrophy in the thymus was observed in 1 treated male. The injection site reactions corresponded to the gross pathology findings in these same animals. The lymphoid atrophy in the thymus corresponded, in some cases, to the gross findings and decreased thymus weights. The thymus findings were likely the result of stress or secondary to the injection site reactions, and were therefore considered nonadverse. The injection site reactions were considered adverse at ≥30 mg/kg when given once monthly subcutaneously, at 75 mg/kg when given once monthly intramuscularly, and at 100 mg/kg when given once weekly subcutaneously.

26-Week Oral Toxicity Study in Rats With a 6-Week Recovery (Study #RD2009/00031)

Key Study Findings

- NOAEL=1000 mg/kg/dose ($AUC_{0\text{-}24h}$r=3992 µg·hr/mL, C_{max}=186 µg/mL on week 26). No adverse, drug-related toxicities were observed up to the highest dose tested.
- One mid-dose female was found dead on day 61, and one high-dose male was euthanized prematurely on day 126. Causes of death in these animals were T cell lymphoma and B cell lymphoma, respectively. As the lymphomas were from different cell lineages, the clinical and histopathological presentations were different in both animals, and were not entirely dose-dependent, these were considered incidental and unrelated to treatment.
- Minimal mixed cell infiltration and hemorrhage, and minimal to slight increased apoptosis in the squamous mucosa, were observed in the stomach (two males/1 female at the mid-dose, and six males/7 females at the high dose). The slight findings were limited

to three males/4 females at the high dose. As these were primarily minimal findings with no associated changes in body weight or food consumption, these changes were considered nonadverse.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 63. 26-Week Rat Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	0, 0.5, 5, and 1,000 mg/kg/dose; Once daily
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Sprague-Dawley rats (b) (4)
Number/sex/group:	12/sex/main group (all doses) 6/sex/recovery group (control and high dose only)
Age:	7 weeks
Satellite groups/unique design:	3/sex/dose
Deviations affecting interpretation:	None

Abbreviations: HPMC = hydroxypropyl methylcellulose

Table 64. 26-Week Rat Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	One mid-dose female was found dead on day 61, and one high-dose male was euthanized on day 126 due to a poor and deteriorating condition. Causes of death in the mid-dose female and high-dose male were T cell lymphoma and B cell lymphoma, respectively. As the lymphomas were from different cell lineages, the clinical and histopathological presentations were different in both animals, and there were no apparent drug-related leukocyte changes, these were considered unrelated to treatment.
Clinical signs	Examined at least once daily. No drug-related findings.
Body weights	Measured once weekly. Body weight was increased 11% in mid-dose males only throughout the treatment period. As this was not dose-dependent and was seen only in males, this was considered incidental and unrelated to treatment.
Food consumption	Measured once weekly. Food consumption was increased 8-11% in mid-dose males from week 12 to 25. This corresponded to increased body weight in this group. As this was not dose-dependent and was seen only in males, this was considered incidental and unrelated to treatment.
Ophthalmoscopy	Evaluated pretreatment and predose on weeks 13 and 25. No drug-related findings.
Hematology/coagulation	Evaluated on weeks 4, 13, 26 and 32. Eosinophils were increased 51-64%, and RBCs, hemoglobin and hematocrit were decreased 4-5%, at the high dose on week 4 only. These changes were considered nonadverse because of the high variability among groups and the low magnitude of the changes.
Clinical chemistry	Evaluated on weeks 4, 13, 26 and 32. No drug-related findings.
Urinalysis	Evaluated on weeks 4, 13, 26 and 32. No drug-related findings.
Gross pathology	Evaluated at necropsy (weeks 26 and 32). No drug-related findings.
Organ weights	Evaluated at necropsy (weeks 26 and 32). Liver weight was decreased 13% in mid- and high-dose females on week 26 only. This was considered nonadverse due to a lack of a histopathological correlate.
Histopathology Adequate battery: Yes	Evaluated at necropsy (weeks 26 and 32). Week 26 histopathology findings in the stomach are as follows:

Parameters	Major Findings
Peer review: Yes	• Minimal mixed cell infiltration in 1 mid-dose male and 4 males/5 females at the high dose. • Minimal hemorrhage in 1 male and 1 female at the mid-dose. • Minimal to slight increased apoptosis in the squamous mucosa with vacuolar degeneration and regenerative hyperplasia in 1 mid-dose male and 6 males/7 females at the high dose (slight findings limited to 3 males/4 females at the high dose). Minimal increased apoptosis in the squamous mucosa with vacuolar degeneration and regenerative hyperplasia was still present in the stomach in 1 male/1 female at the high dose in the recovery group, indicating partial reversibility. According to the study report, these findings "were only present in the limiting ridge of the nonglandular stomach with the vast majority of the nonglandular stomach unaffected." Given that these were primarily minimal findings with no associated changes in body weight or food consumption, these findings were considered nonadverse. Minimal to moderate turbinate fusion, inflammation (both acute and chronic), and degeneration/regeneration were observed in the nasal cavity at week 26 (3 males and 6 females at the high dose only) but were not present in the recovery animals. The nasal cavity findings were considered secondary to gavage reflux rather than a true drug-related effect. Lymphoma metastasis was also observed in many organs in both animals that died prematurely, but as mentioned above, this was considered unrelated to treatment.

7-Day Oral Dose-Range Toxicity Study in Monkeys (Study #CD2007/00577)

Key Study Findings

- A NOAEL was not defined in this study due to the low number of animals per group. Based on the limited information on this study, findings appeared limited to the GI tract (emesis, decreased food consumption, excessive salivation, and abnormal feces).

Conducting laboratory: (b) (4)

GLP compliance: No

This study was conducted to identify appropriate dose levels for use in the pivotal repeat-dose toxicology studies in cynomolgus monkeys. Cynomolgus monkeys (1/sex/group) were treated once daily for 7 days by oral gavage with either vehicle (0.5% hydroxypropyl methylcellulose [HPMC] and 0.1% Tween™ 80 in dH_2O) or GSK1265744 (50, 150, and 1,000 mg/kg/day). Endpoints included mortality, clinical examinations, body weight, food consumption, hematology, clinical chemistry, and TK. There were no unscheduled deaths. Emesis, decreased food consumption, and excessive salivation were observed between days 5 and 8 in the high-dose male. Abnormal feces was observed in the high-dose female as well as all low- and mid-dose animals.

2-Week Oral Toxicity Study in Monkeys (Study #CD2007/00680)

Key Study Findings

- NOAEL=25 mg/kg/dose ($AUC_{0\text{-}24hr}$=232.2 µg·hr/mL, C_{max}=22.4 µg/mL at day 14) due to severe GI toxicities (weight loss, decreased food consumption, adverse clinical signs, and histopathology findings in the stomach, colon, and small intestines) that resulted in the euthanasia of all 3 high-dose males 1 day prior to the scheduled necropsy. Immunosuppression (bone marrow depletion, thymic lymphoid atrophy, and decreased WBC subsets, platelets, and reticulocytes) were also observed in the high-dose males.
- No adverse, drug-related effects were observed in the high-dose females.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 65. 2-Week Monkey Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	0, 8, 25, and 1,000 mg/kg/dose; Once daily
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Cynomolgus monkeys
Number/sex/group:	3/sex/group
Age:	3.8-5.2 years
Satellite groups/unique design:	None
Deviations affecting interpretation:	None

Abbreviations: HPMC = hydroxypropyl methylcellulose

Table 66. 2-Week Monkey Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	All 3 high-dose males were euthanized in extremis about 4 hours postdose on day 14 due to adverse body weight loss and clinical signs (emesis, loose/watery/discolored feces, inappetence, severe dehydration, decreased activity, hunched posture, and reluctance to move). The causes of death were not clearly stated, but were likely due to the gastrointestinal and immune changes described in the "Histopathology" section.
Clinical signs	Examined at least once daily. Findings in the high-dose males are covered in the "Mortality" section. Emesis and tan-colored feces were also observed in the high-dose females, and salivation was observed at the mid- and high doses. With the exception of the high-dose male findings, all findings were considered nonadverse due to their low severity.
Body weights	Measured at least twice weekly. Body weights were decreased 7.3% in high-dose males prior to unscheduled euthanasia on day 14. No other drug-related changes were observed.
Food consumption	Measured qualitatively only. Inappetence was observed in high-dose males prior to unscheduled euthanasia on day 14. No other drug-related findings were observed.
Ophthalmoscopy	Evaluated pretreatment and 7 hours postdose on day 12. No drug-related findings.
Electrocardiography	Measured pretreatment and on day 12 predose and 2 hours postdose. No drug-related findings.

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Parameters	Major Findings
Hematology/coagulation	Measured pretreatment and on day 13. Decreases in reticulocytes (91.6%), platelets (63.2%), WBCs (39.8%), lymphocytes (70.4%), monocytes (60.8%), eosinophils (94.5%), basophils (60.2%), and large unstained cells (76.1%) were observed in the high-dose males on day 13 (1 day prior to unscheduled euthanasia). All changes were considered secondary to bone marrow depletion in these animals. These changes were considered adverse.
Clinical chemistry	Measured pretreatment and on day 13. Serum urea levels were increased 2-fold in high-dose males on day 13 (1 day prior to unscheduled euthanasia). This may be secondary to severe dehydration and was therefore likely not a direct drug-related toxicity.
Urinalysis	Measured pretreatment and on day 13. No drug-related findings.
Gross pathology	Evaluated at necropsy (day 14-15). Generalized and marked distention in the gastrointestinal tract was observed in all high-dose males, along with red foci in the stomach and duodenal mucosa and ileocecal valve. Red, multifocal discoloration of the endocardium was also seen in the left ventricle in 2 high-dose males, and a red focus was observed on the liver capsular surface in 1 high-dose male. All of these findings correlate to histopathology findings seen at the high dose. No other drug-related changes were observed.
Organ weights	Evaluated at necropsy (day 14-15). Organ weights from the high-dose males were not recorded. No drug-related findings were observed in all other groups.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy (day 14-15). The following were observed in the high-dose males: • Minimal to moderate degeneration/regeneration in the glandular and fundic regions of the stomach with mucous depletion, glandular dilatation and/or inflammation. Minimal to mild degeneration/regeneration of the lamina propria in the cecum and colon (characterized by edema, inflammation, fibrin and extracellular matrix expansion in the mucosa). Minimal villous atrophy in the duodenum, ileum, and jejunum. Minimal inflammatory cell infiltrate in the submucosa of the esophagus. • Mild to moderate decreased cellularity in the bone marrow. Moderate lymphoid atrophy in the thymus. • Mild localized acute hemorrhage in the liver (only 1 animal). • Minimal focal hemorrhage in the myocardium (only 1 animal). • Minimal hypertrophy of the adrenal cortex. • Moderate hemorrhage of the sciatic nerve. As previously stated, the cause of death for the high-dose animals was not clearly stated, but was likely due to these microscopic findings in the gastrointestinal tract and immune system. The gastrointestinal findings correspond to the adverse clinical signs and decreased body weight and food consumption, and was considered adverse. The immune findings correspond to the hematology changes and may be stress-related, but was also considered adverse. The heart and liver findings were likely agonal or moribund changes and not direct toxicities. The sciatic nerve finding was likely incidental. The adrenal findings were also observed in 1 low-dose female and all mid-dose animals, and may be secondary to stress. Minimal to moderate thymic lymphoid atrophy was also observed in 1 control, 1 low-dose and 2 mid-dose males (not dose-dependent), and was considered adverse at the high dose only.

Abbreviations: WBC = white blood count

4-Week Oral Toxicity Study in Monkeys With a 2-Week Recovery (Study #CD2008/00632)

Key Study Findings

- NOAEL=500 mg/kg/dose ($AUC_{0\text{-}24hr}$=902·5 µg·hr/mL, C_{max}=61.6 µg/mL on day 28). No adverse, drug-related toxicities were observed up to the highest dose tested.
- Mild, multifocal, unilateral, perivascular mononuclear cell infiltrate was observed in the kidney in one high-dose female. Kidney weight was also increased 23% in high-dose females (not statistically significant). As the immune cell infiltrate was unilateral and in a single animal, the kidney weight change was not significant, and no associated clinical pathology changes were observed, this was considered incidental.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 67. 4-Week Monkey Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	0, 5, 50, and 500 mg/kg/dose; Once daily
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Cynomolgus monkeys
Number/sex/group:	3/sex/main group (all doses) 2/sex/recovery group (control and high dose only)
Age:	3.8-5.8 years
Satellite groups/unique design:	None
Deviations affecting interpretation:	None

Abbreviations: HPMC = hydroxypropyl methylcellulose

Table 68. 4-Week Monkey Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. Discolored feces and excessive salivation were observed intermittently at the high dose. This was considered nonadverse.
Body weights	Measured at least twice weekly. No drug-related findings.
Food consumption	Measured qualitatively only. No drug-related findings.
Ophthalmoscopy	Evaluated pretreatment and 7 hours postdose on day 26. No drug-related findings.
Electrocardiography	Measured pretreatment and on day 22 predose and 2 hours postdose. No drug-related findings.
Hematology/coagulation	Measured pretreatment and on days 27 and 42. No drug-related findings.
Clinical chemistry	Measured pretreatment and on days 27 and 42. No drug-related findings.
Urinalysis	Measured pretreatment and on days 27 and 42. No drug-related findings.
Gross pathology	Evaluated at necropsy (days 29-30 and 44). No drug-related findings.

Parameters	Major Findings
Organ weights	Evaluated at necropsy (days 29-30 and 44). Kidney weight was increased 23% in high-dose females on day 28. Prostate weight was increased 78% in high-dose males on day 28. Both changes were not statistically significant. The prostate finding is likely incidental due to the lack of a microscopic correlate. The kidney finding corresponds to the mild, unilateral mononuclear cell infiltrate in the 1 high-dose female. However, since the kidney weight change was not significant and the immune cell infiltrate was unilateral and present in a single animal, and no associated clinical pathology changes were observed, this was likely incidental.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy (days 29-30 and 44). Mild, multifocal, unilateral, perivascular mononuclear cell infiltrate was observed in the kidney in 1 high-dose female on day 30. This was localized to the cortical arteries in a small portion of one kidney, and was associated with thickened arterial walls and occasional plump endothelial cells. Large, pale eosinophilic inclusion bodies were observed in the nuclei of multiple endothelial and smooth muscle cells. Kidney weight was also increased in this animal (32.3% in this animal and 23% for all high-dose females relative to concurrent controls), but this change was not statistically significant. However, since this was unilateral and in a single animal, and no associated clinical pathology changes were observed, this was likely incidental. Transmission electron microscopy for viral particles was conducted in the kidney to determine if this finding was due to an underlying viral infection, but no viral particles were identified.

39-Week Oral Toxicity Study in Monkeys With a 6-Week Recovery (Study #RD2009/00027)

Key Study Findings

- NOAEL=500 mg/kg/dose ($AUC_{0\text{-}24hr}$=547 µg·hr/mL, C_{max}=34.6 µg/mL on week 39). No adverse, drug-related toxicities were observed up to the highest dose tested.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 69. 39-Week Monkey Oral Toxicity Study Design

Methods	Details
Dose and frequency of dosing:	0, 5, 50, and 500 mg/kg/dose; Once daily
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Cynomolgus monkeys
Number/sex/group:	4/sex/main group (all doses) 2/sex/recovery group (control and high dose only)
Age:	2 years
Satellite groups/unique design:	None
Deviations affecting interpretation:	None

Abbreviations: HPMC = hydroxypropyl methylcellulose

Table 70. 39-Week Monkey Oral Toxicity Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined once daily. No drug-related findings.

Parameters	Major Findings
Body weights	Measured once weekly. No drug-related findings.
Food consumption	Measured qualitatively only. No drug-related findings.
Ophthalmoscopy	Evaluated pretreatment and 7 hours postdose on week 39. No drug-related findings.
Electrocardiography	Measured pretreatment and on week 38 predose and 2 hours postdose. No drug-related findings.
Hematology/coagulation	Measured pretreatment and on weeks 4, 13, 26, and 39. No drug-related findings.
Clinical chemistry	Measured pretreatment and on weeks 4, 13, 26, and 39. No drug-related findings.
Urinalysis	Measured pretreatment and on weeks 4, 13, 26, and 39. No drug-related findings.
Gross pathology	Evaluated at necropsy (weeks 39 and 45). No drug-related findings.
Organ weights	Evaluated at necropsy (weeks 39 and 45). No drug-related findings.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy (weeks 39 and 45). No drug-related findings.

13.1.5.2. Genetic Toxicology

Table 71. Genetic Toxicology Studies

Study Title (Study No.)	Key Study Findings
In Vitro Bacterial Reverse Mutation Assay (Ames Test) (Study #WD2007/00787) GLP compliance: Yes Study is valid: Yes	*Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and *E. coli* (WP2 *uvrA* pKM101) were treated for 72 hours with up to 238 µg/plate of GSK1265744B in the presence and absence of S9. Insolubility of the drug was observed at ≥238 µg/plate, but no precipitation or cytotoxicity were observed up to this concentration. Vehicle (DMSO) and positive controls (2-nitrofluorene, sodium azide, 9-aminoacridine, 4-nitroquinolone-1-oxide, benzo[a]pyrene, and 2-aminoanthracene) produced appropriate responses. No drug-related increases in the number of revertant colonies (≥2-fold) were observed in either the presence or absence of S9. **GSK1265744B was therefore considered ***negative*** under the conditions of this study.**
In Vitro Mouse Lymphoma L5178Y Cell TK Assay (Study #WD2007/01740) GLP compliance: No Study is valid: Yes	L5178Y mouse lymphoma cells were treated with up to 140 µg/mL of GSK1265744A for 3 hours in the presence of S9 and up to 20 µg/mL for 24 hours in the absence of S9. The concentrations used were limited by cytotoxicity, and relative total growth was decreased to 26% and 14% at the highest concentrations with and without S9, respectively. Vehicle (DMSO) and positive controls (methyl methanesulfonate and dimethylbenzanthracene) produced appropriate responses. No drug-related increases in mutant frequency were observed at 3 hours in the presence of S9, but a 3-fold increase in mutant frequency was observed at 20 µg/mL at 24 hours in the absence of S9. As the mutant frequency exceeded the sum of the mean control mutant frequency plus the global evaluation factor at this concentration and was concentration-dependent, **GSK1265744A was considered ***positive in the absence of S9 only*****. This increase occurred in the presence of cytotoxicity, however, given that relative total growth was decreased to 14% in this group.

Study Title (Study No.)	Key Study Findings
In Vitro Mouse Lymphoma L5178Y Cell TK Assay (Study #WD2007/00788) GLP compliance: Yes Study is valid: Yes	This study was conducted as a follow-up to the non-GLP study in mouse lymphoma cells (study #WD2007/01740). L5178Y mouse lymphoma cells were treated with up to 23.8 µg/mL of GSK1265744B for 3 hours in the presence of S9, and for 3 and 24 hours in the absence of S9. Insolubility of the drug was observed at ≥23.8 µg/mL, and a slight increase in cytotoxicity was observed at this concentration at 24 hours without S9. Vehicle (DMSO) and positive controls (methyl methanesulfonate and benzo[a]pyrene) produced appropriate responses. No drug-related increases in mutant frequency were observed in the presence or absence of S9. **GSK1265744B was therefore considered ***negative*** under the conditions of this study.**
In Vivo Bone Marrow Micronucleus Assay in Rats (Study #WD2007/00789) GLP compliance: Yes Study is valid: Yes	Sprague-Dawley rats (3-6 males/group) were treated by oral gavage with either GSK1265744B (1000 or 2000 mg/kg/dose) or vehicle (0.5% HPMC w/ 0.1% Tween™ 80 in dH_2O) on days 1 and 2, or positive control (20 mg/kg cyclophosphamide) on day 2 only, and were euthanized on day 3. Doses were selected based on a dose range finding test. Vehicle and positive controls produced appropriate responses. No drug-related increases in polychromatic erythrocytes or micronucleated cells were observed. **GSK1265744B was therefore considered ***negative*** under the conditions of this study.**

Abbreviations: DMSO = dimethyl sulfoxide, GLP = good laboratory practice, HPMC = hydroxypropyl methylcellulose

13.1.5.3. Carcinogenicity

2-Year Oral Carcinogenicity Study in Mice (Study #2017N310750):

The carcinogenicity potential of GSK1265744B was evaluated in an oral 2-year mouse carcinogenicity study. CD1(ICR) mice were administered either vehicle (0.5% HPMC and 0.1% Tween™ 80 in dH_2O) or drug (males=2.5, 10, and 75 mg/kg/dose; females=2.5, 5, and 35 mg/kg/dose) once daily by oral gavage for 104 weeks (60/sex/main group; 9-42/sex/satellite group). No drug-related neoplastic or non-neoplastic findings were observed in this study up to the highest dose tested. NOAEL=75 mg/kg/dose in males and 35 mg/kg/dose in females (AUC_{0-t}=1140 µg·hr/mL in males and 1,060 µg·hr/mL in females at week 26). The statistics reviewer, Dr. Feng Zhou, stated that no statistically significant dose–response relationship in tumor incidence was observed.

2-Year Oral Carcinogenicity Study in Rats (Study #2017N310751):

The carcinogenicity potential of GSK1265744B was evaluated in an oral 2-year rat carcinogenicity study. Sprague-Dawley rats were administered either vehicle (0.5% HPMC and 0.1% Tween™ 80 in dH_2O) or drug (0.25, 2.5, and 75 mg/kg/dose) once daily by oral gavage for up to 102 weeks in males and 101 weeks in females (70/sex/main group; 3/sex/satellite group). No drug-related neoplastic or non-neoplastic findings were observed in this study up to the highest dose tested. NOAEL =75 mg/kg/dose (AUC_{0-t} =3820 µg·hr/mL at week 26). The statistics reviewer, Dr. Feng Zhou, stated that no statistically significant dose–response relationship in tumor incidence was observed.

13.1.5.4. Reproductive Toxicology

Oral Male Fertility and Early Embryonic Development Study in Rats (Study #2014N207479)

Key Study Findings

- NOAEL for male fertility=1,000 mg/kg/dose (TK not evaluated). No adverse, drug-related toxicities were observed up to the highest dose tested.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 72. Rat Oral Male Fertility Study Design

Methods	Details
Dose and frequency of dosing:	0, 0.5, 5, and 1,000 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Sprague-Dawley rats (b) (4)
Number/sex/group:	25 males/group
Satellite groups:	None
Study design:	Males were treated for 15 days and then cohabitated with untreated females for up to 14 days. Due to equivocal fertility results from the first cohabitation, males were cohabitated for 7 more days starting on day 50. Males that did not mate were paired with an alternate female for up to another 7 days. Males were treated throughout cohabitation until euthanasia on day 65-67. Mated females and their litters were euthanized on day 20 postcoitum. Unmated females were euthanized 8 days postcohabitation.
Deviations affecting interpretation:	None

Abbreviations: HPMC = hydroxypropyl methylcellulose

Table 73. Rat Oral Male Fertility Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Assessed at least once daily. Increased salivation and urine-stained abdominal fur were observed in 11 high-dose and 3 high-dose males, respectively. Vocalization to touch, movement, and/or when handled was reported in 1 control, 3 low-dose, 3 mid-dose, and 2 high-dose males. All were considered nonadverse.
Body weights	Measured once daily in males and once weekly in females. Decreased 9-10% on days 1-15 and days 1-22 in high-dose males (not statistically significant), and increased 11-14% on days 1-43, 1-50, and 1-57 in mid-dose males only. These were considered nonadverse.
Food consumption	Measured once weekly in males only. Decreased 5-6% on days 1-8 and 8-15 in high-dose males (not statistically significant). This was considered nonadverse.

Parameters	Major Findings
Fertility parameters	The fertility index was decreased at the high dose (84% vs. 100% in controls), and the number of days in cohabitation and days needed for mating were decreased at the high dose (2.3 days vs. 3.4 days in controls) after the first cohabitation period. No changes were observed after the second cohabitation period. The decreased fertility index in the first cohabitation was also within historical control ranges (78.3-100.0%). As this finding was within historical ranges and was not repeated in the second cohabitation after a longer dosing period, these changes were likely incidental.
Cesarean sections	The number of pregnant females was decreased from 25 in controls to 21 at the high dose (84% vs. 100% in controls) after the first cohabitation, but no changes were observed after the second cohabitation. This finding corresponds to the decreased fertility index in this group (see Fertility parameters), and is within historical control ranges (78.3-100.0%). As this finding was within historical ranges and was not repeated in the second cohabitation after a longer dosing period, these changes were likely incidental.
External fetal exams	No drug-related changes.
Necropsy findings	Bilateral small epididymis were present in 1 high-dose male. Small and/or flaccid right and/or left testes were present in 1 control and 1 high-dose males. These were considered unrelated to treatment.
Organ weights	No drug-related changes.
Sperm evaluation	Sperm count and density were decreased 6-18% at all doses relative to controls (1,091.79-1,227.94/g epididymis vs. 1330.42/g epididymis in controls), but these changes were not statistically significant and were within historical control ranges (599.62-1,713.08/g epididymis). These changes were therefore considered nonadverse.

Oral Female Fertility, Early Embryonic and Embryofetal Development Study in Rats (Study #CD2009/00105)

Key Study Findings

- NOAEL for female fertility and maternal toxicity=1,000 mg/kg/dose. No adverse, drug-related effects on female fertility were observed up to the highest dose level.
- NOAEL for embryofetal development=1,000 mg/kg/dose (TK not evaluated). Fetal body weight was decreased 6% in both sexes at the high dose relative to concurrent controls. These changes were outside of historical control ranges, and occurred in the absence of significant effects on maternal body weight or food consumption, but were considered nonadverse due to the low magnitude of the change. No drug-related fetal variations or malformations were observed in this study.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 74. Rat Oral Female Fertility and Embryofetal Developmental Study Design

Methods	Details
Dose and frequency of dosing:	0, 0.5, 5, and 1,000 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Sprague-Dawley rats (b) (4)

Methods	Details
Number/sex/group:	25 females/group
Satellite groups:	None
Study design:	Females were treated for 15 days prior to cohabitation, throughout cohabitation with untreated males for up to 7 days, and throughout GD 17. Mated females and their litters were euthanized on GD 21. Unmated females were cohabited with a second male for another 7 days, and were removed from the study immediately postcohabitation if no evidence of mating occurred.
Deviations affecting interpretation:	None

Abbreviations: GD = gestation day, HPMC = hydroxypropyl methylcellulose

Table 75. Rat Oral Female Fertility and Embryofetal Developmental Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. No drug-related findings.
Body weights	Measured once daily. No drug-related findings.
Food consumption	Measured 1-3× weekly. No drug-related findings.
Estrous cycle	Evaluated once daily. No drug-related findings.
Fertility parameters	No drug-related findings.
Necropsy findings	No drug-related findings.
Cesarean sections	No drug-related findings.
Fetal examinations	No drug-related fetal variations or malformations. Fetal body weights were decreased 6% at the high dose (5.47 g and 5.15 g in males and females, respectively) vs. concurrent controls (5.81 g and 5.46 g in males and females, respectively). These changes were also outside historical control ranges (5.24-5.61 g in females, and 5.54-5.96 g in males). These changes were considered drug-related as they occurred in the absence of any significant effects on maternal body weight and food consumption, but were considered nonadverse due to the low magnitude of the change.

Oral Dose Range Embryofetal Development Study in Rabbits (Study #CD2008/01276):

Key Study Findings

- A NOAEL was not defined in this study due to the low number of animals and litters per group, but no adverse, drug-related effects were observed up to the highest dose tested (2,000 mg/kg/day; $AUC_{0\text{-}24hr}$=99.2 µg·hr/mL at PND 19).
- As a result of this study, doses of 30, 500, and 2,000 mg/kg/day were selected for the pivotal rabbit embryofetal development study.

Conducting laboratory and location: (b) (4)

GLP compliance: No

This study was conducted to identify appropriate dose levels for use in the pivotal rabbit embryofetal developments study (study #CD2009/00842). Pregnant female Dutch Belted rabbits (b) (4); 2 to 4 pregnant females/group) were treated by oral gavage from GD 7 to 19 with either vehicle (0.5% HPMC and 0.1% Tween™ 80 in dH_2O) or GSK1265744 (30, 250, 500, 1,000, and 2,000 mg/kg/day). The highest dose was administered in two separate groups as either a single 2,000 mg/kg dose or two separate 1,000 mg/kg doses spaced ~6 hours apart. All animals

were euthanized on GD 29. Endpoints included mortality, clinical examinations, body weight, food consumption, uterine weights, numbers of corpora lutea, implantations, resorptions, and live/dead fetuses, fetal weights, fetal external morphology, and TK. There were no unscheduled deaths and no drug-related effects on maternal body weight, food consumption, or developmental parameters. Pale feces was observed at 2,000 mg/kg/day (both as a single dose or two separate doses), which was considered drug-related but nonadverse. The highest systemic exposures were observed at 2,000 mg/kg/day administered once daily.

Oral Embryo-Fetal Development Study in Rabbits (Study #CD2009/00842):

Key Study Findings

- NOAEL for maternal toxicity=500 mg/kg/dose ($AUC_{0\text{-}24h}$r=47.4 µg·hr/mL, C_{max}=3.39 µg/mL on GD 11) due to transient drug-related decreases in maternal body weight gain (6%) and food consumption (16%) at the high dose.
- NOAEL for embryofetal development=2,000 mg/kg/dose ($AUC_{0\text{-}24h}$r=96.1 µg·hr/mL, C_{max}=3.39 µg/mL on GD 11). No drug-related effects were observed up to the highest dose tested.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 76. Rabbit Oral Embryofetal Developmental Study Design

Methods	Details
Dose and frequency of dosing:	0, 30, 500, and 2,000 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Dutch Belted rabbits (b) (4)
Number/sex/group:	22 pregnant rabbits/group
Satellite groups:	None
Study design:	Pregnant female rabbits were treated once daily from GD 7-19, and were euthanized on GD 29.
Deviations affecting interpretation:	None

Abbreviations: GD = gestation day, HPMC = hydroxypropyl methylcellulose

Table 77. Rabbit Oral Embryofetal Developmental Study Findings

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined at least once daily. Spontaneous abortions were observed in 1 mid-dose and 1 control females on GD 28, and a second control female delivered early on GD 29. These were considered unrelated to treatment due to the lack of a dose-response and their occurrence in the control group. Pale feces was observed in one high-dose animal, which was considered drug-related but nonadverse.
Body weights	Measured once daily. Maternal body weight gain was decreased 15% from GD 7-20 at the high dose, which was attributed mostly to weight loss (2%) after the first dose from GD 7-8. Despite having recovered by GD 10, this was considered drug-related and adverse.

Parameters	Major Findings
Food consumption	Measured once daily. Maternal food consumption was decreased 16% at the high dose from GD 7-8. Despite having recovered by GD 10, this was considered drug-related and adverse.
Necropsy findings	No drug-related findings.
Cesarean section data	Postimplantation loss was increased from 5.2% in controls to 16.6% at the high dose. This increase was attributed to a single female, which experienced total litter resorption. This was considered incidental as the change was not statistically significant and was within historical control ranges (0.0-18.3%).
Fetal examinations	No drug-related fetal variations or changes in fetal body weight. A cardiac malformation (membranous ventricular septal defect, or VSD) was observed in the following: • 3/151 fetuses (1.99%) across 3/21 litters (14.29%) at the low dose. • 1/159 fetuses (0.63%) in 1/21 litters (4.76%) at the mid-dose. • 5/140 fetuses (3.57%) across 5/21 litters (23.81%) at the high dose. • No fetuses/litters from control animals. The increase at the high dose was also statistically significant. According to the study report on pages 24-25, this malformation was not drug-related "because there was no distinct similarity of the 5 VSDs in that some occurred in multiply malformed fetuses (persistent truncus arteriosus) and some in isolation, there was a lack of dose response and the historical control database reports up to 4 affected fetuses in 4 litters." However, of the 5 high-dose fetuses with VSDs, only one had multiple malformations (persistent truncus arteriosus), while 2 occurred independently, 1 occurred alongside skeletal variations, and 1 was accompanied by excessive fluid in the abdomen. Further, the historical control data state that this malformation was observed in 15/1942 fetuses (0.77%) across 14/295 litters (4.75%), indicating that this malformation exceeded historical background levels. However, as noted above, the historical data also indicate that this malformation was present in up to 4 affected fetuses in 4 litters. In addition, an independent analysis of the background incidence of embryofetal developmental parameters in rabbits[7] specifies that this is a common finding in this strain (Dutch Belted rabbits), with a 30.2% chance of occurring in ≥2 out of 22 litters. Lastly, historical control data from (b) (4) indicate that VSDs were observed in up to 10.6% of fetuses across 47.4% of litters in Dutch Belted rabbits. As a result, this finding was considered incidental and unrelated to treatment.

Abbreviations: GD = gestation day, HPMC = hydroxypropyl methylcellulose, VSD = ventricular septal defects

Oral PPND Study in Rats (Study #2015N236973)

Key Study Findings

- NOAEL for maternal toxicity=1,000 mg/kg/dose (F_0 toxicokinetics not evaluated).
- NOAEL for PPND=5 mg/kg/dose (C_{max}=555 ng/mL) due to drug-related decreases in F1 pup survival and viability that resulted in reduced litter sizes during the first 4 days of life. These decreases were attributed to increases in the number of both stillbirths and early deaths by PND 4. Drug was detected in the serum of the F1 pups on PND 10, indicating that drug is present in milk, though it was unclear in this study if the decreases in F1 pup viability were due to exposure during gestation or lactation. A slight increase in the time to delivery in the F_0 animals was also detected at the high dose (22.2 days in controls versus 22.7 days at the high dose), and no milk was present in the stomachs of

some F_1 pups which died early, but it is unclear if either of these factors contributed to the early F_1 pup deaths. The follow-up investigative PPND study in rats (study #2016N281797) confirmed that the increased gestation time and numbers of stillbirths and early postnatal deaths occurred predominantly in the same animals and was due to gestational exposure to drug.

- The total number of F_2 stillbirths was 2 across 2 litters in controls, 5 across 2 litters at the low dose, 6 across 4 litters at the mid-dose, and 6 across 5 litters at the high dose. However, a total of 6 control, 5 low-dose, 3 mid-dose and 3 high-dose F_2 pups were found dead by PND 7. Because of this, no differences in F_2 pup viability were observed. Given the large number of pups per group (291 to 339), the additional F_2 pup deaths before PND 7 that were not clearly dose-dependent, and the lack of a difference in the F_2 pup viability index, this was considered unrelated to treatment.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 78. Rat Oral Pre- and Postnatal Development (PPND) Study Design

Methods	Details
Dose and frequency of dosing:	0, 0.5, 5, and 1,000 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	(b) (4) HPMC and 0.1% (v/v) Tween™ 80 in dH_2O
Species/strain:	Sprague-Dawley rats (b) (4)
Number/sex/group:	25 females/group
Satellite groups:	None
Study design:	Pregnant F_0 females were treated daily from GD 6 to either PND 21 (for dams that delivered litters) or GD 23 (for dams that did not deliver litters). F_0 females that did not deliver litters were euthanized on GD 24. All remaining F_0 females were euthanized on PND 21. F_1 and F_2 animals were untreated. On PND 21, F_1 animals were either euthanized or selected for further analysis (72/sex/group). On PND 73, F_1 animals were paired for up to 14 days. After mating, F_1 males were euthanized 24 days postcoitum. F_1 females were euthanized either 21 days postcoitum (if pregnant) or 24 days postcoitum (if not pregnant). F_2 pups were euthanized on PND 7.
Deviations affecting interpretation:	None

Abbreviations: GD = gestation day, HPMC = hydroxypropyl methylcellulose, PND = postnatal day

Table 79. Rat Oral Pre-and Postnatal Development (PPND) Study Findings (F_0 Generation)

Parameters	Major Findings
Mortality	One mid-dose female was found dead about 1 hour postdose on PND 18 (after 35 doses). This animal had clinical signs (decreased activity, thin/ungroomed appearance, and soft/liquid feces on PND 18, and lost 35 g (about 10%) body weight from PND 17 to 18. Necropsy showed pyometra (infection of uterus) with cloudy brown fluid in left uterine horn and abdominal cavity. As this occurred in a single animal at the mid-dose well after treatment initiation, this was considered unrelated to treatment.
Clinical signs	Examined at least once daily. No drug-related findings.
Body weights	Measured once daily. No drug-related findings.

Parameters	Major Findings
Food consumption	Measured once daily. Food consumption was decreased 8.5% at the high dose relative to controls from PND 12 to 14. This was attributed to 3 females which had only 3-5 pups per litter. The Applicant attributed these decreases to the smaller litter sizes, which has been shown to affect milk production and food intake.[17] This effect was considered nonadverse.
Pregnancy status	The following were observed at the high dose: • Duration of gestation was increased from 22.2 in controls to 22.7 days (2.2%). • Increased number of stillbirths (8 across 5 litters vs. 2 across 2 litters in controls). Both findings stillbirths were considered drug-related and adverse. It is unclear from these data, however, if the increased gestation length contributed to the increased number of stillbirths.
Necropsy findings	No drug-related findings.

Abbreviations: PND = postnatal day

Table 80. Rat Oral Pre- and Postnatal Development (PPND) Study Findings (F_1 Generation)

Parameters	Major Findings
Mortality	The following were observed at the high dose: • Increased number of stillbirths (8 across 5 litters vs. 2 across 2 litters in controls). • Of the 263 high-dose pups delivered alive on PND 1, 14 were found dead and 19 were missing (presumed or partially cannibalized) by PND 4 (12.5% at the high dose vs. 1.1% in controls). These deaths were primarily seen among 5 litters, of which 4 also had stillbirths or deaths after birth on PND 1. • Decreased percentage of viable pups from 98.9% in controls to 87.4% at the high dose, which is outside the historical control range (93.9-100.0%). Necropsies of these animals revealed no remarkable visceral abnormalities, but 2 low-dose and 3 high-dose pups did not have milk present in the stomach. It is unclear if the absence of milk in the stomach contributed to the deaths of these animals. The increased incidence of stillbirths and early deaths were considered drug-related and adverse.
Clinical signs	Examined at least once daily. Clinical signs (purple skin, cold to touch, slow breathing, and umbilical hernia) were observed in several pups, primarily at the high dose, between PND 1-5. These correlated almost entirely with pup mortality and occurred generally 1 day prior to death.
Body weights	Measured 1-2× weekly. Body weight was increased 5% at the high dose relative to controls at PND 21. This was considered nonadverse due to the low magnitude of the change.
Food consumption	No drug-related findings.
Sexual maturation	Parameters included preputial separation in males and vaginal patency in females. No drug-related findings.
Behavior and activity	Acoustic startle habituation was evaluated on PND 27-29 and 70-77. Motor activity was evaluated on PND 54-61. Learning and retention of a spatial navigation task were evaluated with a Morris water maze on PND 65-85. No drug-related findings.
Fertility parameter	No drug related finding

Parameters	Major Findings
Pregnancy parameters	The following were observed: • The number of F_2 litters with stillbirths was increased to 4 (19%) at the mid-dose and 5 (22.7%) at the high dose relative to 2 (9.5%) in the concurrent control group and 2.8% in historical controls. • The total number of stillbirths was 5 across 2 litters at the low dose, 6 across 4 litters at the mid-dose, and 6 across 5 litters at the high dose (2 across 2 litters in the control group). • However, a total of 6 control, 5 low-dose, 3 mid-dose and 3 high-dose F_2 pups were found dead by PND 7. Because of the inverse dose response in the number of early F_2 pup deaths by PND 7, no differences in F_2 pup viability were observed at any dose level. Given the large number of pups per group (between 291 and 339), the additional F_2 pup deaths before PND 7 that were not clearly dose-dependent, and the lack of a difference in the F_2 pup viability index, this was considered unrelated to treatment.
Necropsy observations	No drug-related findings.

Abbreviations: PND = postnatal day

Table 81. Rat Oral Pre- and Postnatal Development (PPND) Study Findings (F_2 Generation)

Parameters	Major Findings
Mortality	The following were observed (also mentioned in the previous table): • The total number of stillbirths was 5 across 2 litters at the low dose, 6 across 4 litters at the mid-dose, and 6 across 5 litters at the high dose (2 across 2 litters in the control group). • However, a total of 6 control, 5 low-dose, 3 mid-dose and 3 high-dose F_2 pups were found dead by PND 7. Because of the inverse dose response in the number of early F_2 pup deaths by PND 7, no differences in F_2 pup viability were observed at any dose level. Given the large number of pups per group (between 291 and 339), the additional F_2 pup deaths before PND 7 that were not clearly dose-dependent, and the lack of a difference in the F_2 pup viability index, this was considered unrelated to treatment.
General observations	Examined at least once daily. No drug-related findings.
Body weights	Measured on PND 1 and 7. No drug-related findings.

Abbreviations: PND = postnatal day

Oral Investigative PPND Study in Rats (Study #2016N281797)

Key Study Findings

- A NOAEL was not identified in this study. An adverse, drug-related increase in the number of stillbirths and F_1 pup deaths primarily within the first 4 days of life was attributed to drug exposure during gestation rather than lactation.
- The duration of gestation was also increased in the treatment group, with the majority of treated dams delivering on GD 23 rather than 22. Most stillbirths and early F_1 pup deaths, particularly those which occurred within a few hours of delivery, occurred in litters delivered on GD 23 rather than 22. It remains unclear, however, if or how the increased gestation time is related to the increases in F_1 mortality.

Conducting laboratory: (b) (4)

GLP compliance: No

- The purpose of this study was to determine whether the increased F_1 pup deaths observed in the pivotal rat PPND study (study #2015N236973) was due to drug exposure during either gestation or lactation. Pregnant F_0 females were treated once daily by oral gavage with either vehicle (0.5% HPMC and 0.1% Tween™ 80 in dH_2O) or GSK1265744B (1,000 mg/kg/day only) from GD 6 to PND 7. At the time of delivery, all F_0 animals were assigned to one of four groups (A through D), and all F_1 pups were subject to fostering procedures as described in the following table. Pups in subset A, which were exposed to the drug during gestation, were fostered to vehicle-exposed dams. Likewise, pups in subset C, which were exposed to vehicle during gestation, were fostered to drug-exposed dams. Pups in subset A were therefore exposed to the drug during gestation only, and pups in subset C were exposed to the drug during lactation only. Pups in subsets B (vehicle-treated) and D (drug-treated) were not fostered and therefore served as vehicle and positive controls, respectively. All animals were euthanized on PND 8.

Table 82. Rat Investigative Pre- and Postnatal Development (PPND) Study Design

Lactation Subset	Dose (mg/kg)	Characteristics of F_1 Foster Litter on PND 1	#F_0 Females (F_1 Litters)	Postnatal Objective
A	0	Litters from drug-exposed dams were fostered to vehicle-treated dams postnatally/during lactation.	24	Investigate F_1 deaths due to drug exposure during gestation only.
B	0	Litters exposed to vehicle during gestation and lactation (no fostering).	12	Vehicle control.
C	1000	Litters from vehicle-exposed dams were fostered to drug-treated dams postnatally/during lactation.	24	Investigate F_1 deaths due to drug exposure during lactation only.
D	1000	Litters exposed to drug during gestation and lactation (no fostering).	23[a]	Positive control.

[a] One female and litter euthanized on GD 22 due to prolapsed uterus during delivery.
Abbreviations: PND = postnatal day

- Prior to subset assignment, the number of stillbirths was increased from 2 across 2 litters in controls (0.4%; 457 pups total) to 24 across 8 litters in the treatment group (4.2%; 577 pups total). In addition, 5 control pups across 4 litters (1.1%; 457 pups total) and 18 treatment-group pups across 10 litters (3.1%; 577 pups total) died shortly after birth or within hours of delivery completion. Also, 11 pups from a single treatment-group litter were euthanized shortly after the respective dam experienced a prolapsed uterus during delivery on GD 22 (it is unclear if this is drug-related or incidental). This female delivered 13 pups in total, the last 2 of which were stillbirths.
- The numbers and percentages of early postnatal deaths in each lactation subset in this study are presented in the following table. No major differences were observed between subsets B and C or between subsets A and D, but a clear drug-related and adverse increase in the number of stillbirths and deaths were observed in subsets A and D from PND 2 to 4. These data indicate that drug exposure during gestation, rather than during lactation, is most likely responsible for the F_1 pup deaths.

Table 83. Early Postnatal Deaths From the Investigative Pre- and Postnatal Development (PPND) Study

Lactation Subset	PND 1	PND 2-4	PND 5-8	Total
A (gestation only)	2.7% (8/297)	16.6% (48/289)	0.4% (1/241)	19.2% (57/297)
B (vehicle control)	0.0% (0/142)	0.7% (1/142)	0.0% (0/141)	0.7% (1/142)
C (lactation only)	1.0% (3/308)	1.0% (3/305)	0.3% (1/302)	2.3% (7/308)
D (positive control)	0.0% (0/227)	17.2% (39/227)	0.5% (1/188)	17.6% (40/227)

Results are presented as "% deaths (# deaths/total pups)"
Abbreviations: PND = postnatal day

Duration of gestation was also increased from 22.3 days in controls to 22.8 days in the treatment group, indicating that a greater number of treated animals delivered on GD 23 than on GD 22 (83.3% in the treatment group compared to 25.0% in the control group). Of the animals in the treatment group, 22 stillbirths across 7 litters and 17 early deaths across 9 litters were observed among the litters delivered on GD 23, while only 2 stillbirths among 2 litters and a single early death were observed among those delivered on GD 22. By comparison, both control-group stillbirths were delivered on GD 23, and all 5 early deaths were delivered on GD 22. These data suggest a correlation between gestation duration and incidence of stillbirth/early death following exposure to the drug, but it remains unclear whether the increased gestation time directly caused the increased F_1 pup mortality. Interestingly, however, no clear correlation was seen between the day of delivery and F_1 pup death from PND 1 to 8 (after subset assignment). It is therefore conceivable that an increased gestation time following drug exposure may be related to an increased number of stillbirths and very early deaths (within hours of delivery) but may not be related to deaths occurring post-PND 1.

Oral Investigative Toxicokinetics Study in Pregnant Rats (Study #2017N311115)

Key Study Findings

- A NOAEL was not identified in this study. This study was conducted to evaluate the TK of CAB exposure in pregnant rats and fetuses late in gestation.
- Fetal CAB tissue concentrations increased proportionally to maternal plasma levels, and did not accumulate substantially within fetal tissues with repeat dosing. Further, higher fetal drug exposures do not appear to correlate to an increased likelihood of stillbirth or early postnatal death.

Conducting laboratory: (b) (4)

GLP compliance: No

This study was conducted to evaluate the TK of CAB in pregnant rats and fetuses late in gestation, to determine if CAB accumulates in the fetus after repeat dosing, and to determine if the increased stillbirths and early deaths observed in the pivotal rat PPND study (study #2015N236973) were due to increased fetal CAB exposures. Pregnant female Sprague-Dawley (b) (4) rats were treated by oral gavage either once on GD 20 only (groups 1 and 2) or once daily from GD 6 to GD 20 (groups 3 and 4). Groups 1 and 3 received 5 mg/kg/dose, and groups 2 and 4 received 1,000 mg/kg/dose. All litters were delivered by cesarean section 9 hours postdose on GD 20. Maternal blood samples were collected 1, 2, 4, and 8 hours postdose on GD

20 (predose samples were not collected). Drug concentrations in fetal tissues were also measured 9 hours postdose on GD 20.

There were no unscheduled deaths, and no differences in body weight, food consumption, or cesarean section parameters. Abnormal breathing sounds were observed in one group 4 animal on GD 15 to 16. Maternal drug exposure values (C_{max} and AUC_{0-t}) were approximately 5-fold higher on GD 20 following a single dose of 1,000 mg/kg (group 2) compared to a single dose of 5 mg/kg (group 1), though maternal exposures from repeat dosing of 5 mg/kg (group 3) remained comparable to those from repeat doses of 1,000 mg/kg (group 4). AUC_{0-t} and C_{max} values also increased about 3-fold with repeat dosing, relative to a single dose, of 5 mg/kg. No meaningful differences in fetal tissue to maternal plasma ratio were observed regardless of dosing regimen, indicating that fetal exposure increased proportionally to maternal plasma concentrations, and that the drug did not accumulate substantially within the fetus with repeat dosing. Likewise, no meaningful differences in drug concentration within the fetuses were observed in any given litter, suggesting that higher fetal drug exposures do not appear to correlate to an increased likelihood of stillbirth or early postnatal death.

As noted above, maternal blood samples were collected from 1 to 8 hours postdose on GD 20 only, but predose samples were not collected and the predose maternal serum concentrations were assumed to be zero. The maternal AUC_{0-8hr} values for groups 3 and 4, which were treated from GD 6 to 20, were therefore underestimated and were an inaccurate representation of the actual CAB exposure in pregnant rats. As a result, these data were not used to calculate exposure multiples in pregnant rats. TK data from the 26-week GLP toxicology study in rats were used to calculate exposure multiples for the label instead.

13.1.5.5. Other Toxicology/Specialized Studies

28-Day Oral TDAR Study in Rats (Study #2013N179070)

This study was conducted to evaluate the effect of CAB on the immune response to a T-dependent antigen, keyhole limpet hemocyanin (KLH). Sprague-Dawley (b) (4) rats (10/sex/group) were treated with either vehicle (0.5% HPMC and 0.1% Tween™ 80 in dH_2O) or CAB (0.5, 5, and 1,000 mg/kg/dose) once daily for 28 days by oral gavage. All animals were immunized with KLH (300 µg IV injection) on day 12. Anti-KLH IgM and IgG antibody levels were measured prior to immunization on day 1, postdose on days 17, 18, and 19 (for IgM), and postdose on days 26 and 29 (for IgG). No drug-related effects were observed on the anti-KLH IgM response at any dose. Drug-related decreases in anti-KLH IgG levels were observed in high-dose males on days 26 (70%) and 29 (86%). Similar, albeit nonstatistically significant) decreases in anti-KLH IgG levels were observed in high-dose females on days 26 (65%) and 29 (66%). Despite this decrease, measurable levels of anti-KLH IgG were detected in the majority of high-dose males (8/10 and 10/10 on days 26 and 29, respectively), indicating that these animals were still able to mount an immune response. Interestingly, as KLH was only administered at a single timepoint, only the primary immune response was evaluated in this study. The effect of CAB on the immune response to a KLH challenge remains unclear. This study was therefore considered positive for immunosuppressive potential, but was repeated under Study #2018N367799.

39-Day Oral TDAR Study in Rats With a 8-Week Recovery (Study #2018N367799)

This study was conducted to follow up on the previous TDAR study (study #2013N179070), which was positive for immunosuppressive potential and also did not evaluate the secondary immune response to antigen challenge. Sprague-Dawley (b) (4) rats (10/sex/group) were treated with either vehicle (group 1; 0.5% HPMC and 0.1% Tween™ 80 in dH_2O) or CAB (groups 2 and 3; 5 and 1,000 mg/kg/dose) once daily for 39 days by oral gavage. An 8-week recovery period was also added to groups 1 and 3 only (10/sex/group). Two additional groups of 10 rats/sex/group received cyclosporine (groups 4 and 5; 0 and 5 mg/kg/dose) instead of CAB once daily from days 8 to 39 as a positive control for immunosuppression. All main study animals were immunized with KLH (300 µg IV injection) on days 12 and 26, and all recovery animals received KLH on days 68 and 82. In the main study animals, Anti-KLH IgM and IgG antibody levels were measured prior to immunization on day 1, postdose on days 17, 19, 31, and 33 (for IgM), and postdose on days 22, 26 (pre-KLH), 36, and 40 (for IgG). Serum samples were also collected from the recovery animals on days 68 (pre-KLH), 73, 75, 78, 82 (pre-KLH), 87, 89, 92, and 96, but these samples were not evaluated. No drug-related effects were observed in response to either the primary or secondary KLH challenges. All animals produced robust responses to KLH, and the positive control performed as expected. This study was therefore considered negative for immunosuppressive potential.

Because of the positive response observed in the first TDAR study (study #2013N179070), the Applicant was asked to conduct a human vaccine challenge study to evaluate the immunosuppressive potential of CAB in humans. After several communications, however, the Applicant chose to perform the second, more robust TDAR study in rats (study #2018N367799). Because the follow-up TDAR study demonstrated that no drug-related effects on the T-cell–dependent immune response, the Agency agreed that no further assessments of immune function with CAB, including the aforementioned human vaccine challenge study, would be needed.

Local Lymph Node Assay in Mice (Study #2019N396237)

This study was conducted to evaluate the potential of CAB to induce dermal sensitization. Five female CBA/Ca mice were treated with 25 µL drug (25% w/w in propylene glycol) on the dorsal surface of both ears from day 1 to 3. 250 µL ^{3}H-methyl thymidine (80 µCi/mL in PBS) was administered intravenously on day 6, and all animals were euthanized 5 hours later. No drug-related increases in immune cell proliferation in lymph nodes or changes in ear thickness or local skin irritation were observed. CAB was considered to be a nonsensitizer under the conditions of this test.

Determination of Skin Irritation Potential (Study #2019N396399)

This study was conducted to evaluate the potential of CAB to induce dermal irritation. Reconstituted human skin was treated in vitro with 53.3 mg/mL (16 mg in 300 µL) drug for 42 minutes, after which cell viability was measured with a colorimetric MTT assay. No meaningful, drug-related decreases in skin cell viability were observed. CAB was considered to be a nonirritant under the conditions of this test.

Determination of Eye Irritation Potential (Study #2019N396400)

This study was conducted to evaluate the potential of CAB to induce corneal irritation. Transformed human keratinocytes from the HCE cell line were treated with 37.5 mg/mL (30 mg in 800 µL) drug for 10 and 60 minutes, after which cell viability was measured with a colorimetric MTT assay. No meaningful, drug-related decreases in skin cell viability were observed. CAB was considered to be a nonirritant under the conditions of this test.

Determination of Phototoxicity Potential

A dedicated phototoxicity study with CAB was not conducted. Analysis of the CAB absorption spectrum identified multiple peaks from 200 to 390 nm with a λ_{max} =257 nm, and the molar absorption coefficients ranged from 2,670 to 20,800 L mol^{-1} cm^{-1}. No meaningful differences in CAB exposure in pigmented versus nonpigmented skin in the eye and skin were noted in the rat tissue distribution study, and no drug-related toxicities in the skin or eyes were observed in the repeat-dose toxicology studies. The phototoxic potential of CAB was determined to be low.

Assessment of Folate Transporter/Receptor Inhibition (Study #2019N396076)

This study was conducted to evaluate the potential of CAB, other INIs (DTG, RAL, BIC, and EVG), valproic acid, and methotrexate to inhibit key mediators of folate transport in humans—PCFT, reduced folate carrier (RFC), and folate receptor α (FRα). Madin-Darby Canine Kidney-II cells transfected with either PCFT, RFC, or FRα were incubated with up to 100µM CAB for 30 minutes, after which the uptake of folic acid (PCFT and FRα) or methotrexate (RFC) were measured over either 5 minutes (PCFT or RFC) or 2 hours (FRα). No meaningful inhibition of PCFT or RFC by CAB was detected up to the highest concentration tested. FRα was inhibited 36.7% at 100µM CAB only (actual measured CAB concentration was 25.8µM), and an IC_{50} value was not determined.

13.1.6. Impurities/Degradants

The qualification of specified and unspecified impurities within the CAB drug substances, and degradants in the CAB drug products (both oral and IM formulations), are described below. Overall, the proposed specifications, or lack of specifications, are considered acceptable from a pharmacology/toxicology perspective. This conclusion is based on the general toxicology studies, Ames tests, and/or quantitative structure–activity relationship analysis using DEREK Nexus or Leadscope software.

Specified Organic Impurities

Six specified impurities have been identified in the CAB drug substance in both the oral and IM forms. The (b) (4) The proposed specifications for all six impurities, including (b) (4), which are not covered by International Conference on Harmonisation (ICH) Guidance for Industry Q3A(R2) *Impurities in New Drug Substances* (October 2006), are acceptable because they do not exceed the ICH Q3A(R2) qualification threshold (the lower of (b) (4)% or (b) (4) mg/day for (b) (4) g drug/day).[18] Summary

information is provided in the following table. All specified impurities were evaluated by quantitative structure–activity relationship analysis, which is acceptable under ICH M7 for impurities below (b) (4) mg/day,[19] and no structural alerts were detected. All proposed specifications for the specified impurities are therefore considered acceptable.

Table 84. Specified Organic Impurities in the Cabotegravir Drug Substance

Organic Impurities[a]	Toxicology Study Content	NOAEL (mg/kg/day)	Qualified Levels	Proposed Specification
(b) (4)	-	-	(b) (4) %[b]	(b) (4) %
	-	-	%[b]	%
	-	-	%[b]	%
	-	-	%[b]	%
	-	-	%[b]	%
	-	-	%[b]	%

[a] (b) (4)
[b] ICH Q3A(R2) qualification threshold for drugs with maximum daily dose (b) (4) g[18]
Abbreviations: NOAEL = no observed adverse effect level

Residual Solvents

Three residual solvents have been identified. (b) (4) was specified in the oral drug substance, while the remainder were specified in the IM form. All three are listed in ICH (b) (4) and the proposed specifications are within the option 1 limit. Summary information is provided in the following table.

Table 85. Specified Residual Solvents in the Cabotegravir Drug Substance

	ICH Q3C Limit		Proposed Specification	
Residual Solvents	Concentration Limit (Option 1)	PDE (Option 2)	Concentration	Clinical Exposure
(b) (4)	(b) (4) ppm (b) (4) %)	(b) (4) mg/day	(b) (4) %	12 µg/day
	(b) (4) ppm (b) (4) %)	mg/day	%	107 µg/day
	ppm (b) (4) %)	mg/day	%	107 µg/day

[a] Based on cabotegravir oral dose of 30 mg/day
[b] Based on cabotegravir intramuscular loading dose of 600 mg/month, or approximately 21.4 mg/day
Abbreviations: ICH = International Council on Harmonisation, PDE = permitted daily exposure

Elemental Impurities

There are no specified elemental impurities in the CAB drug substance. (b) (4) were identified as potential impurities, but testing of representative drug batches demonstrated that the levels of these impurities are well below (b) (4) % of the permitted daily exposure (PDE) for oral administration as outlined in (b) (4) and no further tests for elemental impurities were included. In addition, (b) (4) was identified as an impurity in the CAB and RPV drug substances by the product quality review team. Because a PDE for (b) (4) is not defined in (b) (4) the Applicant proposed a PDE of (b) (4) µg/day, or (b) (4) ppm, based on a lowest observed adverse effect level of (b) (4) mg/kg/day.[22] However, review of this document indicated that the (b) (4) PDE should be set at (b) (4) µg/day, or (b) (4) ppm. Based on the data provided, the maximum observed (b) (4) levels were (b) (4) ppm (or (b) (4) µg/dose in a 3-mL solution) for RPV, and (b) (4) µg/dose in a 3-mL solution for CAB. The highest conceivable (worst-case) (b) (4) exposure would therefore be (b) (4) µg/dose for the CAB/RPV loading dose injectable. However,

because this is administered only once monthly, a 30-fold safety factor can be applied, which lowers the theoretical daily exposure to (b) (4) µg/day. Further, because this is a worst-case scenario (based on the 3-mL loading dose), and because the known (b) (4) toxicities are minimal when administered orally (minor changes in body weight, cholesterol and serum glucose levels only), the levels of (b) (4) in the CAB and RPV drug products are considered acceptable.

Unspecified Impurities

An assessment of the commercial route of synthesis for CAB was conducted to determine whether any known or potential mutagens might be present in the final drug substance. This assessment included quantitative structure–activity relationship analysis and Ames tests on several production intermediates. Of these, (b) (4) and the hypothetical impurity, (b) (4), were identified as mutagenic. However, as these are intermediates, one of which is hypothetical, the risk of exposure in the drug substance is low. All unspecified impurities are appropriately controlled under (b) (4) and all proposed specifications are considered acceptable.

Drug Product Specifications

There are no specified impurities or degradants in either the oral or IM CAB drug product. Summary information is provided in the following table.

Table 86. Impurity Specifications in the Cabotegravir Drug Product

		Proposed Specifications	
Impurities/Degradants	**Qualified Levels**	**Release**	**Shelf Life**
Cabotegravir, oral			
Individual, unspecified	(b) (4) %[a]	(b) (4) %	(b) (4) %
Total	-	%	%
Cabotegravir, intramuscular			
Individual, unspecified	(b) (4) %[a]	(b) (4) %	(b) (4) %
Total	-	%	%

[a] ICH Q3B(R2) qualification threshold for drugs with max daily dose of 100 mg to 2 g (0.20% or 3 mg/day)[23]

13.1.7. Referenced NDAs, BLAs, DMFs

Not applicable.

13.1.8. Individual Reviews of Studies Submitted to the NDA

Not applicable.

13.2. RPV

13.2.1. Summary Review of Studies Submitted Under IND

Nonclinical toxicology studies to support oral RPV were reviewed under NDA 202022, including safety pharmacology, repeat-dose, genotoxicity, and developmental and reproductive toxicology, as well as carcinogenicity studies. Studies specific to the RPV LA formulation for IM administration were reviewed under IND 106273. Summaries of studies conducted under NDA 202022 are provided below as well as reviews and summaries for pivotal studies that pertain to the LA formulation.

13.2.2. Pharmacology (Primary and Secondary)

The primary and secondary pharmacodynamic effects of RPV were investigated in in vitro and in vivo studies under the original oral RPV NDA 202022. RPV did not cause in vitro inhibition of α- or β-adrenergic, dopaminergic, muscarinergic, serotonergic, opioid, interleukin, or chemokine receptors (up to 10μM, 3.7 μg/mL), or human DNA polymerase α, β, or γ (up to 1,000μM, 366 μg/mL).

13.2.3. Safety Pharmacology

The effects of oral RPV on a core battery of safety pharmacology parameters were evaluated in a series of in vitro and in vivo studies. For the safety pharmacology study results, please refer to the original NDA for the oral RPV formulation (NDA 202022). A brief summary is provided here. No adverse effects of RPV on the cardiovascular, respiratory, or central nervous systems were noted during initial safety pharmacology studies. Subsequently, a phase 1 clinical trial (NDA 202022) demonstrated a QT interval-prolongation effect of RPV at supratherapeutic doses. In follow-up nonclinical safety pharmacology studies, RPV at concentrations approximately 10-fold greater than the clinical exposures demonstrated the potential to inhibit some potassium channels involved in cardiac action potential repolarization. Given the clinical and nonclinical findings, AEs that could be related to cardiac conduction abnormalities or to rate and rhythm disturbances were closely monitored in the phase 2b and phase 3 clinical trials under NDA 202022. No clinically relevant QTc prolonging effect was observed with the recommended therapeutic dose of RPV 25 mg once daily (up to 50 mg once daily), although it should be noted that patients with known risk for QT interval prolongation or Torsade de Pointes were excluded from the phase 3 trials. A thorough QT study was not conducted under the current NDA for RPV LA because exposures from the RPV LA to-be-marketed dose is similar to the exposure from the approved oral dose of 25 mg.

13.2.4. Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics

This summary focuses on the pharmacokinetic data after IM administration of RPV LA (TMC278 LA), focusing on the final clinical formulation G001 containing 300 mg RPV base/mL suspension and poloxamer 338 (P338; 50 mg/mL). Absorption was examined in rabbits and minipigs. Limited distribution studies were conducted in rabbits and rats. Excretion studies and

in vivo and in vitro metabolism studies with RPV, as well as the enzymes involved in the metabolism of RPV in the human hepatocytes and enzyme induction and inhibition studies have been described in detail in the original NDA for oral RPV under NDA 202022. Detailed pharmacokinetic data is also presented here for both the 9-month minipig and 4-week dog toxicology studies.

Absorption

- Several studies were performed in rabbits and minipigs, mainly comparing different formulations containing P338 to the final P338-containing formulation (G001). No relevant changes in plasma profiles across studies were observed.
- In minipigs and rabbits, after a single IM administration of RPV LA as the final P338-containing formulation (G001), RPV release was fast, with a C_{max} reached within 24 h in minipigs and slower in rabbits, after which mean plasma concentrations declined, remained fairly constant thereafter and were still quantifiable after 3 months (Table 87 and Table 88).
- The absolute bioavailability (F_{abs}) was 67% in rabbits at 150 mg/kg and between 35 and 62% in minipigs at 600 mg (Table 87).

Table 87. Mean Plasma Pharmacokinetic Parameters of Rilpivirine (RPV) LA After Single Dose Administration of RPV Formulated in Clinical Formulation G001

Species	Route	Formulation	Dose	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	CL_p (CL_b) (L/h/kg)	Vd_{ss} (L/kg)	F_{abs} (%)
Female rabbits	IV[a]	(b) (4)	1.25 mg/kg	8531[f]	NA	43,840	12	0.03 (0.049)	0.32	-
	IM[b]	G001	150 mg/kg	6453	78.3	3,561,529	-	-	-	67
Male minipigs	IV[c]	(b) (4)	2 mg/kg	1701[f]	NA	2797	8	0.75	4.9	-
	IM[d]	G001	600 mg (~67 mg/kg[f])	2245	100	152,011	-	-	-	62
	IM[c]	G001	600 mg (69 mg/kg)	234	2.67	24,806	-	-	-	35[g]
	IM[e]	G001	600 mg (22-30 mg/kg)	120	0.5-24	15,662				43[h]

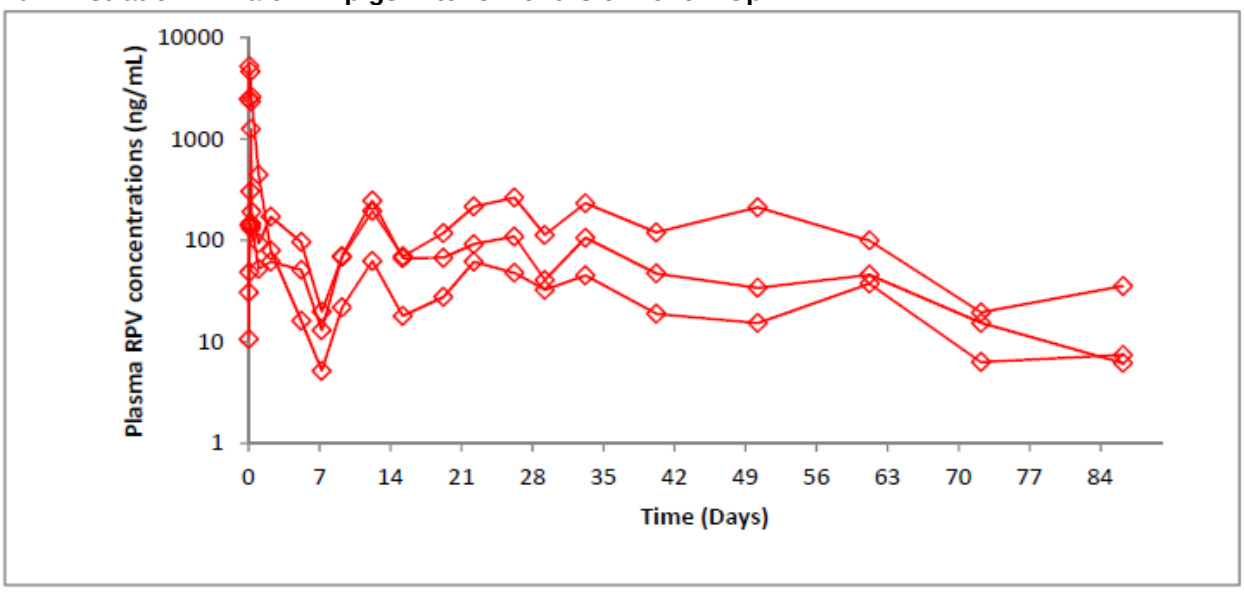
[a] NDA202022/0000/Mod4.2.2.2/FK4293; [b] Mod4.2.2.2/26831_14279 (FK7521); [c] Mod4.2.2.2/2683_14125 (FK7520); [d] Mod4.2.3.6/NC359-TOX9403; [e] Mod4.2.2.2/2683_0040908 (FK10294); [f] C_0; [g] calculated using the minipig receiving IV and RPV LA (G001) after a wash out of 1 week; [h] the mean weight 26 mg/kg was used for calculation

$AUC_{0-\infty}$: area under the plasma-concentration versus time curve from time 0 to infinity; CL_b: blood clearance; CL_p: plasma clearance; C_{max}: maximum plasma concentration; F_{abs}: absolute bioavailability; IM: intramuscular; IV: intravenous; NA: not applicable; PEG: polyethylene glycol; $t_{1/2}$: half-life; t_{max}: time at C_{max}; Vd_{ss}: volume of distribution at steady state

Abbreviations: LA = long-acting

- Plasma concentration of RPV LA in minipigs dosed with 600 mg fluctuated or remained constant until a drop in the plasma concentrations occurred between day 1 and 7. Thereafter, relatively flat profiles were observed between day 9 and 84 (Table 88). The mean C_{max} and $AUC_{0\text{-}3months}$ values of RPV LA at 600 mg/minipig (G001) were 2,245 ng/mL and 152,011 ng·h/mL, respectively.

Table 88. Individual Plasma Profiles of Rilpivirine (RPV) LA After a Single 600 mg IM Administration in Male Minipigs After 3 Months of Follow-Up



Abbreviations: IM = intramuscular, LA = long-acting

Distribution

- Protein binding and distribution in blood cells has been described in detail in the original NDA 202022 for oral RPV. In short, serum protein binding of RPV was above 99% for all species tested (including humans) over a wide range of concentrations.
- In rabbits injected IM with 150 mg/kg G001, RPV LA concentrations were high (1,456-fold) at the administration side compared those in the contralateral side. In the lymph nodes, the RPV LA concentrations were similar between the injection and contralateral side in most rabbits. This was a limited distribution study.
- In rats, the highest exposures of RPV LA after IM injection were measured in left popliteal and medial iliac lymph nodes, adjacent to injection site with tissue/plasma $AUC_{0\text{-day }42}$ ratios of 12,203 and 2,256, respectively. The tissue/plasma $AUC_{0\text{-day }42}$ ratios were lower than 1 in brain (0.4), heart (0.8), spleen (0.97), and thymus (0.87).

Table 89. Tissue, Plasma, and Blood Concentrations of Rilpivirine (RPV) LA and Tissue:Plasma or Tissue:Blood Ratios of RPV After IM Administration of RPV LA in Rats

Tissue/organs	C_{max} (µg/mL or g)	t_{max} (h)	$AUC_{0\text{-day}42}$ (µg.h/mL or g)	Tissue to plasma $AUC_{0\text{-day}42}$ ratio	Tissue to blood $AUC_{0\text{-day}42}$ ratio
Blood	0.061	2	15.1	0.64	1
Plasma	0.129	2	23.7	1	1.6
Adrenal gland	0.16	168	73.5	3.2	4.9
Brain	0.023	168	2.7[a]	0.4	0.7
Eye	BLQ	-	-	-	-
Heart	0.046	24	12.5[b]	0.8	1.2
Kidney	0.16	168	84.8	3.7	5.6
Liver	0.069	24	24[b]	1.5	2.3
Lung	0.075	24	33.9	1.5	2.2
Lymph Node (Medial iliac left)	409	168	51,200	2256	3391
Lymph Node (Medial iliac right)	0.088	24	58.2	2.6	3.9
Lymph Node (Popliteal left)	1100	504	277,000	12,203	18,344
Lymph Node (Popliteal right)	1.2	24	153	6.7	10
Pancreas	0.058	168	28.1	1.2	1.9
Spleen	0.048	168	22.1	0.97	1.5
Thymus	0.094	24	19.7	0.87	1.3
Thyroid	0.050	168	-	-	-

[a] $AUC_{0\text{-day}7}$; [b] $AUC_{0\text{-day}21}$; BLQ: below the limit of quantification <10.0 ng/g

- Comparing the distribution after 40 mg/kg oral and 60 mg/kg IM administration of RPV in rats, the tissue/plasma exposure (AUC) ratios of RPV in adrenal gland and brain were in the same order of magnitude and the liver ratio was higher (2.5× [tissue/plasma] to 6× [tissue/blood]), in line with the oral route of administration. In addition, the tissue/blood exposure (AUC) ratios of RPV after RPV LA were in the same ranking as after oral administration of [^{14}C]-RPV, except again in the liver (Table 90).

Table 90. Tissue/Plasma or Blood Ratios of Rilpivirine (RPV) After Oral Administration of RPV or RPV LA in Rats

Organs/tissue	Tissue/plasma ratio after RPV LA at 60 mg/kg ADME_58575	Tissue/plasma ratio after oral RPV at 40 mg/kg FK4195	Tissue/blood ratio after RPV LA at 60 mg/kg ADME_58575	Tissue/blood ratio after oral ^{14}C-RPV at 40 mg/kg TMC278-NC108-FK4951
Adrenal gland	3.2	2.6	4.9	4.9
Brain	0.29	0.49	0.4	0.66
Heart	0.69	-	1.0	1.9
kidney	3.7	-	5.6	3.6
Liver	1.4	3.4	2.1	12
Lung	1.5	-	2.2	2
Pancreas	1.2	-	1.9	2.9
Spleen	0.97	-	1.5	-
Thymus	0.87		1.3	-

Abbreviations: ADME = absorption, distribution, metabolism, excretion, LA = long-acting

Table 91. Toxicokinetic Data

Study/Study No. | **Major Findings**

General Toxicology Studies/Local Tolerance/Bridging

4-Week Dog Intramuscular Injection Toxicology Study with TMC278 LA With a 2-Week Recovery Period (TOX10759/EDMS-ERI-84839483)

Sample collection times: Predose and 0.5, 2, 4, 6, 24, 72, 120, 192, 264, 336*, 432*, 528*, 624*, and 672* hours postdose on days 1 and 15
*designated recovery animals only

NOAEL: 1200 mg

Exposure multiple: 6.4

Based on day 15 dog gender average values and human individual post hoc estimates from the final population PK models for subjects enrolled in phase 3 studies (AUC_{tau} =65,603 ng·hr/mL)

Day 1					
Dose (mg)	**Sex**	**T_{max} (hr)**	**C_{max} (ng/mL)**	**$AUC_{(0-336h)}$ (ng·h/mL)**	**$AUC_{(0-264h)}$ (ng·h/mL)**
150	Female	24	245	45700	39300
	Male	264	116	28800	21500
1200	Female	24	1220	204000	175000
	Male	24	1220	218000	185000
Day 15					
Dose (mg)	**Sex**	**T_{max} (hr)**	**C_{max}**	**$AUC_{(0-264h)}$ (ng·h/mL)**	**$AUC_{(0-600h)}$ (ng·h/mL)**
150	Female	24	394	48500	94200
	Male	24	177	34500	63400
1200	Female	24	1230	206000	410000
	Male	24	1440	217000	435000

9-Month Minipig Intramuscular Injection Toxicology Study with TMC278 LA (TOX9517/ EDMS-ERI 20094817)

Sample collection times: Days 0, 3, 7, 10, 14, 17, 21, 24, 28, 227, 231, 234, 238, 241, 245 and 248.

NOAEL: 600 mg

Exposure multiple: 0.72

Based on day 224 minipig gender average values and human individual post hoc estimates from the final population PK models for subjects enrolled in phase 3 studies (AUC_{tau} =65,603 ng·hr/mL)

	Male	Female
Dose (mg /4 weeks)	600	600
	Day 0	
C_{max} (ng/ml)	189	637
T_{max} (h)	7.0	4.3
$AUC_{0-672\ h}$ (ng.h/ml)	20696	34964
	Day 224	
C_{max} (ng/ml)	349	402
T_{max} (h)	6.0	26.0
$AUC_{0-672\ h}$ (ng.h/ml)	50071	44342

Abbreviations: LA = long-acting, NOAEL = no observed adverse effect level, PK = pharmacokinetic

13.2.5. Toxicology

13.2.5.1. General Toxicology

Pivotal studies evaluating the final G001 clinical formulation (RPV LA at 300 mg/mL in P338 at 50 mg/mL) with IM administration were conducted in dogs (4-week bridging study) and minipigs (6-week and 9-month studies).

TOX10759/EDMS-ERI-84839483: 4-Week Dog IM Injection Toxicology Study With TMC278 LA With a 2-Week Recovery Period (Bridging Study)

Key Study Findings

- Injection site findings were noted at both the 150- and 1,200-mg doses.
- Increases in 17α-(OH)-progesterone were noted in dogs dosed with 1,200 mg and were not reversible. This was consistent with oral administration toxicology studies in dogs (NDA 202022).
- Exposure was consistent with that observed in 52-week dog study with 5 mg/kg/day oral administration of TMC278 LA (study reviewed under NDA 202022). In that study, 5 mg/kg/day was the lowest observed adverse effect level. Exposure in this study was higher than exposure at 600 mg in humans with RPV LA (TMC-LA; C_{max} and AUC levels).

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 92. 4-Week Dog Study With IM Injection of TMC278 LA-Methods

Study Features and Methods	Details
Dose and frequency of dosing:	0, 150, and 1,200 mg on days 1 and 15
Route of administration:	Intramuscular
Formulation/vehicle:	Test article:JNJ-16150108-AAA-G001 – 300 mg/mL – (b) (4) for injection (also known as TMC278, TMC278 LA, and JNJ-16150108) Control article: JNJ-16150108-AAA-G002 – 0 mg/mL – solution for injection
Species/strain:	Beagle dog
Number/sex/group:	3/sex/group (main); 2/sex/group (recovery- control and high dose only)
Age:	Eight months old
Satellite groups/unique design:	None
Deviations affecting interpretation:	None

Abbreviations: IM = intramuscular, LA = long-acting

Table 93. 4-Week Dog Study With IM Injection of TMC278 LA-Observations and Results

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined once daily. No drug-related findings.
Dermal observations	Examined once daily. Swelling, edema, and skin thickening were observed in dogs dosed with 1,200 mg. These findings were not recoverable.
Body weights	Measured once weekly. No drug-related findings.
Ophthalmoscopy	Evaluated pretreatment, day 15 and during the last week of recovery (week 6). No drug-related findings.
Electrocardiography	Measured pretreatment, day 15 and during the last week of recovery. No drug-related findings.

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Parameters	Major Findings
Hematology	Measured pretreatment, day 15 and during the last week of recovery (week 6). On day 16, eosinophil levels in males and females dosed with 1,200 mg were slightly elevated as compared to controls and predose values. This change was not observed after the recovery period.
Coagulation	Measured pretreatment, day 15 and during the last week of recovery (week 6). On day 16, fibrinogen levels in males and females dosed with 1200 mg were slightly elevated as compared to controls and predose values. This change was not observed after the recovery period.
Clinical chemistry	Measured pretreatment, day 15 and during the last week of recovery (week 6). No drug-related findings.
Urinalysis	Measured pretreatment, day 15 and during the last week of recovery (week 6). No drug-related findings.
Gross pathology	Evaluated at necropsy (day 29 and 43): Gross findings were observed at the administration site (white deposits) and at the draining lymph nodes (pale discoloration) and at both 150 and 1,200 mg. These changes were also noted in recovery animals.
Organ weights	Evaluated at necropsy (day 29 and 43): Organ weight changes were noted in the liver of females (increase of approx. 20% in main but not in recovery animals) and in the prostate of males (increases between 2 and 3-fold in main and recovery animals) at 1,200 mg, with no microscopic or clinical pathology correlates. As such, the changes were not considered adverse.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy (day 29 and 43): Microscopic findings were observed at the administration site (amorphous eosinophilic deposit, macrophage aggregation, mononuclear cell infiltration) and drainage lymph nodes (macrophage aggregation) at both the 150 and 1,200-mg dose in both main and recovery animals.
Endocrinology	Measured pretreatment and days 1,2, 8, 15, 22, 29, and 43. At a dose of 1,200 mg, minimal to slight increases in 17α-(OH)-progesterone were noted from day 1 onwards up to the end of recovery in males only. There were no drug-related findings in cortisol.

Abbreviations: IM = intramuscular, LA = long-acting

Two repeat-dose general toxicology studies were performed in the minipig with the clinical formulation G001, a 6-week toxicity study and a 39-week (9-month) toxicity study. Since the overall toxicity profiles were the same in both the 6-week and the 39- studies, only the 39-week pivotal toxicology study is reviewed in detail (TOX9517/EDMS-ERI-20094817) while a summary review of the 6-week study is presented below.

TOX9508/TMC278-TiDP15-NC368: Six-Week Intramuscular Toxicity Study of a TMC278 Long-Acting Formulation (G001) in the Minipig

Three male and female Gottingen minipigs were dosed with either buffer, Poloxamer 338 at 50 mg/mL or 160 mg/mL, or Poloxamer 338 50 mg/ml TMC278 LA 300 mg/mL. Animals in all groups showed increases in an acute phase inflammatory marker, C-reactive protein at 24 hours after an IM injection on day 0 and day 28. Although C-reactive protein was increased across groups, animals that received TMC278 LA appeared to show an earlier onset. Slight erythema (2 cm to 5 cm) was seen in all animals dosed with TMC278 LA with no accompanying swelling, induration, or tenderness at the injection site. At necropsy, the injection sites showed white deposits (3 cm to 6 cm) and white discoloration of the draining lymph nodes. One male showed swelling of the medial iliac lymph node. Histopathology showed correlating lesions of

macrophage infiltration, filled with eosinophilic material — presumably TMC278 LA, and extracellular amorphous pale eosinophilic deposits with inflammatory infiltrates in some females. The draining lymph nodes (medial iliac and/or deep inguinal) showed similar histopathology with macrophage infiltrates and multinucleated macrophages (with eosinophilic contents) with focal amorphous eosinophilic deposits seen in one female in a deep inguinal lymph node. In conclusion, TMC278 LA was overall well-tolerated following IM injections every 2 weeks for 6 weeks, with the exception of local effects at the injection sites (erythema) and draining lymph nodes (swelling with white deposits containing macrophages and eosinophilic material). The lesions are indicative of inflammation and the local uptake of TMC278 LA by macrophages at the injection site.

TOX9517/EDMS-ERI-20094817: Nine-Month Minipig Intramuscular Injection Toxicology Study With TMC278 LA

Key Study Findings

- The toxicities identified with TMC278 LA repeat IM dosing in the minipig mainly consisted of ISRs, swollen lymph nodes and white deposits/inflammatory cell infiltrates at the injection site.
- The ISRs and lymph node findings were indicative of inflammation and the local uptake of TMC278 LA by macrophages at the injection site and draining lymph nodes. In addition, testicular immaturity (decreased spermatogenesis or Leydig cell persistence) was seen in 1/3 control males versus 3/3 TM278 LA treated males; this finding was also observed with the oral formulation in dogs and was previously associated with an inhibitory effect of TMC278 LA on steroidogenesis.
- Steroidogenesis effects have not been observed in humans. The phase 3 clinical data for oral RPV indicated that 21-hydroxylase was not affected by treatment with RPV. However, there was a small mean decrease in basal cortisol levels, and the cortisol response to ACTH stimulation was attenuated.
- Because HIV-1–infected patients are an at-risk population for adrenal insufficiency, the label includes information with regards to the potential effect of RPV on adrenal function.

Conducting laboratory: (b) (4)

GLP compliance: Yes

Table 94. 9-Month Minipig Study With IM Injection of TMC278 LA-Methods

Study Features and Methods	Details
Dose and frequency of dosing:	600 mg; monthly for 10 months
Route of administration:	Intramuscular injection
Formulation/vehicle:	Control/buffer- (b) (4) Glucose (b) (4) (b) (4) Sodium dihydrogen phosphate monohydrate, (b) (4) Citric acid monohydrate (b) (4) Water for injection, pH (b) (4) Vehicle- poloxamer 338 50 mg/ml, (b) (4) Glucose anhydrous parenteral, (b) (4)

Study Features and Methods	Details
	Sodium dihydrogen phosphate monohydrate, (b) (4) Citric acid monohydrate (b) (4) Water for injection, pH (b) (4)
Species/strain:	Minipigs/Gottingen
Number/sex/group:	3/sex/group
Age:	4-6 months
Satellite groups/unique design:	None
Deviations affecting interpretation:	None

Abbreviations: IM = intramuscular, LA = long-acting

Table 95. 9-Month Minipig Study With IM Injection of TMC278 LA – Observations and Results

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined once daily. Clinical signs included slight erythema (<2 cm) in 2 males and 1 female dosed with the TMC278 on day 1 after the first injection – erythema was not seen beyond day 1.
Body weights	Measured weekly. No drug-related findings.
Food consumption	Measured weekly. No drug-related findings.
Ophthalmoscopy	Not evaluated.
Electrocardiography	Not evaluated.
Hematology	Measured pretreatment and on days 91, 182, and 255. A minimal increase in thrombocytes was seen in 1 male and 1 female treated with TMC278 LA from week 13 until the end of the study. In addition, one female showed a minimal increase in white blood cell counts at 37 weeks. Since these changes were small and not correlated with histopathology or other endpoints, it is unlikely that they are toxicologically significant and were considered nonadverse.
Clinical chemistry	Measured pretreatment and on days 91, 182, and 255. A minimal increase in ALT (1.88-fold) and AST (1.67-fold) was noted in one TMC278 LA dosed male. In addition, one TMC278 LA dosed female showed a slight increase in potassium and another TMC278 dosed female showed a slight increase in creatinine. These changes were small and not correlated with histopathology or other changes, and were considered nonadverse.
Coagulation	Measured pretreatment and on days 91, 182, and 255. Activated partial thromboplastin was increased in one TMC278 LA dosed male. Additionally, a minimal increase in fibrinogen was observed in two TMC278 dosed females that the Applicant possibly associated with the findings at the injection site. Changes in coagulation were previously identified with the oral formulation.
Urinalysis	Measured pretreatment and on days 92, 183/184, and 254. No drug-related findings.
Gross pathology	Evaluated at necropsy on week 37 (day 258). Gross pathology at necropsy showed bilateral white deposits at the injection site in TMC278 LA-treated animals. In addition TMC278 LA-treated animals exhibited changes in the draining lymph nodes that included swollen and/or discolored lymph nodes. Swollen popliteal lymph nodes were seen in one male, swollen and/or discolored medial iliac lymph nodes were observed in 3 males, and finally swollen and/or discolored external iliac lymph nodes were seen in 3 females.

Parameters	Major Findings
Organ weights	Evaluated at necropsy on week 37 (day 258). One TMC278 LA-treated male showed an increased prostate weight by absolute weight (2.6-fold higher), mean % body weight (1.8-fold), and mean % brain weight (2.3-fold) compared with the vehicle control group mean values. Since this was only seen in one male, it is unclear whether this finding is test article related or not. In addition, although males appeared to show an increased medial iliac lymph node weight compared with vehicle-treated animals, the absolute weights were within the female vehicle control range and therefore were not treatment related.
Histopathology Adequate battery: Yes Peer review: Yes	Evaluated at necropsy on week 37 (day 258). Histologic findings at the injection site included marked infiltrations of large, pale, foamy macrophages that were located in the subcutaneous space as well as in muscle tissue bundles. There was no muscle necrosis associated with the finding. In males, in the right injection site (the last administered dose), there were large pale eosinophilic deposits, which the study report concluded is "nonabsorbed or nonphagocytosed compound." The macrophage infiltrates and eosinophilic deposits correlated with the white deposits observed grossly. Lymph node findings included infiltrates of large, pale, foamy macrophages that affected the popliteal and external and medial iliac lymph nodes; these findings correlate with the gross observations of swollen and/or discolored nodes. Testicular immaturity was seen in 1/3 control males (grade 2), 0/3 vehicle control males, and 3/3 TMC278 LA-treated males (1 – slight, and 2- moderate observations). Testicular immaturity was characterized by the persistence of Leydig or interstitial cells and/or a decrease in spermatogenesis. This finding correlated with a similar incidence of epididymal hypospermia seen in the same control male and 2/3 of the TMC278 LA-treated males. Testicular immaturity was previously observed with the rilpivirine oral toxicity studies
Special evaluation	Measured pretreatment and on days 0, 3, 7, 10, 14, 21, 24, 28, 224, 227, 231, 234, 238, 241, 245, 248, and 252. C-reactive protein was measured as an acute phase inflammatory biomarker. Increases in CRP were seen across groups at 24 hours postdose. A higher increase in CRP was seen in TMC278 LA males and females on day 0 and 224 (approx. 10%), with a more pronounced effect in females, compared to the vehicle group.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, IM = intramuscular, LA = long-acting

13.2.5.2. Genetic Toxicology

TMC278 genetic toxicology studies previously reviewed for NDA 202022 were negative. The Applicant conducted new genotoxicity studies with Poloxamer 338 to qualify the use of this novel excipient. These studies are reviewed briefly below (Table 96).

Table 96. Genetic Toxicology

Study No./ Study Title	Key Study Findings
TMC278-TiDP15-NC357, TOX9535/ In Vitro Reverse Mutation Assay in Bacterial cells (Poloxamer 338) GLP compliance: Yes Study is valid: Yes	*S. typhimurium* (TA98, TA100, TA102, TA1535, and TA1537) were treated for up to 72 hours with up to 10,000 µg/plate of Poloxamer in the presence and absence of S9. Vehicle and positive controls (2-nitrofluorene, sodium azide, 9-aminoacridine, 2-aminoanthracene, 4-nitroquinoline-N-oxide) produced appropriate responses. No drug-related increases in the number of revertant colonies (≥2-fold) were observed in either the presence or absence of S9. **Poloxamer 338 was therefore considered negative under the conditions of this study.**
TMC278-TiDP-NC358, TOX9523/ Assay for Chromosomal Aberrations In Vitro in Chinese Hamster Ovary Cells (Poloxamer 338) GLP compliance: Yes Study is valid: Yes	Primary human lymphocytes were treated with up to 10,000 µg/mL of Poloxamer 338 for 3 hours in the presence of S9 and 21 hours in the absence of S9. No evidence of chromosomal aberrations were seen in metaphase or polyploidy analyses of human lymphocytes treated with Poloxamer 338 in the presence and absence of S9. The vehicle and positive controls (mitomycin C, cyclophosphamide) produced appropriate responses. **No evidence of chromosomal aberrations were seen in metaphase or polyploidy analyses of human lymphocytes treated with Poloxamer 338 in the presence and absence of S9.**

Abbreviations: GLP = good laboratory practice

13.2.5.3. Carcinogenicity

RPV carcinogenicity studies were previously reviewed under NDA 202022. Two-year carcinogenicity studies in mice and rats were conducted with RPV. In rats, no drug-related increases in tumor incidence were observed up to RPV exposures approximately 3× higher than those in humans at the RHD. In mice, RPV was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific. At the lowest tested dose in the mouse carcinogenicity study, the systemic exposure to RPV was 21× that observed in humans at the RHD.

13.2.5.4. Reproductive Toxicology

RPV reproductive and developmental toxicology studies were previously reviewed for NDA 202022. No adverse developmental outcomes were observed when RPV was administered orally at exposures up to 15× (rats) and 70× (rabbits) the exposure in humans at the RHD. In a PPND study, RPV was administered orally up to 400 mg/kg/day through lactation. No adverse effects were noted in the offspring at maternal exposures up to 63× the exposure in humans at the RHD. Animal lactation studies with RPV have not been conducted. However, RPV was detected in the blood of nursing pups on lactation day 7 in the rat PPND study

13.2.5.5. Other Toxicology/Specialized Studies

TMC278-TiDP15-NC301: In Vitro Hen's Egg Chorioallantoic Membrane Irritation Test

The in vitro irritation potential of TMC278 formulated at 200 and 300 mg/mL showed mild effects on coagulation. The TMC278 batch used in this study did not contain Poloxamer 338 and was not representative of the clinical material but did assess TMC278 at the same concentration as the clinical material (300 mg/mL). Irritation was assessed by measuring hemorrhage, lysis, and coagulation, on the chorioallantoic membrane (CAM) of fertilized chicken eggs. The CAM provides a vascularized but not innervated membrane as a model for eye irritation (CAM

simulates the conjunctiva) and blood vessel irritation. TMC278 at 200 mg/ml and 300 mg/ml was evaluated on CAMs (N=3) from 10-day-old fertilized chicken eggs treated with TMC278 for 5, 15, 30, and 60 minutes. Study controls included a negative control (0.9% NaCl), vehicle controls for each test formulation, and a positive control, N,N-dimethylformamide. The 5-minute endpoint provided an assessment of eye irritation and at >15 minutes provided an assessment of vascular irritation. None of the test formulations showed evidence of irritation after 5 minutes. At later time points (>15 min to 60 min), the negative and vehicle controls showed no signs of irritation. The positive control showed the maximal positive irritation response in the assay. The 200 mg/ml TMC278 formulation showed marginal coagulation (scored as an in vitro vascular irritation index of 2.7±4.6) and the 300 mg/ml TMC278 formulation showed mild coagulation (with a score of 16.0±6.9). The study report notes that the coagulation effect could be due to the viscous properties of TMC278 rather than a direct effect of TMC278; however, effects on coagulation have been seen in the in vivo toxicology studies. Therefore, a direct treatment related effect cannot be ruled out.

TMC278-TiDP15-NC199: Evaluation of the Sensitization Potential of TMC278 and Various (b) (4) of TMC278 (Base) in the Local Lymph Node Assay

A local lymph node assay showed no potential for skin sensitization. Skin sensitization was evaluated three ways by determining T-cell proliferation at different locations and after different applications in different formulations: 1) at lymph nodes draining the site of test article application with test article applied as a 5, 10, or 35% w/v preparation in (b) (4) 2) following topical application with test article applied as (b) (4) or Poloxamer 338; 3) at draining lymph nodes following subcutaneous administration with test article administered SC as 2.5% TMC278 in (b) (4)% Poloxamer 338 and (b) (4)% TMC278 in (b) (4)% (b) (4) No skin sensitization was detected in the assay with the various formulations and test article applications. The positive control streptozotocin, showed strong sensitization in the assay.

Excipient Studies

Embryofetal toxicity studies were conducted in the rat and rabbit with Poloxamer 338 in order to qualify the novel excipient. No adverse developmental outcomes were observed. A summary of the studies is presented below.

TOX9679/TMC278-TiDP15-NC347: Oral Developmental Toxicity Study of Poloxamer 338 in the Rat

Pregnant female rats were dosed with control or 1,600 mg/kg/day Poloxamer 338 (maximum feasible dose) via gavage from day 6 to day 17 of gestation. Animals were necropsied on day 21. Reduced maternal body weight gain (approx. 10%) was noted in dams dosed with 1,600 mg Poloxamer 338, however this was not statistically significant. No fetal abnormalities were observed in the study.

TOX9680/TMC278-TiDP15-NC348: Oral Developmental Toxicity Study of Poloxamer 338 in the Rabbit

Pregnant female rabbits were dosed with 1,600 mg/kg/day Poloxamer 338 (maximum feasible dose) via gavage from day 6 to day 19 of gestation. Animals were necropsied on day 28. Toxicology findings in pregnant rabbits included statistically significant decreases in food consumption (down to -22%), marked decreases in body weight gain from day 9 to 19 (down to -31%) and soft feces in a majority of animals ranging in severity from slight to severe. No fetal abnormalities were observed in the study.

13.2.6. Impurities/Degradants

Table 97. Specified Organic Impurities in Drug Substance

Organic Impurity	Toxicology Study Content	NOAEL	Qualified %[a]	Proposed Specification
(b) (4)	(b) (4) %[b]	(b) (4) mg/kg/day	(b) (4) %	(b) (4) %
	%[b]	mg/kg/day	%	%
	%[b]	mg/kg/day	%	%
	%[b]	mg/kg/day	%	%
	(b) (4) %[c]	mg/kg/day	%	%
Individual, unspecified	--	--	--	%
Total	--	--	--	≤ (b) (4)

[a] Qualified level = (b) (4))

[b] From 1-month oral repeat-dose study in rat

[c] From 1-month oral repeat-dose study in dog. NOAEL was not identified in dog study. LOAEL was (b) (4) mg/kg/day

Abbreviations: NOAEL = no observed adverse effect level

Genotoxic Impurity (b) (4) in Drug Substance

(b) (4) are genotoxic synthesis impurities in the RPV drug substance. The analytical method does not discriminate between the (b) (4) therefore, the test results cover all three impurities. From the dosing scheme with 900 mg as a maximum dose with a once monthly dosing interval; a threshold of toxicological concern of (b) (4) ppm was established. This calculation was based on the worst-case scenario in terms of impurity exposure, where an RPV LA initiation dose of 900 mg (followed by a once monthly continuation dose) translates into a daily dose of 30 mg RPV over 30 days. A monthly dosing schedule leads up to a total of 912 dosing days or 2.5 years over a life time period. Therefore, based on the staged threshold of toxicological concern of (b) (4) µg/day over a 10-year dosing period, the maximum allowable limit of (b) (4) would be (b) (4) ppm. This limit also adequately covers the other treatment scenarios (using a lower dose, e.g., 600 mg, or a longer treatment interval, e.g., every 2 months). The actually measured levels of (b) (4) in batches representative of the commercial process are below 1 ppm, and therefore well below the threshold of toxicological concern-based allowable limit.

(b) (4)

(b) (4)

13.2.7. Referenced NDAs, BLAs, DMFs

NDA 202022

13.2.8. Individual Reviews of Studies Submitted to the NDA

Not applicable.

14. Clinical Pharmacology Assessment: Additional Information

14.1. Clinical Pharmacology Assessment: CAB

14.1.1. In Vitro

Note: For assessment of the clinical relevance of CAB concentrations evaluated in in vitro studies, note that in phase 3 studies the 5th percentile of CAB C_{tau} was 1700 ng/mL (3.98µM) and the 95th percentile of CAB C_{max} was 11,900 ng/mL (27.8µM). In in vitro studies where the CAB concentrations evaluated are relevant to interpretation of the results, such as protein binding and inhibition or induction of enzymes or transporters, clinically relevant CAB concentrations were used.

Table 98. Report: The In Vitro Protein Binding of GSK1265744 in Plasma From Human Donors

Test drug(s) and concentrations	GSK1265744 (500, 1,000, 5,000, 10,000 and 20,000 ng/mL)
Report number	2015N235936 (Study 8309868)
Study system	Human plasma
Method	Equilibrium dialysis
Results	Determination of GSK1265744 Binding to Plasma Proteins Binding of GSK1265744 to plasma proteins of human was determined at 500, 1,000, 5,000, 10,000, and 20,000 ng/mL. Two groups of QC samples (750 and 15,000 ng/mL GSK1265744) were also included with this experiment. Plasma protein binding of GSK1265744 was high, with percent unbound ranging from 0.47% at 500 ng/mL to 0.62% at 20,000 ng/mL. Mean percent recovery ranged from 99.7 to 107% among all concentrations. The data trended toward increasing percent unbound with increasing GSK1265744 concentration. However, the only statistically significant difference was between percent unbound at 500 ng/mL and percent unbound at 20,000 ng/mL. Thus, there is slight concentration dependence for the range of GSK1265744 concentrations tested.
Discussion/ conclusion	GSK1265744 was highly bound to plasma proteins in human in vitro. Plasma protein binding was concentration dependent between the lowest and highest concentrations tested, with unbound GSK1265744 ranging from 0.47% at 500 ng/mL to 0.62% at 20,000 ng/mL.

Table 99. Report: An In Vitro Study to Investigate the Metabolism of [^{14}C]GSK1265744 in Rat, Monkey, and Human Hepatocytes

Study type	ADME
Test drug(s) and concentrations	[^{14}C]GSK1265744 and nonradiolabeled GSK1265744 (final concentration 50µM)
Positive control(s) and concentrations	7-ethoxycoumarin (final concentration 250µM)

Report number	RD2008/00073 **(**Study 08DMR007**)**
Study system	Cryopreserved hepatocytes
Method	[^{14}C]GSK1265744 was incubated at 37°C with rat, monkey, and human hepatocytes at approximately 1.5 million viable cells/mL for approximately 4 and 24 hours. Controls without hepatocytes were performed in parallel over the same time period. Metabolic viability of the cells was evaluated with the probe substrate, 7-ethoxycoumarin. Following incubation, samples were analyzed using liquid scintillation counting and HPLC. 24 hour samples were subjected to LC fractionation. Fractions of interest were analyzed by using mass spectrometry for structural characterization.
Results	In human hepatocyte incubations, ~6.0% of [^{14}C]GSK1265744 was metabolized. Two radiocarbon peaks were identified, accounting for 97.5% of the total radiochemical peak area (TRPA). [^{14}C]GSK1265744, at a retention time of 60.0 minutes, represented 94.0% of the TRPA. Metabolite M1 (glucuronidation of [^{14}C]GSK1265744), at retention time 43.6 minutes, represented 3.5% of the TRPA. In rat hepatocyte incubations, ~9.6% of [^{14}C]GSK1265744 was metabolized. Two radiocarbon peaks were identified, accounting for 94.8% of the TRPA. [^{14}C]GSK1265744, at a retention time of 59.9 minutes, represented 90.4% of the TRPA. Metabolite M1 (glucuronidation of [^{14}C]GSK1265744), at retention time 43.3 minutes, represented 4.4% of the TRPA. In monkey hepatocyte incubations, ~6.0% of [^{14}C]GSK1265744 was metabolized. Two radiocarbon peaks were identified, accounting for 97.4% of the TRPA. [^{14}C]GSK1265744, at a retention time of 59.9 minutes, represented 94.0% of the TRPA. Metabolite M1 (glucuronidation of [^{14}C]GSK1265744), at retention time 43.5 minutes, represented 3.4% of the TRPA. Results from incubating 7-ethoxycoumarin with hepatocytes indicated that the hepatocytes from all species were metabolically active in both phase 1 metabolism (O-demethylation) and phase 2 metabolism (glucuronidation and sulfation).
Discussion/ conclusion	The metabolic turnover of [^{14}C]GSK1265744 in rat and monkey hepatocytes (~9.6% and 6.0% turnover, respectively) was similar to that observed in human hepatocytes (~6.0% turnover). The route of metabolism for [^{14}C]GSK1265744 in rat, monkey, and human hepatocytes was glucuronidation. The human metabolite of [^{14}C]GSK1265744 was observed in monkey and rat hepatocyte incubations justifying the selection of monkey and rat for toxicological investigations of GSK1265744. This in vitro data is in accordance with in vivo data where glucuronidation was the major route of GSK1265744 metabolism in monkey, rat and human.

Table 100. Report: An In Vitro Investigation of the Glucuronidation of [^{14}C]GSK1265744 in Human Liver, Intestinal and Kidney Microsomal Fractions

Test drug(s) and concentrations	[^{14}C]GSK1265744E (final concentration 5µM)
Report number	2014N222268 (Study 14DMR030)
Study system	Human liver, intestinal and kidney microsomes

Method	Definitive Human Liver, Kidney and Intestinal Microsomal Incubations Human liver and kidney microsomes were diluted to a final protein concentration of 0.5 mg/mL and human intestine to a final protein concentration of 1 mg/mL. Microsomes were preincubated with [^{14}C]GSK1265744 (final concentration of 5µM) for 5 minutes. Incubations were performed, in duplicate, for 120 minutes (liver and kidney) and 60 minutes (intestinal) at 37ºC while shaking. Control incubations were performed in the absence of cofactor and in the absence of microsomes. Samples were analyzed by radio-HPLC. Structural confirmation of the glucuronide in this study was by LC/MS analysis.
Results	In human liver, kidney and intestinal microsomal incubations, [^{14}C]GSK1265744 (5µM) was metabolized to a single UDPGA-dependent metabolite, M1 (ether glucuronide), comprising ~17%, 8.4% and 4.0% of the total radioactivity, respectively. The estimated mean (n=2) rate of metabolite formation (pmol/min/mg) in human liver, kidney, and intestinal microsomes were 14, 7.0, and 3.3 pmol/min/mg, respectively.
Discussion/ conclusion	Incubation of [14C]GSK1265744 with UDPGA cofactor in human liver, kidney and intestinal microsomes resulted in the formation of a single UDPGA-dependent metabolite, M1 (ether glucuronide). The estimated mean rate of metabolite formation (pmol/min/mg) in human liver, kidney, and intestinal microsomes were 14, 7.0 and 3.3 pmol/min/mg, respectively.

Table 101. Report: An In Vitro Investigation of the Human Enzymes Involved in the Glucuronidation of [^{14}C]GSK1265744

Test drug(s) and concentrations	[^{14}C]GSK1265744E (final concentration 5µM)
Report number	2012N145430 (Study 12DMR018)
Study system	Human liver microsomes and cDNA-expressed UGT enzymes
Method	Incubation of GSK1265744 with UGT Supersomes [^{14}C]GSK1265744 incubations with Supersomes™ containing overexpressed individual UGT enzymes were performed for 2 hours at 37ºC. Each incubation contained 5µM [^{14}C]GSK1265744 and 0.5 mg/mL of UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, or 2B15. Enzyme kinetic parameters were determined for [^{14}C]GSK1265744 glucuronide formation in human liver microsomes and in recombinant UGT1A1 and 1A9 enzymes. Final concentrations of [^{14}C]GSK1265744 were 2, 5, 10, 25, 50, and 100µM. Microsomes were diluted to a final concentration of 0.5 mg/mL. Incubations were performed for 2 hours at 37ºC. Supernatants from [^{14}C]GSK1265744 incubations with human liver microsomes and recombinant UGT enzymes were analyzed by radio-HPLC. Representative samples were analyzed by LC/MS with off-line radiochemical detection to assist in the identification of metabolites and to confirm peak assignments.

Results	In human liver microsomal incubations [^{14}C]GSK1265744 (5μM) was metabolized to a single UDPGA-dependent metabolite, M1 (ether glucuronide), comprising ~22% of the total radioactivity. The estimated kinetic constants, K_m, V_{max}, and CL_{int}, for its formation in human liver microsomes were 496μM, 1298 pmol/min/mg, and 2.6 μL/min/mg, respectively. [^{14}C]GSK1265744 (5μM) was metabolized in recombinant UGT1A1 and 1A9 incubations resulting in calculated K_m, V_{max}, and CL_{int} values of 148μM, 660 pmol/min/mg, and 4.5 μL/min/mg, respectively for UGT1A1, and 90μM, 200 pmol/min/mg, and 2.2 μL/min/mg, respectively for UGT1A9. The fraction of GSK1265744's total clearance (fCL) mediated by UGT1A1 and 1A9 in vitro was 0.67 and 0.33, respectively. M1 was not observed in UGT1A3, 1A4, 1A6, 2B4, 2B7, 2B15 or control UGT incubations. Under these in vitro conditions, the glucuronidation of GSK1265744 was primarily mediated by UGT1A1 with some contribution from UGT1A9.
Discussion/ conclusion	The data from human liver microsomes and recombinant UGT enzyme incubations suggest that UGT1A1 is the primary UGT enzyme involved in the glucuronidation of GSK1265744 with contribution from UGT1A9.

Table 102. Report: An In Vitro Evaluation of the Effect of GSK1265744 on mRNA Levels of Cytochrome P450 Genes in Cultured Human Hepatocytes

Test drug(s) and concentrations	GSK1265744B (final concentrations 0.03, 0.1, 0.3, 1.0, 3.0, 10, and 30μM).
Positive control(s) and concentrations	Omeprazole (50μM) for CYP1A2, phenytoin (50μM) for CYP2B6 and rifampicin (10μM) for CYP3A4.
Report number	2013N166279 (Study 12DMM040)
Study system	Human hepatocytes
Method	Hepatocytes were incubated with test compound, positive control or solvent for 24 hours at 37ºC. Following incubation, cells were lysed and total RNA was extracted. Total RNA isolates were quantified using the RiboGreen™ assay kit. cDNA was prepared by performing reverse transcription (RT). An RT minus plate was used to evaluate the efficiency of the DNase process. The specific mRNA level was quantitatively detected for the following genes: CYP1A2,CYP2B6, CYP3A4 and the housekeeping gene, glyceraldehyde 3-phosphate dehydrogenase (GAPDH).
Results	Incubation with Prototypical Inducers: Omeprazole (50μM) caused an increase in the mRNA expression levels of CYP1A2 to a mean ratio of treated over control of 88±75. Phenytoin (50μM) caused an increase in the mRNA expression levels of CYP2B6 to a mean ratio of treated over control of 15±6.3. Rifampicin (10μM) caused an increase in the mRNA expression levels of CYP3A4 to a mean ratio of treated over control of 11±1.8. Incubation with GSK1265744: Based on the previous datasets, a ratio ≥5 is considered as a notable induction response for CYP1A2 and a ratio ≥2 is considered as notable induction responses for CYP2B6 and CYP3A4. Following exposure of cultured human hepatocytes to GSK1265744 for 24 hours, no notable increases in the mean mRNA levels of CYP1A2 and CYP3A4 were observed. Mean CYP2B6 levels were increased by 2.1-fold at the 0.03μM GSK1265744 dose only, however this was not a dose dependent effect. No notable increases in mean mRNA levels of CYP2B6 were observed from 0.1 to 30μM GSK1265744.

Discussion/ conclusion	Following exposure of cultured human hepatocytes to GSK1265744 for 24 hours, no notable increases in the mean mRNA levels of CYP1A2 and CYP3A4 were observed at concentrations up to 30µM. No notable increases in mean mRNA levels of CYP2B6 were observed from 0.1 to 30µM GSK1265744. A clinical drug interaction study has demonstrated that GSK1265744 does not affect the pharmacokinetics of midazolam, a sensitive substrate of CYP3A [Report 2014N208332]. Based on the absence of induction of CYP3A4, CAB is not expected to induce CYP2C9 and CYP2C19 because both CYP3A4 and CYP2C enzymes are induced via activation of the pregnane X receptor (PXR).

Table 103. Report: In Vitro Evaluation of GSK1265744 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes

Test drug(s) and concentrations	GSK1265744B (final concentrations 0.1 to 100µM)
Positive control(s) and concentrations	**Direct inhibition**: α-Naphthoflavone (0.5µM) for CYP1A2, Nicotine (300µM) for CYP2A6, Orphenadrine (750µM) for CYP2B6, Montelukast (0.05µM) for CYP2C8, Sulfaphenazole (2.0µM) for CYP2C9, Modafinil (250µM) for CYP2C19, Quinidine (0.5µM) for CYP2D6, Ketoconazole (0.15µM when atorvastatin or nifedipine was the marker substrate and 0.075µM when midazolam was the marker substrate) for CYP3A4/5. **Metabolism dependent inhibitors**: Furafylline (1µM) for CYP1A2, 8-Methoxypsoralen (0.05µM) for CYP2A6, Phencyclidine (30µM) for CYP2B6, Gemfibrozil glucuronide (5µM) for CYP2C8, Tienilic acid (0.25µM) for CYP2C9, S-fluoxetine (20µM) for CYP2C19, Paroxetine (0.3µM) for CYP2D6, Troleandomycin (20µM when atorvastatin or nifedipine was the marker substrate and 7.5µM when midazolam was the marker substrate) for CYP3A4.
Report number	2012N151766 (Study XT125015)
Study system	Human liver microsomes
Method	To examine its ability to act as a direct inhibitor of CYP enzymes, GSK1265744 was incubated with marker substrate and human liver microsomes. To examine its ability to act as a metabolism-dependent inhibitor of CYP enzymes, GSK1265744 was preincubated at 37±1°C with human liver microsomes and an NADPH-generating system for approximately 30 minutes. To examine its ability to act as a time-dependent inhibitor of CYP enzymes, additional samples at all GSK1265744 concentrations were preincubated for 30 minutes in the presence of pooled human liver microsomes, but in the absence of NADPH.
Results	Under the experimental conditions examined, GSK1265744 directly inhibited CYP3A4/5 (atorvastatin ortho-hydroxylation) with an IC_{50} value of 84µM. In addition, there was evidence of direct inhibition of CYP2B6 and CYP3A4/5 (nifedipine oxidation) by GSK1265744, as approximately 20% and 28% inhibition, respectively, was observed at the highest concentration of GSK1265744 evaluated (100µM), and the IC_{50} values were reported as greater than 100µM. There was little or no evidence of direct inhibition of CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6 or 3A4/5 (midazolam 1′-hydroxylation) by GSK1265744. The IC_{50} values for these enzymes were reported as greater than 100µM GSK1265744. After a 30-minute preincubation with pooled human liver microsomes in the presence of NADPH, a greater than 20% increase in inhibition and/or a greater than 1.5-fold shift decrease in IC_{50} values was observed indicating that GSK1265744 is a metabolism-dependent inhibitor of CYP3A4/5 (atorvastatin ortho-

	hydroxylation, midazolam 1′-hydroxylation and nifedipine oxidation). There was little or no evidence of time-dependent or metabolism-dependent inhibition of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, or 2D6 by GSK1265744. In some cases, some loss in activity of the enzyme tested was observed regardless of the presence of GSK1265744. The positive control inhibitors for direct inhibition and metabolism-dependent inhibition inhibited enzyme activity as expected.
Discussion/ conclusion	GSK1265744 did not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, or 2D6. GSK1265744 was a metabolism-dependent inhibitor of CYP3A4/5 and directly inhibited CYP3A4/5 with an IC_{50} value of 84μM. Based on the draft FDA guidance for In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies 2017, R_1=1.004 and $R_{1,gut}$ =7.7, suggesting no concern for CYP3A inhibition at clinically relevant concentrations.

Table 104. Report: Evaluation of Inhibition of Catalytic Activities of Human Uridine 5'-Diphospho-Glucuronosyltransferases (UGTs) by the Test Substance, GSK1265744

Test drug(s) and concentrations	GSK1265744B (final concentrations 100, 30, 10, 3, 1, 0.3, 0.1 and 0μM).
Positive control(s) and concentrations	Estradiol (200μM) for UGT1A1, 2-Hydroxyestradiol (100μM) for UGT1A3, Hecogenin (50μM) for UGT1A4, Naphthol (50μM) for UGT1A6, Propofol (50μM) for UGT1A9, Eugenol (100μM) for UGT2B7. No positive control inhibitors have been qualified for UGT2B4, UGT2B15 or UGT2B17.
Report number	2013N159049 (Study 440000344)
Study system	Human liver microsomes (HLM, UGT1A1 only) and cDNA-expressed human UGT enzymes (all enzymes)
Method	Substrates are listed below. All incubations were at 37ºC. Metabolites were quantified using HPLC.

Enzyme	Substrate	Incubation Time (Min)
UGT1A1	Bilirubin	12
UGT1A1	Bilirubin	30
UGT1A3	17 β -Estradiol	30
UGT1A4	Trifluoperazine	20
UGT1A6	7HFC	10
UGT1A9	7HFC	20
UGT2B4	7HFC	20
UGT2B7	7HFC	20
UGT2B15	7HFC	20
UGT2B17	Eugenol	20

7HFC =7-Hydroxy-4-trifluoromethylcoumarin

Results	GSK1265744 inhibited UGT1A3 and UGT1A9, with IC_{50} values of 12µM and 46µM, respectively. At the highest concentration tested (100µM) GSK1265744 inhibited UGT1A1 by 15% (human liver microsomes) and 33% (recombinant UGT1A1 enzyme) and UGT2B17 by 24%. The IC_{50} values for these enzymes were >100µM. There was little (<20% at the highest concentration tested) to no inhibition of UGT1A4, 1A6, 2B4, 2B7, or 2B15. The IC_{50} values for these enzymes were >100µM. Positive control results, where available, demonstrated a properly functioning test system.
Discussion/ conclusion	GSK1265744 inhibited UGT1A3 with an IC_{50} value of 12µM. A mechanistic static mathematical model was used to predict the effect of GSK1265744 on the exposure of substrates of UGT1A3. The results of the model showed GSK1265744 has low risk of being a perpetrator of drug interactions with substrates of UGT1A3 (predicted AUC change <1.2-fold) [Report 2015N258625]. Based on these data, there is low potential for GSK1265744 to affect the pharmacokinetics of co-administered drugs that are substrates of UGT enzymes; therefore, the Applicant did not conduct a clinical drug interaction study with UGT substrates.

Table 105. Report: An In Vitro Investigation of Both the Transport Via Heterologously Expressed Human P-Glycoprotein and the Passive and Absorptive Membrane Permeability of [^{14}C]GSK1265744 in MDCKII-MDR1 Cells

Test drug(s) and concentrations	[^{14}C]GSK1265744E (final concentration 3µM)
Positive control(s) and concentrations	[^{3}H]Amprenavir (final concentration 3µM)
Report number	2012N146040 (Study 12DMR021)
Study system	MDCKII-MDR1 cell line heterologously expressing human P-gp
Method	Transport studies: The transport of [^{14}C]GSK1265744 and [^{3}H]amprenavir was measured in two directions (apical to basolateral [A→B] and basolateral to apical [B→A]). Following preincubation, cells were incubated at 37°C for 90 minutes. Receiver and donor compartments contained 2µM GF120918. All samples were analyzed for total radioactivity using a liquid scintillation counter. The cell monolayer integrity was evaluated by measuring the Lucifer yellow concentrations in the receiver wells. Fluorescence was determined using a cytofluorimeter. A sample of the donor working solutions for [^{14}C]GSK1265744 with and without GF120918 inhibitor were taken at the beginning and end of the experiment for analysis by radio-HPLC to confirm the radiochemical purity of the test articles in transport medium. Membrane permeability studies: The passive membrane permeability at pH 7.4 of [^{14}C]GSK1265744 and [^{3}H]amprenavir, was measured in one direction (apical to basolateral [A→B]) in DMEM medium. To inhibit P-gp activity, both receiver and donor compartments contained 2µM GF120918. The absorptive membrane permeabilities at pH 7.4 and pH 5.5 of [^{14}C]GSK1265744, were measured in one direction [A→B]. FaSSIF (at pH 5.5 or pH 7.4) was used as the transport medium in the apical compartment, and DMEM (pH 7.4) with 1% NAÏVE in the basolateral compartment. To inhibit P-gp activity, both receiver and donor compartments contained 2µM GF120918. Following preincubation, cells were incubated at 37°C for 90 minutes. All samples were analyzed for total radioactivity using a liquid scintillation counter. The cell monolayer integrity for all wells was evaluated by

	measuring the Lucifer yellow concentration in the receiver compartments. Fluorescence was determined by a cytofluorimeter.
Results	Transport assay: The apical efflux ratio for [^{3}H]amprenavir was 15 collapsing to 0.88 in the presence of the P-gp inhibitor, GF120918. This demonstrated the functional expression of human P-gp in the MDCKII-MDR1 cell line. The mass balance for [^{3}H]amprenavir was considered acceptable. The apical efflux ratio of [^{14}C]GSK1265744 at 3µM was determined as 3.0 and 0.83 in the absence and presence of 2µM GF120918, respectively. These results indicate that, under the assay conditions used, [^{14}C]GSK1265744 is a substrate of human P-gp. Membrane permeability assay: In MDCK-MDR1 cells in the presence of the potent P-glycoprotein inhibitor GF120918, the passive membrane permeability of the positive control [^{3}H]amprenavir, was high with a $P_{7.4}$ of 546 nm/s and was considered acceptable under these assay conditions. The passive membrane permeability at pH 7.4 of [^{14}C]GSK1265744 was high with a $P_{7.4}$ of 256 nm/s. In the presence of FaSSIF (fasted state simulated intestinal fluid), the absorptive membrane permeability of [^{14}C]GSK1265744 was high at pH 7.4 and at pH 5.5 with a $P_{7.4}$[abs] of 1088 nm/s and $P_{5.5}$[abs] of 1374 nm/s, respectively. The mass balance for [^{14}C]GSK1265744 and [^{3}H]amprenavir was considered acceptable for all assays.
Discussion/ conclusion	[^{14}C]GSK1265744 was a substrate for human P-gp with a moderate efflux ratio of 3.0 at a concentration of 3µM. [^{14}C]GSK1265744 was determined to have high passive membrane permeability at pH 7.4 with $P_{7.4}$ of 256 nm/s. The absorptive membrane permeability of [^{14}C]GSK1265744 in the presence of FaSSIF was high at pH 7.4 with a $P_{7.4}$[abs] value of 1088 nm/s and high at pH 5.5 with a $P_{5.5}$[abs] value of 1374 nm/s. The Applicant did not conduct a clinical drug interaction study with a P-gp inhibitor because considering the high passive membrane permeability of GSK1265744, it is not expected to show significant P-gp mediated efflux.

Table 106. Report: An In Vitro Investigation of the Transport via Heterologously Expressed Human Breast Cancer Resistance Protein of [^{14}C]GSK1265744 in MDCKII-BCRP Cells

Test drug(s) and concentrations	[^{14}C]GSK1265744 (final concentration 3µM)
Positive control(s) and concentrations	[^{14}C]Cimetidine (final concentration 3µM)
Report number	2012N155942 (Study 12DMR032)
Study system	MDCKII-BCRP cell line heterologously expressing human BCRP
Method	Cell culture: MDCKII-BCRP cells were cultured to confluency, trypsinized, and seeded onto Transwell multiwell membrane inserts at a density of approximately 3×10^{5} cells/cm^{2}. The cell monolayers were fed 24 hours postseeding with culture medium (Dulbecco's modified eagle medium with glutamine, 10% (v/v) fetal bovine serum) and transport studies conducted 48 hours later. Transport studies: The transport of [^{14}C]GSK1265744 and [^{14}C]cimetidine was measured in two directions (apical to basolateral [A→B] and basolateral to apical [B→A]). Following preincubation, cells were incubated at 37°C for 90

	minutes. All samples were analyzed for total radioactivity using a liquid scintillation counter. The cell monolayer integrity was evaluated by measuring the Lucifer yellow concentrations in the receiver wells. Fluorescence was determined using a cytofluorimeter.
Results	The radiochemical purity of [^{14}C]GSK1265744 determined at the beginning of the study was 98.1% (n=2) with no single impurity accounting for ≥1% of the detected radioactivity. The radiochemical purity of the stock solution of the positive control [^{14}C]cimetidine used in this study was 98.81 (n=2) with no single impurity accounting for ≥1% of the detected radioactivity. The apical efflux ratio for [^{14}C]cimetidine was 6.1 collapsing to 1.2 in the presence of the BCRP inhibitor, GF120918. This demonstrated the functional expression of human BCRP in the MDCKII-BCRP cell line. The mass balance for [^{14}C]cimetidine was considered acceptable. The apical efflux ratio of [^{14}C]GSK1265744 at 3µM was determined as 2.6 and 1.1 in the absence and presence of 2µM GF120918, respectively. These results indicate that, under the assay conditions used, [^{14}C]GSK1265744 is a substrate of human BCRP. The mass balance for [^{14}C]GSK1265744 and [^{14}C]cimetidine was considered acceptable.
Discussion/ conclusion	The data demonstrate that [^{14}C]GSK1265744 was a substrate for human BCRP with an efflux ratio of 2.6 at a concentration of 3µM. The Applicant did not conduct a clinical drug interaction study with a BCRP inhibitor because considering the high passive membrane permeability of GSK1265744, it is not expected to show significant BCRP mediated efflux.

Table 107. Report: An In Vitro Investigation Into the Hepatic Uptake of GSK1265744B

Test drug(s) and concentrations	GSK1265744B (final concentrations 0.5 and 10µM
Positive control(s) and concentrations	[^{3}H]Estradiol Glucuronide (0.02µM.)
Report number	2018N391028 (Study18DMW024)
Study system	Cryopreserved human hepatocytes
Method	Uptake of the compound in the absence and presence of the inhibitor cocktail was determined at multiple time points. Following preincubation, GSK1265744 with or without inhibitor was added and cells were incubated at 37°C for 0.5, 1, 2, 5, and 10 minutes. After lysis of cells, samples were measured on a liquid scintillation counter. The positive control substrate, [^{3}H]EG was run simultaneously to demonstrate organic anion transporter function in the cryopreserved hepatocytes. The concentrations of GSK1265744 samples were determined by UPLC-MS/MS.
Results	The uptake of control probe substrate [^{3}H]-EG (0.02µM) in pooled cryopreserved human hepatocytes was inhibited by the cocktail of inhibitors with a signal-to-noise ratio of 9 and 6.3 confirming the functionality of the test system. The hepatic uptake of GSK1265744 was determined in pooled cryopreserved human hepatocytes in the presence and absence of a cocktail of hepatic uptake inhibitors. No carrier-mediated uptake of GSK1265744 was observed over the 10 minute time course at both concentrations of the test compound.
Discussion/ conclusion	The in vitro hepatic uptake of GSK1265744 was not mediated by the transporters OATP1B1, OATP1B3, OATP2B1 or OCT in pooled human cryopreserved hepatocytes, therefore clinical interaction studies with inhibitors of these transporters were not conducted.

Table 108. Report: An In Vitro Investigation into the Inhibition by GSK1265744 of Xenobiotic Transport Via Human P-Glycoprotein Heterologously Expressed in MDCKII Cells

Test drug(s) and concentrations	GSK1265744 (final concentration 0.3µM to 30µM)
Positive control(s) and concentrations	GF120918 (final concentration 2µM)
Report number	2012N146041 (Study 12DMR022)
Study system	Madin-Darby canine kidney MDCKII-MDR1 cell line
Method	Cell culture: MDCKII-MDR1 cells were cultured to confluency, trypsinized and seeded onto Transwell multiwell membrane inserts at a density of approximately $3x10^5$ cells/cm^2. The cell monolayers were fed 24 hours postseeding with culture medium (Dulbecco's Modified Eagle Medium with glutamine, 10% (v/v) Fetal Bovine Serum) and transport studies conducted 48 hours later. Transport inhibition studies: The effect of GSK1265744 on the P-gp-mediated transport of [^{3}H]digoxin was assessed by determining the basolateral (donor well) to apical (receiver well) ([B→A]) transport of [^{3}H]-digoxin for 90 minutes, in the absence or presence of GSK1265744 at target concentrations of 0.03, 0.05, 0.1, 0.3, 0.5, 1, 3, 5, 10, and 30µM (applied in both apical and basolateral wells). The dose range was determined due to the limited solubility of GSK1265744 at concentrations >30µM. GF120918, a potent inhibitor of P-gp, was included at a nominal concentration of 2µM as a positive control for P-gp inhibition. Measurement of inhibition of transport: Following preincubation, plates were incubated at 37ºC for 90 minutes. All samples were analyzed for total radioactivity using a liquid scintillation counter. The cell monolayer integrity was evaluated by measuring the Lucifer yellow concentrations in the receiver wells. Fluorescence was determined using a cytofluorimeter.
Results	The measured radiochemical purity of the [^{3}H]digoxin used in this study was 98.8% (n=2) with no single impurity accounting for >1.5% of the detected radioactivity. Experiments were regarded as valid where quality control parameters were within acceptable limits. Acceptable values for the assay were: Lucifer yellow $P_{7.4}$≤50 nm/sec; digoxin mass balance 80 – 120%; digoxin transport rate ≥1.5 pmoles transported/cm^2/h; digoxin transport rate in the presence of 2µM GF120918≤30% of uninhibited rate. The upper concentration range examined was limited due to a lack of solubility of GSK1265744 at concentrations greater than 30µM. The [B→A] transport rate for [^{3}H]-digoxin in the absence of inhibitor was 2.9±0.074 pmole/cm^2/h and in the presence of the P-gp inhibitor GF120918 (positive control) was 0.64±0.021 pmole/cm^2/h (22±0.73% of digoxin alone transport). These results demonstrated the functional expression of human P-gp in the MDCKII-MDR1 cell line. The positive control rate is considered to represent the passive transport component of [^{3}H]digoxin. At all tested concentrations, no marked inhibition of digoxin transport was observed with GSK1265744. The data demonstrate that GSK1265744 up to 30µM does not inhibit digoxin transport via P-gp under these assay conditions.

Discussion/ conclusion	GSK1265744 did not inhibit human transport of digoxin via human P-glycoprotein in vitro at the concentration range of 0.03-30µM. Based on the draft FDA guidance for In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies 2017, the I_{gut} /IC_{50} value did not exceed 10 (assuming an IC_{50} value of 30µM) therefore GSK1265744 has no potential to inhibit P-glycoprotein in vivo and a clinical drug interaction study with a P-glycoprotein substrate was not conducted.

Table 109. Report: An In Vitro Investigation of the Inhibition by GSK1265744 of Xenobiotic Transport Via Human Breast Cancer Resistance Protein Heterologously Expressed in MDCKII Cells

Test drug(s) and concentrations	GSK1265744 (final concentration 0.03 to 30µM)
Positive control(s) and concentrations	GF120918 (final concentration 2µM)
Report number	2012N150360 (Study 12DMR027)
Study system	Polarized Madin-Darby canine kidney MDCKII-BCRP cell line heterologously expressing human BCRP
Method	Cell culture: The MDCKII-BCRP cells were cultured to confluency, trypsinized, and seeded onto Transwell multiwell membrane inserts at a density of approximately $3x10^5$ cells/cm^2. The cell monolayers were fed 24 hours postseeding with culture medium (Dulbecco's Modified Eagle Medium with glutamine, 10% (v/v) Fetal Bovine Serum) and transport studies conducted 48 hours later. Transport inhibition studies: The effect of GSK1265744 on the BCRP-mediated transport of [^{14}C]cimetidine was assessed by determining the basolateral (donor well) to apical (receiver well) ([B→A]) transport of [^{14}C]cimetidine for 90 minutes, in the absence or presence of GSK1265744 at target concentrations of 0.03, 0.05, 0.1, 0.3, 0.5, 1, 3, 5, 10, 30µM (applied in both apical and basolateral wells). The dose range was determined due to the limited solubility of GSK1265744 at concentrations >30µM. GF120918, a potent inhibitor of BCRP, was included at a nominal concentration of 2µM as a positive control for BCRP inhibition. Measurement of inhibition of transport: Following preincubation, plates were incubated at 37ºC for 90 minutes. All samples were analyzed for total radioactivity using a liquid scintillation counter. The cell monolayer integrity was evaluated by measuring the Lucifer yellow concentrations in the receiver wells. Fluorescence was determined using a cytofluorimeter.

Results	The measured radiochemical purity of the [^{14}C]cimetidine used in this study was 98.8% (n=2) with no single impurity accounting for >1% of the detected radioactivity. Experiments were regarded as valid where quality control parameters were within acceptable limits. Acceptable values for the assay were: Lucifer yellow $P_{7.4}$≤50 nm/sec; cimetidine mass balance 80 – 120%; cimetidine transport rate ≥1.5 pmoles transported/cm^2/h; cimetidine transport rate in the presence of 2µM GF120918≤30% of uninhibited rate. The [B→A] transport rate for [^{14}C]cimetidine in the absence of inhibitor was 8.0±0.42 pmole/cm^2/h and in the presence of the BCRP inhibitor GF120918 (positive control) was 2.1±0.095 pmole/cm^2/h (26% of cimetidine alone transport). These results demonstrated the functional expression of human BCRP in the MDCKII-BCRP cell line. The positive control rate is considered to represent the passive transport component of [^{14}C]cimetidine.
Discussion/ conclusion	GSK1265744 inhibited human BCRP-mediated the transport of cimetidine in vitro by 22% at 30µM. However, the degree of inhibition was insufficient to allow the calculation of an IC_{50} value under the assay conditions. Based on the draft FDA guidance for In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies 2017, the Igut /IC_{50} value did not exceed 10 (assuming an IC_{50} value of 30µM); therefore, GSK1265744 has no potential to inhibit BCRP in vivo and a clinical drug interaction study with a BCRP substrate was not conducted.

Table 110. Report: An In Vitro Investigation into the Inhibition by GSK1265744 of Xenobiotic Transport via Human OATP1B1 and OATP1B3

Test drug(s) and concentrations	GSK1265744B (final concentration 0.1, 0.3, 1, 3, 10, and 30µM)
Positive control(s) and concentrations	Rifamycin (final concentration 10µM)
Report number	2013N164529 (Study 12DMM039)
Study system	Human Embryonic Kidney MSRII cell line transduced with BacMam baculovirus containing the human organic anion transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3)
Method	Cell culture: Vials of HEK-MSRII cells added to Dulbecco's modified Eagle's medium F12. A small aliquot was removed for counting by Trypan Blue exclusion. Cells were pelleted and resuspended in media containing Geneticin and sodium butyrate. OATP1B1 or OATP1B3 BacMam reagent was added to cell suspension to give the required multiplicity of infection (MOI, a function of the HEK-MSRII density and the number of plaque forming units for the BacMam reagent). The MOI for OATP1B1 was 300 and OATP1B3 was 140. Cells were cultured for ~48 hours prior to use in transport assays. Uptake studies: Cell monolayers were preincubated (37ºC) for 15 to 30 minutes in 1 mL transport medium containing the target concentration of GSK1265744 or rifamycin without [^{3}H]EG. GSK1265744 at the target concentration plus the probe substrate, [^{3}H]EG was added. Separate sets of triplicate wells were designated for probe substrate only and probe substrate plus the OATP inhibitor rifamycin to determine maximal uptake rate and maximal inhibition of uptake respectively. Cells were incubated at 37ºC for 3 minutes for OATP1B1 and 10 minutes for OATP1B3. For analysis of total radioactivity, the contents of each well were determined by liquid scintillation.

	Cell viability: To evaluate cell viability, one 24-well plate per transporter was treated at room temperature for 30 minutes with 1 mL of preincubated transport medium containing the target concentration of GSK1265744 without [3H]EG. To determine the integrity of the cells, Adenosine Triphosphate (ATP) was quantified using a Promega CellTitre-Glo Luminescent Cell Viability assay. Relative light units (RLU), indicative of metabolically active cells were recorded using a luminometer.
Results	The measured radiochemical purity of [^{3}H]EG was 97% (n=2), with no single impurity accounting for ≥1% of the detected radioactivity. For OATP1B1, the uptake rates of 0.02µM [^{3}H]EG in the absence and presence of the control OATP inhibitor rifamycin were 3.5±0.11 fmoles/cm^2/min and 0.74±0.04 fmoles/cm^2/min, respectively, and demonstrated the functional expression of human OATP1B1 in the HEK MSRII cell line. For OATP1B3, the uptake rates of 0.02µM [^{3}H]EG in the absence and presence of the control OATP inhibitor rifamycin were 1.9±0.088 fmoles/cm^2/min and 0.18±0.005 fmoles/cm^2/min, respectively, and demonstrated the functional expression of human OATP1B3 in the HEK MSRII cell line. OATP1B1 and OATP1B3 mediated uptake of [^{3}H]EG by GSK1265744 was not inhibited up to 30µM. At the highest concentration tested, 30µM, a 1.6-fold increase in uptake was observed. The cause of the increase in uptake is unknown; however, all preceding experiments performed with OATP1B3 showed the same trend.
Discussion/ conclusion	GSK1265744 did not inhibit human OATP1B1 and OATP1B3 in vitro up to 30µM. Based on the draft FDA guidance for In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies 2017, the R value did not exceed 1.1 (assuming an IC_{50} value of 30µM); therefore, GSK1265744 has no potential to inhibit OAT1B1/1B3 in vivo and a clinical drug interaction study with an OATP substrate was not conducted.

Table 111. Report: An In Vitro Evaluation of GSK1265744B as an Inhibitor of OCT1 and OCT2

Test drug(s) and concentrations	GSK1265744B (final concentrations 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 30µM)
Positive control(s) and concentrations	Cimetidine (final concentrations 3, 1, 3, 10, 30,100, 300 and 1000µM), Quinidine (100 and 300µM)
Report number	2012N146057 (Study XS-0376)
Study system	HEK293 cells expressing human OCT1 or OCT2 cDNA)
Method	The assay buffer for the OCT1 and OCT2 assays was HBSS. Cells in HBSS containing the test article or typical inhibitor (DMSO for zero concentration) were pre-incubated at 37°C for 15 minutes. Buffer was then replaced with HBSS containing the typical substrate and the test article or typical inhibitor (DMSO for zero concentration). After incubation, cells were washed then dissolved in PBS. Radioactivity was measured using liver stopping criteria (LSC). In addition, the solution was subjected to a protein content assay.

Results	In OCT1-expressing cells, GSK1265744B inhibited the uptake of [^{14}C]metformin, a prototypical substrate of OCT1, in a concentration-dependent manner (56.2% of control at 30μM, the highest concentration tested). However, the data were insufficient to calculate an IC_{50}. In OCT2-expressing cells, GSK1265744B inhibited the uptake of [^{14}C]metformin, a prototypical substrate of OCT2, in a concentration-dependent manner (60% of control at 30μM, the highest concentration tested). However, the data were insufficient to calculate an IC_{50}. Furthermore, the cell toxicities of GSK1265744B and cimetidine were investigated, and the cell viability ranged from 98.8% to 103.7% of control at all concentrations determined in this study. These results suggest that this compound has no toxicity towards the cell lines used this study.
Discussion/ conclusion	GSK1265744B inhibited the OCT1 and OCT2-mediated uptake of metformin. However, the degree of inhibition was insufficient to allow the calculation of an IC_{50} value under these assay conditions. Based on the draft FDA guidance for In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies 2017, the $I_{max,u}/IC_{50}$ value did not exceed 0.1 (assuming an IC_{50} value of 30μM) therefore GSK1265744 has no potential to inhibit OCT in vivo and a clinical drug interaction study with an OCT substrate was not conducted.

Table 112. Report: In Vitro Evaluation of GSK1265744 as an Inhibitor of OAT1, OAT3, MATE1, MATE2-K, and MRP4

Test drug(s) and concentrations	GSK1265744B (final concentrations 0.3, 0.5, 1, 3, 5, 10, 30, 50, 100, and 300μM)
Positive control(s) and concentrations	All positive control inhibitor final concentrations were 0.1, 0.3, 0.5, 1, 3, 5, 10, 30, 50, and 100μM. Inhibitors were indomethacin (MRP4), probenecid (OAT1 and OAT3), and cimetidine (MATE1 and MATE2-K).
Report number	2013N174474 (Study XS-0446)
Study system	Membrane vesicles expressing human MRP4, S2 cells expressing human OAT1 or OAT3 cDNA, and HEK293 cells expressing human MATE1 or MATE2-K.
Method	Vesicular assay: Reaction tubes and Assay-mix (Mg-ATP solution, GSK1265744 and [^{3}H]estradiol 17β-D-glucuronide (E2G) with reaction buffer) solution were pre-incubated at 37°C for 5 min. After start of reaction, tubes were incubated at 37°C for 2 min. S2 cell-based assay: Medium in the plate seeded with transporter expressing or control cells was removed by aspiration and replaced with D-PBS. Solution was replaced with D-PBS solution containing GSK1265744 or probenecid, and the plate was pre-incubated at 37°C for 15 min. Buffer was then replaced with D-PBS solution containing the radio-labeled probe substrate ([^{3}H]*p*-aminohippuric acid (PAH) for OAT1 and [^{3}H]ES for OAT3) and GSK1265744 or probenecid, and each mixture was incubated at 37°C for 2 min. Cells were washed then dissolved in NaOH. Samples were analyzed by liver stopping criteria (LSC). MATE1 HEK293 cell based assay: Medium was replaced with HBSS. HBSS was replaced with HBSS solutions containing GSK1265744 or cimetidine, and the plate was pre-incubated at 37°C for 15 min. Buffer was then replaced with HBSS containing [^{14}C]metformin and GSK1265744 or cimetidine, and each mixture was incubated at 37°C for 5 min. Cells were then washed and dissolved in NaOH. Radioactivity was measured using LSC. In addition, the solution was subjected to a protein content assay. MATE2-K HEK293 cell-based assay: 1) Medium in plates was replaced with HBSS. HBSS was replaced with HBSS solutions containing GSK1265744 or cimetidine, and the plate was pre-incubated at 37°C for 15 min. Buffer was

	then replaced with HBSS solutions containing [^{14}C]metformin and GSK1265744 or cimetidine, and each mixture was incubated at 37°C for 5 min. Cells were then washed and dissolved in NaOH. Radioactivity was measured using LSC. In addition, the solution was subjected to a protein content assay.
Results	In MRP4-expressing vesicles, GSK1265744 did not inhibit the uptake of [^{3}H]E2G, a substrate of MRP4, at the concentration range 0.03 to 30μM. Indomethacin inhibited MRP4-mediated [^{3}H]E2G transport with an estimated IC_{50} value of 5.07±1.36μM. In OAT1-expressing cells, GSK1265744 inhibited the uptake of [^{3}H]PAH, a substrate of OAT1, with an estimated IC_{50} value of 0.812±0.087μM. Probenecid inhibited OAT1-mediated [3H]PAH transport with an estimated IC_{50} value of 9.08±2.62μM. In OAT3-expressing cells, GSK1265744 inhibited the uptake of [^{3}H]ES, a substrate of OAT3, with an estimated IC_{50} value of 0.411±0.115μM. Probenecid inhibited OAT3-mediated [^{3}H]ES transport with an estimated IC_{50} value of 3.15±0.74μM. In MATE1-expressing cells, GSK1265744 inhibited the uptake of [^{14}C]metformin, a substrate of MATE1, with an estimated IC_{50} value of 18.2±5.1μM. Cimetidine inhibited MATE1-mediated [^{14}C]metformin transport with an estimated IC_{50} value of 0.789±0.157μM. In MATE2-K-expressing cells, GSK1265744 inhibited the uptake of [^{14}C]metformin, a substrate of MATE2-K, with an estimated IC_{50} value of 14.2±2.2μM. Cimetidine inhibited MATE2-K-mediated [^{14}C]metformin transport with an estimated IC_{50} value of 10.5±2.2μM.
Discussion/ conclusion	GSK1265744 had no inhibitory effect on the MRP4-mediated uptake of [^{3}H]E2G. GSK1265744 inhibited the OAT1-mediated uptake of [^{3}H]PAH and the OAT3-mediated uptake of [^{3}H]ES with estimated IC_{50} values of 0.812 and 0.411μM, respectively. GSK1265744 inhibited the MATE1- and MATE2-K-mediated uptake of [^{14}C]metformin with estimated IC_{50} values of 18.2 and 14.2μM, respectively. Based on the draft FDA guidance for In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies 2017, the $Imax,u/IC_{50}$ value for OAT transporters exceeded 0.1 therefore a mechanistic static model [Report 2015N258625] and a PBPK model [Report 2018N389974] was used to quantify the potential drug interaction. The results of both models showed GSK1265744 has low risk of perpetrator drug interactions with OAT substrates (predicted AUC change <1.26-fold and 1.18-fold, respectively) (14.3). Based on the draft FDA guidance for In Vitro Metabolism and Transporter-Mediated Drug-Drug Interaction Studies 2017, the $Imax,u/IC_{50}$ value for MATE transporters did not exceed 0.02 therefore GSK1265744 has no potential to inhibit MATE transporters in vivo. A mechanistic static mathematical model [Report 2015N258625[confirmed that GSK1265744 has low risk of perpetrator drug interactions with MATE substrates (predicted AUC change 1.01-fold) therefore a clinical drug interaction study with MATE substrates was not conducted.

Table 113. Report: An In Vitro Investigation of GSK1265744 as an Inhibitor of the Human Bile Salt Export Pump Transporter and Multidrug Resistance Associated Protein-2 Transporter

Test drug(s) and concentrations	GSK1265744B (final concentrations 0.03, 0.05, 0.1, 0.3, 0.5, 1, 3, 5, 10, and 30μM)
Positive control(s) and concentrations	Benzbromarone (MRP2) and rifampicin (BSEP) at final concentrations 0.3, 0.5, 1, 3, 5, 10, 30, 50, 100 and 150μM) for both inhibitors
Report number	2013N174589 (Study 13DMR019)
Study system	Membrane vesicles prepared from recombinant baculovirus infected Sf9 cells expressing the human MRP2 and BSEP transporter
Method	MRP2: MRP2 membrane vesicles were preincubated for 10-15 minutes at 37°C in reaction buffer in the presence or absence of GSK1265744 or positive control inhibitor benzbromarone. Five minute incubations were performed in the absence of inhibitor and in the presence of 10mM MgAMP solution containing 50μM [^{3}H]EG for passive transport. Sample radioactivity was measured using a liquid scintillation counter. BSEP: Membrane vesicles were preincubated for 10-15 minutes at 3°C in reaction buffer in the presence or absence of GSK1265744 or positive control inhibitor rifampicin. Five minute incubations were performed in the absence of inhibitor and in the presence of 10mM MgAMP solution containing 2μM [^{3}H]TC for passive transport. Sample radioactivity was measured using a liquid scintillation counter.
Results	The rate of EG uptake in the presence of benzbromarone was inhibited with an IC_{50} value of 23μM. The inhibition response to benzbromarone demonstrates the functional expression of human MRP2 in the vesicles. GSK1265744 did not inhibit EG transport at concentrations up to 30μM. The rate of TC uptake in the presence of rifampicin was inhibited with an IC_{50} value of 7.2μM. The inhibition response to rifampicin demonstrates the functional expression of human BSEP in the vesicles. GSK1265744 did not inhibit TC transport at concentrations up to 30μM.
Discussion/ conclusion	GSK1265744 did not inhibit MRP2 or BSEP, at concentrations up to 30μM.

14.1.2. In Vivo

Note: The oral CAB formulation used in phase 3 studies was the 30 mg (b) (4) tablet (b) (4)

Table 114. Study LAI117008

Title	An Open Label, Nonrandomized, Mass Balance Study to Investigate the Recovery, Excretion, and Pharmacokinetics of ^{14}C-GSK1265744 Administered as a Single Oral Dose and a Placebo-Controlled, Randomized Study to Describe the Pharmacokinetics of a Supratherapeutic Dose of GSK1265744 in Healthy Adult Subjects
Brief description of trial design	This was a 2-part study in healthy adults. Part A was a phase 1, nonrandomized, open-label, single-dose, single-center mass balance study in healthy adult male subjects. Subjects in Part A (n=6) received a target CAB dose of 30 mg (actual mean dose of 26.7 mg) as an oral solution containing [^{14}C]-CAB of approximately 70 µCi (0.96 MBq) of radioactivity under fasted conditions. Blood, urine, and fecal samples were collected for a minimum of 336 h (14 days) to a maximum of 504 h (21 days) following study drug administration. The Entero-Test capsule was swallowed 2 h postdose; at 5 h postdose gall bladder emptying was stimulated using food cues and the string was retrieved 1 h later (at 6 h postdose). In Part B, subjects received a single supratherapeutic dose of CAB 150 mg (5×30 mg tablets) (n=8) or placebo (n=2). Subjects enrolled in Part B were not the same subjects enrolled in Part A of the study. Serial plasma PK samples for analysis of CAB were collected for a minimum of 336 hours (14 days) after dosing.
PK sample collection times	Part A A 6ml K3EDTA blood sample (whole blood and plasma) will be collected at predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 288, 312 336 and 360 hours postdose. Collections continue every 24 hours until the morning of day 16 or the stopping criteria, whichever occurred first. Part B Blood samples for plasma GSK1265744 PK evaluation (2 mL K3EDTA) were collected predose (within 15 minutes prior to dosing) 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72hrs (day 4), 120hr (day 6), 168hrs (day 8), 240hrs (day 11) and 312hrs (day 14) after dose.
Results	
The overall mean recovery of radioactivity in urine and feces samples was 85.3% over the 384-hour study, with recovery in individual subjects ranging from 74.5% to 92.2%. The mean percentage radioactivity recovered was 58.5% of the dose in feces and 26.8% of the dose in urine. The mean blood-to-plasma concentration ratio was 0.437–0.571.	

Summary of Plasma GSK1265744 Pharmacokinetic Parameters Following [^{14}C]GSK1265744 Single Dose Administration [1]

Treatment	n	C_{max} (μg/mL)	$AUC_{(0-\infty)}$ (μg·h/mL)	CL/F (L/hr)	Vz/F (L)	$T_{1/2}$ (hr)	T_{max}[2] (hr)
[^{14}C]GSK1265744	6	2.48 (21)	96.5 (25)	0.29 (25)	16.4 (22)	38.8 (10)	2.00 (0.98-3.00)

[1] Geometric mean (CV%) with GSK744 Dose: 28.0-28.4 mg
[2] Median (range) Data Source: CPSR Table 10

Summary of Radioactivity Pharmacokinetic Parameters in Blood and Plasma Following [^{14}C]GSK1265744 Single Dose Administration [1]

Treatment	n	C_{max} (μg/g)	$AUC_{(0-\infty)}$ (μg·h/g)	$T_{1/2}$ (hr)	T_{max}[2] (hr)
			Blood		
[^{14}C]GSK1265744	6	1.43 (21)	56.1 (26)	39.4 (14)	1.52 (0.98-4.00)
			Plasma		
	6	2.65 (21)	107 (24)	41.2 (16)	1.52 (0.98-2.00)

[1] Geometric mean (CV%) with GSK744 Dose: 28.1-28.4 mg
[2] Median (range)
Data source: CSR Table 11

Summary of Plasma GSK1265744 Pharmacokinetic Parameters Following GSK1265744 150 mg Single Dose Administration [1]

Treatment	n	C_{max} (μg/mL)	$AUC_{(0-\infty)}$ (μg·h/mL)	CL/F (L/hr)	Vz/F (L)	$T_{1/2}$ (hr)	T_{max}[2] (hr)
GSK1265744 150 mg	8	10.4 (26)	418 (32)	0.36 (32)	19.7 (29)	38.1 (16)	2.50 (1.00-4.03)

[1] Geometric mean (CV%)
[2] Median (range)
Data source: CSR Table 12

Discussion/Conclusion

Consistent with the results of this study, proposed labeling states that CAB excretion (percent of dose) is 27% in urine and 59% in feces.

Table 115. Study 205696

Title	A phase I study evaluating the effect of a high fat meal on the pharmacokinetics of cabotegravir in healthy adult volunteers
Brief description of trial design	This study was a single-center, randomized, open-label, balanced, two-way crossover study in healthy adult subjects to compare single dose PK of CAB 30 mg, micronized 500 mg core weight oral tablet administered following a high fat (53% fat and 870 calorie) meal relative the fasted state. There was a 14-day washout between doses.
PK sample collection times	PK samples were collected at predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, and 168 hour postdose.

Results

When administered with a high fat meal vs. fasted, CAB C_{max} and AUC were increased (AUC ratios of 1.14-1.17; statistically significant).

Summary of Selected Plasma CAB PK Parameters Following Single Dose Administration With and Without a High Fat Meal

Treatment	$AUC_{(0-\infty)}$ (μg·h/mL)	C_{max} (μg/mL)	T_{max} (h)	C24 (μg/mL)	$T_{1/2}$ (h)	CL/F (L/hr)	Vz/F (L)
A: CAB 30 mg fasted (n=21)	143 [126, 162] (28)	3.33 [2.95, 3.77] (27)	3.0 (1.0-4.0)	1.62 [1.45, 1.81] (25)	40.6 [38.0, 43.5] (15)	0.210 [0.185, 0.239] (28)	12.3 [11.2, 13.6] (22)
B: CAB 30 mg fed (n=21)	163 [144, 185] (29)	3.85 [3.46, 4.28] (24)	3.0 (1.0-8.0)	1.88 [1.69, 2.10] (24)	40.6 [37.8, 43.7] (16)	0.184 [0.162, 0.209] (29)	10.8 [9.8, 11.9] (21)

Data source: CPSR Table 8

Discussion/Conclusion

Consistent with the results of this study, proposed labeling states that the CAB AUC ratio (90% CI) in the presence of a high-fat meal vs. fasted is 1.14 (1.02, 1.28).

Table 116. Study 201480

Title	A Phase I, Open-Label, Parallel-Group Study to Evaluate the Pharmacokinetics and Safety of GSK1265744 in Subjects with Severe Renal Impairment and Healthy Matched Control Subjects
Brief description of trial design	This was a phase 1, open-label, multiple center, single-dose study. The study compared the PK in human subjects with severely impaired renal function (CLCR <30 mL/min based on 24-hour urine collection), who did not require renal replacement therapy, with matched healthy subjects with normal renal function (≥90 mL/min). All subjects received a single oral dose of CAB 30 mg tablet.
PK sample collection times	Plasma PK samples (2 mL of blood per sample) were collected to measure CAB at the following time points: predose (within 15 min prior to dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, 168 hours postdose. Plasma PK samples (9 mL of blood per sample) were collected to measure bound and unbound plasma GSK1265744 concentrations at 2 and 24 hours postdose.

Results

Summary and Comparison of Unbound Plasma CAB Concentration-Time Data by Cohort

Concentration of Unbound Plasma CAB (μg/mL)	Severe Renal Impairment (n=8)[2]	Healthy Matched Controls[1] (n=8)[2]	GLS Mean Ratio (90% CI) Severe Renal Impairment vs. Healthy Match
2 hours	0.0056 (0.0034, 0.0129)	0.0047 (0.0022, 0.0162)	1.32 (0.807, 2.153)
24 hours	0.0030 (0.0022, 0.0050)	0.0020 (0.0013 0.0025)	1.67 (1.33, 2.09)

Healthy control subjects are matched to the severe renal impairment subjects in gender, age (±10 years), and BMI (±25%)
Median (range)
Data Source: CPSR Table 9

Summary and Comparison of Selected Total CAB Pharmacokinetic Parameters Following Single Dose Administration to Severe Renally Impaired Subjects and Healthy Matched Control Subjects (PK Summary Population)

PK Parameter	Geometric Mean [95% CI] (CVb%) Severe Renal Impairment (n=8)	Geometric Mean [95% CI] (CVb%) Healthy Matched Controls (n=8)	GLS Mean Ratio (90% CI) (Severe Renal Impairment vs. Healthy Match)
$AUC_{(0-\infty)}$ (μg·h/mL)	1431 [115, 177] (23)	140 [116, 170] (23)	0.973 (0.835, 1.14)
$AUC_{(0-t)}$ (μg·h/mL)	143 [115, 178] (27)	133 [110, 160] (23)	1.08 (0.885, 1.32)
C_{max} (μg/mL)	3.34 [2.67, 4.17] (27)	3.37 [2.96, 3.83] (15)	1.01 (0.865, 1.17)
C_{24} μg/mL)	1.65 [1.34, 2.02] (25)	1.62 [1.34, 1.96] (23)	1.02 (0.868, 1.20)
T_{max} (h)	2.00 (1.0 – 4.2)	2.00 (1.0- 4.0)	NA
$T_{1/2}$ (h)	39.21 [33.9, 45.4] (16)	40.5 [36.9, 44.5] (11)	0.930 (0.831, 1.04)
FU2H (%)	0.18 [0.14, 0.23] (29)	0.14 [0.08, 0.22] (63)	1.31 (0.843, 2.03)
FU24H (%)	0.17 [0.15, 0.19] (17)	0.11 [0.09, 0.14] (30)	1.51 (1.19, 1.92)
CL/F (L/h)	0.211 [0.17, 0.26] (23)	0.21 [0.18, 0.26] 23	1.03 (0.881, 1.20)

PK Parameter	Geometric Mean [95% CI] (CVb%) Severe Renal Impairment (n=8)	Geometric Mean [95% CI] (CVb%) Healthy Matched Controls (n=8)	GLS Mean Ratio (90% CI) (Severe Renal Impairment vs. Healthy Match)
Vz/F (L)	11.901 [10.3, 13.7] (16)	12.50 [10.4, 15] (22)	0.955 (0.839, 1.09)

N=7; for subject 805002, parameters associated with terminal phase such as $AUC_{(0-\infty)}$, $T_{1/2}$, CL/F and Vz/F, were excluded from PK summary population as the coefficient of determination (R2) was <0.85 and percentage of $AUC_{(0-\infty)}$ extrapolated was >20%"

Discussion/Conclusion

Consistent with the results of this study, proposed labeling states that no clinically significant differences in the PK of CAB are expected in patients with mild, moderate, or severe renal impairment.

Table 117. Study 201479

Title	A Phase I, Open-Label, Parallel-Group Study to Evaluate the Pharmacokinetics and Safety of GSK1265744 in Subjects with Hepatic Impairment and Healthy Matched Control Subjects
Brief description of trial design	This was a phase 1, open-label, parallel group, single-dose adaptive study in adults with moderate HI (defined by Child-Pugh score of 7 to 9) and matched, healthy control subjects with normal hepatic function. In part 1, healthy control subjects (n=8) were matched in gender, age (±10 years), and BMI (±25%) to subjects with moderate (n=8) HI. All subjects received CAB 30 mg tablet as a single oral dose in the fasted state. Since the $AUC_{(0-inf)}$ of CAB did not increase by >2-fold in moderately impaired subjects relative to matched controls, the originally planned part 2 of the study in adults with mild HI was not conducted.
PK sample collection times	Plasma samples (2 mL of blood per sample) were collected to measure CAB at the following time points: predose (within 15 minutes prior to dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, 168 hours postdose. Plasma samples (9 mL of blood per sample) were collected to measure bound and unbound plasma CAB concentrations at 2 and 24 hours postdose.

Results

Unbound plasma CAB concentration:
The unbound plasma CAB concentrations in moderate hepatic impaired subjects were 40% and 55% higher than those in healthy subjects at 2h and 24h postdose, respectively.

Summary and Comparison of Unbound Plasma CAB Concentrations 2h and 24h Following Single Dose Oral CAB 30 mg (PK Concentration and PK Summary Population)

Unbound CAB Conc.	Statistic	Moderate Hepatic Impaired (n=7)*	Healthy Matched[1] (n=7)*	Hepatic Impaired vs. Healthy GLSM Ratio (90% CI)
2h postdose (µg/mL)	Median (range)	0.00831 (0.00289, 0.0234)	0.00591 (0.00364, 0.00958)	----
	Mean (SD)	0.0094 (0.00661)	0.0058 (0.00227)	----
	GLS mean	0.0074	0.0053	1.401 (0.798, 2.459)

Unbound CAB Conc.	Statistic	Moderate Hepatic Impaired (n=7)*	Healthy Matched[1] (n=7)*	Hepatic Impaired vs. Healthy GLSM Ratio (90% CI)
24h postdose (µg/mL)	Median (range)	0.00432 (0.00163, 0.0105)	0.00260 (0.00136, 0.00441)	----
	Mean (SD)	0.0050 (0.00317)	0.0026 (0.00107)	----
	GLS mean	0.0041	0.0026	1.552 (0.820, 2.938)

* For Subject (b) (6) with hepatic impairment and healthy Subject (b) (6) protein binding samples were collected, but due to shipment issues, not received and thus not processed.
1. Healthy control subjects are matched to the moderate hepatic impairment subjects in gender, age (±10 years), and BMI (±25%)
Data Source: CPSR Table 9

Summary of Select Plasma CAB Pharmacokinetic Parameters Following Single Dose Oral CAB 30 mg (PK Summary Population)

CAB PK Parameter (Units)	Moderate Hepatic Impaired (n=8) Geometric Mean [95% CI] (%CVb)	Healthy Matched[1] (n=8) Geometric Mean [95% CI] (%CVb)
$AUC_{(0-\infty)}$ (h*µg/mL)	102 [75.2, 138] (37.3)	127 [94.7, 170] (36.2)
$AUC_{(0-t)}$ (h*µg/mL)	98.2 [73.3, 132] (36.2)	121 [91.0, 162] (35.4)
C_{max} (µg/mL)	2.70 [1.94, 3.76] (41.1)	3.55 [2.90, 4.33] (24.3)
C24 (µg/mL)	1.23 [0.956, 1.58] (30.8)	1.50 [1.13, 2.01] (35.6)
Fraction unbound at 2h (%)[3]	0.307 [0.202, 0.467] (47.6)	0.157 [0.119, 0.207] (30.5)
Fraction unbound at 24h (%)[3]	0.322 [0.184, 0.564] (66.6)	0.166 [0.134, 0.207] (23.9)

1. Healthy control subjects are matched to the hepatic impairment subjects in gender, age (±10 years), and BMI (±25%)
2. Data are represented as median (range)
3. n=7 for both moderate hepatic impaired and healthy matched groups
Data Source: CPSR Table 10

Unbound CAB fractions were statistically higher in subjects with higher albumin score (lower serum albumin concentration) and higher Child-Pugh score. There was no apparent relationship between CAB unbound fraction and total protein concentration.

Statistical Comparison of Plasma CAB Pharmacokinetic Parameters After Single CAB 30 mg Oral Dose (PK Summary Population

Plasma CAB PK Parameter	Ratio of GLS Means (90% CI) Moderate Hepatic Impaired (n=8) vs. Healthy Matched (n=8)
$AUC_{(0-\infty)}$	0.725 (0.497, 1.058)
$AUC_{(0-t)}$	0.731 (0.508, 1.053)
C_{max}	0.685 (0.505, 0.929)

	Ratio of GLS Means (90% CI)
Plasma CAB PK Parameter	**Moderate Hepatic Impaired (n=8) vs. Healthy Matched (n=8)**
C24	0.732 (0.526, 1.018)
Fraction unbound at 2h*	2.137 (1.574, 2.902)
Fraction unbound at 24h*	1.902 (1.139, 3.175)

* n=7 for both moderate hepatic impaired and healthy matched groups.
Data Source: CPSR Table 11

Table 118. Study ITZ111839

Title	A Phase I, Open Label Crossover Study to Evaluate the Effect of Etravirine on GSK1265744 Pharmacokinetics in Healthy Adult Subjects (ITZ111839)
Brief description of trial design	This was a single-center, open-label, 2-period, single-sequence crossover study in healthy adult subjects. CAB 30 mg once daily was administered for 10 days in Period 1 and with ETV 200 mg twice daily for 14 days in Period 2. All doses were administered following a moderate-fat meal. There was no washout between treatment periods.
PK sample collection times	Plasma PK samples (2 mL each) for GSK1265744: Period 1: predose on days 8 and 9; predose (within 15 minutes), 1, 2, 3, 4, 8, 12, and 24hrs postdose on day 10 Period 2: predose on days 8, 11, 12 and 13; predose (within 15 minutes), 1, 2, 3, 4, 8, 12, and 24hrs postdose on day 14. Plasma PK samples (2 mL each) for Etravirine Period 2: predose on days 8, 11, 12 and 13; predose (within 15 minutes), 1, 2, 3, 4, 8, and 12hrs post-AM dose on day 14 in Period 2.

Results

CAB PK parameters were not significantly altered by coadministration with etravirine (C_{max} and AUC ratios of 1.01-1.04; C_{min} ratio of 0.86 with CIs excluding a ratio of 1.00).

Summary of Plasma GSK1265744 Pharmacokinetic Parameters Following Repeat Dose Administration[1]

Treatment	$AUC_{(0-\tau)}$ (μg·h/mL)	C_{max} (μg/mL)	C_{min} (μg/mL)	$C\tau$ (μg/mL)	T_{max}[2] (h)
GSK1265744	183 (13)	9.47 (11)	6.40 (14)	6.50 (14)	3.04 (2.00-12.00)
GSK1265744 + ETV	184 (9)	9.83 (11)	5.52 (12)	6.49 (12)	4.00 (2.00-8.00)

GSK1265744 = GSK1265744 30 mg q24h×10 days
GSK1265744 + ETV = GSK1265744 30 mg q24h×14 days + ETV 200 mg q12h
Geometric mean (CVb%)
Median (range)
Data Source: CPSR Table 8

Discussion/Conclusion

Consistent with the results of this study, proposed labeling states that there is no clinically significant effect of etravirine on the PK of CAB.

Table 119. Study LAI117011

Title	An Open-label Study to Evaluate the Pharmacokinetics of an Oral Contraceptive Containing Levonorgestrel and Ethinyl Estradiol when Co-administered with GSK1265744 in Healthy Adult Female Subjects

Brief description of trial design	This study was an open-label, fixed-sequence crossover study in healthy adult female subjects. All subjects first received microgynon alone on days 1 to 10 (Treatment Period 1), directly followed by concomitant daily dosing of microgynon + CAB on days 11 to 21 (Treatment Period 2). Prior to Period 1, a Run-in Period of microgynon was included for subjects not already stabilized on microgynon.
PK sample collection times	Blood samples (2 mL each) were collected for plasma CAB PK analysis at predose on day 20 and at the following time points, beginning on day 21: predose (within 15 min prior to dose) and at 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose on day 22. Pharmacokinetic sampling for levonorgestrel and ethinyl estradiol were collected at predose on day 9 and at the following time points, beginning on day 10: predose, then 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours postdose of Treatment Period 1. Treatment Period 2, Predose on day 20 and at the following time points, beginning on day 21: predose, then 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours postdose.

Results

Summary of Steady-State Plasma Levonorgestrel Pharmacokinetic Parameters and Treatment Comparisons

	Geometric Mean [95% CI] (CVb%)		**GLS Mean Ratio (90% CI)**
Levonorgestrel Parameter	**Microgynon QD (n=19)**	**Microgynon QD + CAB 30 mg QD (n=19)**	**Microgynon + CAB 30 mg vs. Microgynon**
$AUC_{(0-\tau)}$ (h·ng/mL)	77.4 [64.5, 92.9] (39)	87.0 [72.1, 105] (40)	1.12 (1.07, 1.18)
C_{max} (ng/mL)	6.86 [5.84, 8.06] (34)	7.20 [6.28, 8.26] (29)	1.05 (0.959, 1.15)
$C\tau$ (ng/mL)	2.41 [1.98, 2.95] (43)	2.59 [2.09, 3.22] (47)	1.07 (1.01, 1.15)
T_{max}[1] (h)	1.00 (0.5 –2.5)	1.00 (0.5 – 3.0)	------

Median (range)
Microgynon QD = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg once daily; Microgynon QD + CAB 30 mg = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg + oral cabotegravir/GSK1265744 30 mg coadministered once daily
Data Source: CPSR Table 9

Summary of Steady-State Plasma Ethinyl Estradiol Pharmacokinetic Parameters and Treatment Comparisons

	Geometric Mean [95% CI] (CVb%)		**GLS Mean Ratio (90% CI)**
Ethinyl Estradiol Parameter	**Microgynon QD (n=19)**	**Microgynon QD+CAB 30 mg QD (n=19)**	**Microgynon + CAB 30 mg vs. Microgynon**
$AUC_{(0-\tau)}$[1] (h·pg/mL)	773 [656, 911] (33)	800 [698, 916] (28)	1.02 (0.968, 1.08)

	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio (90% CI)
Ethinyl Estradiol Parameter	Microgynon QD (n=19)	Microgynon QD+CAB 30 mg QD (n=19)	Microgynon + CAB 30 mg vs. Microgynon
C_{max} (pg/mL)	86.2 [72.4, 103] (38)	79.5 [68.0, 92.8] (33)	0.922 (0.827, 1.03)
$C\tau$[1] (pg/mL)	16.0 [12.5, 20.4] (51)	15.7 [12.9, 19.0] (40)	1.00 (0.919, 1.10)
T_{max}[2] (h)	1.00 (0.5 – 2.5)	1.50 (0.5 – 2.6)	-----

n=17 for Microgynon and n=18 for Microgynon + CAB
Median (range)
Microgynon QD = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg once daily; Microgynon QD + CAB 30 mg = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg + oral cabotegravir/GSK1265744 30 mg coadministered once daily
Data Source: CPSR Table 10

Discussion/Conclusions
Consistent with the results of this study, proposed labeling states there is no clinically significant effect of CAB on the PK of ethinyl estradiol or levonorgestrel.

Table 120. Study LAI116815

Title	A Single-Center, Randomized, Open-Label, Study to Assess the Relative Bioavailability of New Formulations of GSK1265744 LAP in Healthy Adult Subjects
Note	The only data from this study impacting labeling are the drug-interaction data for the effect of oral CAB on the PK of midazolam. For this reason the results of the relative bioavailability of IM formulations assessment are not shown below.
Brief description of trial design	This was a single-center, randomized, open-label, 3 parallel treatment arm study in healthy adult subjects to assess the RBA of CAB LA 400 mg IM using drug substance manufactured by a (b) (4) as well as a comparison with CAB LA 400 mg IM using drug substance manufactured by (b) (4) in previous phase 1 studies. During the oral lead-in period, a substudy to examine the potential of 744 to inhibit or induce cytochrome P450 (CYP) 3A activity using midazolam as a probe was conducted (group 1). Subjects received a single oral dose of 3 mg midazolam on the morning of day -29, followed by 24 hours of serial PK collection. Subjects were then dosed with oral GSK1265744 30 mg once daily (QD) for 14 days and returned to research unit on day -16. On day -15, subjects were given a single dose of 30 mg GSK1265744 followed by 24 hours of serial PK. On day -14, subjects were co-administered midazolam + GSK1265744 followed by 24. Hours of serial PK. All subjects underwent a 14 day washout period prior randomization to one of the test CAB LA IM injections. A

PK sample collection times	PK blood samples for MDZ: (days -29 and -14): 2 mL were collected at predose (within 15 minutes midazolam administration), 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24hrs. On day -15: PK sampling for GSK1265744 was collected predose (within 15 minutes of GSK1265744 administration), 1, 2, 3, 4, 8, and 24hrs postdose.

Results

When midazolam was given with CAB vs. alone, midazolam C_{max} and AUC ratios were 1.08-1.09 and CIs did not exclude a ratio of 1.00.

Summary of Plasma 744 Pharmacokinetic Parameters Following 30 mg Oral Dose Administration

Treatment	n	C_{max}[a] (μg/mL)	$AUC_{(0-\tau)}$[a] (μg·h/mL)	CL/F[a] (L/hr)	T_{max}[b] (hr)
744	12	7.01	120	0.25	2.00
PO		(23)	(25)	(25)	(1.00-4.00)

Geometric mean (CV%)
Median (range)
Data Source: CPSR, Table 14

Summary of Plasma Midazolam Pharmacokinetic Parameters Following Dose Administration

Treatment	n	$AUC_{(0-\infty)}$[a] (ng·h/mL)	$AUC_{(0-t)}$[a] (ng·h/mL)	C_{max}[a] (ng/mL)	CL/F[a] (L/hr)	$T_{1/2}$[a] (hr)	T_{lag}[b] (hr)	T_{max}[b] (hr)
Midazolam	12	27.5	25.8	12.3	109	3.99	0.00	0.50
		(53)	(53)	(40)	(53)	(37)	(0.0-0.0)	(0.3-0.5)
Midazolam +744	12	29.7	28.3	13.4	101	3.95	0.00	0.50
		(54)	(54)	(36)	(54)	(47)	(0.0-0.0)	(0.3-1.0)

Discussion/Conclusions

Consistent with the results of this study, proposed labeling states there is no clinically significant effect of CAB on the PK of midazolam.

Table 121. Study 205712

Title	Phase I, single-center, open label, fixed-sequence cross-over study to evaluate the effect of rifabutin on the pharmacokinetics of oral cabotegravir in healthy subjects
Brief Description of Trial Design	This was a phase I, single-center, open-label, fixed-sequence, 2-period crossover study conducted in healthy adults. Subjects received CAB 30 mg once daily for 14 days in Period 1 and RBT 300 mg once daily + CAB 30 mg once daily for 14 days in Period 2. There was no washout between periods.
PK sample collection times	Plasma PK samples (2 mL of blood per sample) were collected to measure CAB at the following time points: Period 1: predose (within 15 minutes prior to dose) on day 13; and predose (within 15 minutes prior to dose), 1, 2, 3, 4, 8, 12, and 24 h after CAB dosing on day 14. Period 2: predose (within 15 minutes prior to dose) on days 26 and 27 and predose (within 15 minutes prior to dose) on day 28 and, 1, 2, 3, 4, 8, 12, and 24 h after CAB +RBT dosing on day 28.

Results

CAB was readily absorbed with median T_{max} values of 3 hours when administered alone and 2.5 hours when administered with RBT. Intersubject variability was low to moderate with coefficient of variation (CV%) ranging from 24.3% to 36.3%. CAB CL/F was higher following repeat-dose coadministration with RBT, resulting in reductions in CAB $AUC_{(0-\tau)}$, C_{max}, and $C\tau$ as compared to CAB alone. Plasma $T_{1/2}$ was not estimated for either period due to limited PK sampling in the terminal phase.

Summary of Derived Plasma Cabotegravir Pharmacokinetic Parameters

Treatment	$AUC_{(0-\tau)}$[1] (h*µg/mL)	C_{max}[1] (µg/mL)	T_{max}[2] (h)	Cτ[1] (µg/mL)	CL/F[1] (L/h)
CAB (n=12)	104 (87.1, 124) [28.3]	6.36 (5.45, 7.42) [24.7]	3.00 (1.00, 4.00)	3.36 (2.72, 4.15) [34.3]	0.289 (0.242, 0.344) [28.3]
RBT+CAB (n=12)	81.7 (67.9, 98.4) [29.9]	5.25 (4.51, 6.11) [24.3]	2.50 (1.00, 4.00)	2.48 (1.98, 3.10) [36.3]	0.367 (0.305, 0.442) [29.9]

[1]Geometric mean (95% CI) [CV%]
[2]Median (range)
CAB: 30 mg once daily × 14 days
RBT + CAB: RBT 300 mg once daily + CAB 30 mg once daily × 14 days
Data Source: CPSR Table 11

RBT increased CAB oral clearance by 27% and reduced CAB $AUC_{(0-\tau)}$, C_{max}, and Cτ by 21%, 17%, and 26%, respectively. The median Cτ observed 24h following the final dose in Period 1 was the same as the median day 14 predose concentration, and the median Cτ observed 24 h following the final dose in Period 2 was similar to the median predose concentrations observed on days 26 and 27.

Summary of Statistical Analysis of Cabotegravir $AUC_{(0-tau)}$ and C_{max} (PK Summary Population)

CAB PK Parameter	Treatment Comparison: RBT + CAB vs. CAB (GLSM Ratio, 90% CI)
$AUC_{(0-\tau)}$	0.786 (0.743, 0.831)
C_{max}	0.825 (0.761, 0.895)
Cτ	0.738 (0.702, 0.776)
CL/F	1.27 (1.20, 1.35)

CAB: 30 mg once daily×14 days
RBT+CAB: RBT 300 mg once daily + CAB 30 mg once daily × 14 days
Data Source: CPSR Table 12

Discussion/Conclusions
When coadministered with rifabutin vs. alone, CAB, C_{max} and AUC are decreased ~20%.

Table 122. Study LAI117010

Title	Phase I, single-center, open label, fixed-sequence cross-over study to evaluate the effect of rifampin on the pharmacokinetics of oral cabotegravir in healthy subjects
Brief description of trial design	This was a phase 1, single-center, open label, fixed-sequence crossover study in healthy adults to evaluate the effect of RIF on the PK and safety of a single oral dose of CAB 30 mg.

Study Design

Subjects	Period 1 Day 1 – Day 7	Period 2 Days 8 – 20	Period 3 Days 21 – 28
N=15	Single dose CAB 30 mg (day 1)	RIF 600 mg once daily for 13 days (days 8 – 20)	Single dose CAB 30 mg on day 21 + RIF 600 mg QD for 8 days (days 21-28)

PK sample collection times	Plasma PK samples (2 mL of blood per sample) were collected to measure CAB at the following time points: Period 1 predose (within 15 minutes prior to dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 (day 3), 72 (day 4), 120 (day 6), 168 hours (day 8 prior to Rifampin dosing) postdose. Period 3 predose day 21 (within 15 minutes prior to dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 (day 3), 72 (day 4), 120 (day 6), 168 hours (day 8) postdose.

Results

Summary of Plasma CAB Pharmacokinetic Parameters in LAI117010

Treatment	$AUC_{(0-\infty)}$[1] (h·μg/mL)	C_{max}[1] (μg/mL)	T_{max}[2] (h)	C24[1] (μg/mL)	$T_{1/2}$[1] (h)	CL/F[1] (L/h)
CAB (n=15)	146 (128, 167) [23.9]	3.61 (3.28, 3.96) [16.9]	2.00 (1.00-6.00)	1.72 (1.49, 1.97) [25.5]	38.5 (35.7, 41.6) [13.9]	0.205 (0.180, 0.234) [23.9]
CAB + RIF (n=15)	59.7 (52.8, 67.5) [22.4]	3.39 (3.05, 3.76) [19.1]	1.00 (1.00-4.00)	0.860 (0.749, 0.988) [25.5]	16.4 (14.7, 18.2) [19.5])	0.502 (0.444, 0.568) [(22.4]

Geometric mean (95% CI) [CVb%]
Median (range)
CAB: Single dose CAB 30 mg (day 1)
CAB+RIF: CAB 30 mg on day 21 (single dose) + steady state RIF 600 mg QD (days 8-28)
Data Source: CPSR Table 9

Summary of Plasma CAB PK Parameters Treatment Comparisons

CAB PK Parameter	Treatment Comparison: CAB+RIF vs. CAB (GLSM Ratio, 90% CI)
$AUC_{(0-\infty)}$	0.41 (0.36, 0.46)
C_{max}	0.94 (0.87, 1.02)
CL/F	2.4 (2.2, 2.8)
$T_{1/2}$	0.43 (0.39, 0.46)

CAB: Single dose CAB 30 mg (day 1)
CAB+RIF: CAB 30 mg on day 21 (single dose) + steady state RIF 600 mg QD (days 8-28)
Data source: CPSR Table 10

Discussion/Conclusions

When coadministered with rifampin in separate DDI studies, the CAB AUC (most affected PK parameter) ratio is 0.41 and the RPV C_{tau} (most affected PK parameter) ratio is 0.11. Proposed labeling states that use of rifampin with CAB+RPV is contraindicated. Due to the HIV and tuberculosis co-infected population being vulnerable and the impact of decreased CAB and RPV exposures being unknown, we agree with the contraindication.

Table 123. Study LAI116181

Title	A Phase 1, Open-Label, Crossover Study to Evaluate the Pharmacokinetics and Safety of GSK1265744 and Rilpivirine and Dolutegravir and Rilpivirine in Healthy Adult Subjects
Brief description of trial design	This was a single-center, 2-cohort, open-label, 3-period, fixed-sequence cross over study in healthy adult subjects. Subjects received CAB 30 mg (5 mg×6 tablets) once daily for 12 days in Period 1, followed by a 14-day washout period, a RPV 25 mg tablet once daily for 12 days in period 2, and CAB 30 mg (5 mg×6 tablets) once daily in combination with a RPV 25 mg tablet once daily for 12 days in Period 3. Study drugs were taken with a moderate-fat meal.
Note	This study also evaluated the PK of DTG with and without RPV. As the DTG-RPV interaction has been previously reviewed by FDA (TIVICAY labeling states there is no clinically significant interaction), these arms of the study are not described here.
PK sample collection times	Plasma PK samples were collected for GSK1265744 (Periods 1 and 3): Predose on days 10 and 11 and on day 12: predose (within 15 minutes of the investigational product administration), 1, 2, 3, 4, 8, 12 and 24hrs postdose hours postmorning dose. Blood samples were collected for rilpivirine (Periods 2 and 3): Period 2, day 11: predose (within 15 minutes of the investigational product administration), 1, 2, 3, 4, 5, 6, 9, 12, 16, and 24hrs postdose hours postmorning dose. (Period 3): day 5 predose (within 15 minutes of the investigational product administration) 1, 2, 3, 4, 5, 6, 9, 12, 16, and 24hrs postdose hours postmorning dose.

Results

In the presence vs. absence of RPV, CAB C_{max} was unchanged (ratio of 1.05, not statistically significant) and CAB AUC and C_{tau} ratios were 1.12-1.14 (statistically significant). In the presence vs. absence of CAB, RPV PK parameters were unchanged (ratios of 0.92-0.99, CIs do not exclude 1.00).

Plasma Pharmacokinetic Parameters of GSK1265744 With and Without RPV (GSK1265744 PK Summary Population)

Plasma GSK1265744 PK Parameter	GSK1265744[1] (n=11)	GSK1265744+RPV[1] (n=11)
$AUC_{(0-\tau)}$ (μg·h/mL)	142 [118, 171] (28)	159 [138, 183] (21)
C_{max} (μg/mL)	8.22 [6.83, 9.89] (28)	8.65 [7.69, 9.72] (18)
Cτ (μg/mL)	4.65 [3.73, 5.78] (33)	5.29 [4.49, 6.23] (25)
T_{max}[2] (h)	4.00 (2.0-4.0)	4.00 (1.0-4.0)

Geometric mean [95% CI] (CVb%)
Median (range)Treatments:
GSK1265744 = GSK1265744 30 mg QD×12 days
GSK1265744 + RPV = GSK1265744 30 mg QD + RPV 25 mg QD×12 days
Data Source: CPSR Table 10

Plasma RPV Pharmacokinetic Parameters (RPV PK Summary Population)

	Cohort 2: RPV With or Without GSK1265744	
Plasma RPV PK Parameter	**RPV[1] (n=11)**	**GSK1265744+RPV[1] (n=11)**
$AUC_{(0-\tau)}$ (ng·h/mL)	2473 [2034, 3008] (30)	2441 [1916, 3110] (37)
C_{max} (ng/mL)	171 [137, 213] (34)	165 [120, 226] (50)
$C\tau$ (ng/mL)	87.4 [66.8, 114] (42)	80.3 [58.6, 110] (50)
T_{max}[2] (h)	4.00 (3.0-6.0)	4.00 (3.0-5.0)

Geometric mean [95% CI] (CVb%)
Median (range)
Treatments:
Cohort 2 RPV = RPV 25 mg QD×12 days
GSK1265744 + RPV = GSK1265744 30 mg QD + RPV 25 mg QD×12 days
Data Source: CPSR Table 11

Discussion/Conclusions
Consistent with the results of this study, proposed labeling states there is no clinically significant interaction between CAB and RPV.

Table 124. Study 200056 (LATTE-2 CSF Substudy)

Title	An assessment of the Pharmacokinetics (PK) of Cabotegravir (CAB) and Rilpivirine (RPV) in the Plasma and Cerebrospinal Fluid (CSF) following LA Intramuscular Administration in Subjects Currently Enrolled into the LATTE-2 Phase 2b Study A Country Specific Amendment to LATTE-2 (200056): A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 for the Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naïve Adult Subjects
Brief description of trial design	The 200056 CSF PK substudy was conducted within the Extension Period of Study 200056. The CSF PK substudy was designed to assess the potential for CAB and RPV to enter the CSF compartment. For the Q8W IM group, all subjects had reached at least week 152 and for the Q4W IM group, all subjects had reached at least week 153 of the 200056 parent study before screening for this substudy. Subjects continued their designated Extension Period IM dosing regimen (Q8W or Q4W dosing). After an injection visit, two time-matched PK samples (one from plasma and the other from CSF) were collected 7 days (±3 days) after an injection visit as per the schedule of events for the CSF PK substudy to assess peak concentrations of CAB and RPV (CSF PK substudy visit). Plasma HIV-1 RNA levels were assessed prior to the injection on day 1. Two samples were collected from plasma and in CSF (via LP) for the assessment of HIV-1 RNA levels 7 days (±3) after the injection visit.

PK sample collection times	Plasma samples for determination of CAB and RPV concentration were collected throughout the Maintenance Period and from week 100 – week 128 in the Extension Period of the study for subjects switching from oral Maintenance period regimen to the optimized IM dosing regimen of their choice. Additional samples were collected for storage during the Extension and Long-Term Follow Up Period. The CSF PK samples were collected 7 days (± 3 days) after an injection visit (Q4W vs. Q8W dosing) during the Extension Phase in LATTE-2.

Results

Summary of Cabotegravir Concentrations in Plasma and CSF (PK Concentrations Population)

	Q8W IM (n=15)	Q4W IM (n=3)
Parameter	**Median (Min, Max)**	**Median (Min, Max)**
C_{max} (μg/mL)	3.92 (1.30, 6.41)	3.02 (2.37, 5.10)
Plasma unbound (μg/mL)	0.0047 (0.0007, 0.0220)	0.0019 (0.0014, 0.0698)
Unbound fraction at C_{max} in plasma (%)	0.103 (0.056, 0.912)	0.075 (0.062, 1.45)
CSF total (μg/mL)	0.0106 (0.0053, 0.0245)[1]	0.0127 (0.0082, 0.0159)
Ratio CSF:plasma (%)	0.304 (0.218, 0.449)[1]	0.344 (0.312, 0.421)

Data Source: ACSR Table 6
Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 weeks (Q4W)
[1]n=13; two subjects had failed attempts at CSF collection during LP

Summary of Rilpivirine Concentrations in Plasma and CSF (PK Concentrations Population)

	Q8W (n=15)	Q4W (n=3)
Parameter	**Median (Min, Max)**	**Median (Min, Max)**
C_{max} (ng/mL)	192 (91.7, 378)	134 (83.0, 187)
CSF total (ng/mL)	1.84 (NQ, 2.90)[1,2]	1.67 (1.40, 2.47)
Ratio CSF:plasma (%)	1.07 (0.0, 1.52)[1]	1.32 (1.25, 1.69)

Data source: ACSR Table 7
Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 weeks (Q4W)
[1]N=13; two subjects had failed attempts at CSF collection during LP
[2]One subject's RPV concentration was nonquantifiable (NQ), which was imputed to 0 for the calculation.

Discussion/Conclusions
Consistent with results of this study, proposed labeling states that the median (range) CSF-to plasma concentration ratio for CAB is 0.003 (0.002-0.004) and for RPV is 0.01 (BQL-0.02).

Abbreviations: BQL = below the limit of quantification

14.1.3. Bioanalytical Methods

We reviewed method validation and sample analysis reports for measurement of CAB and RPV using LC/MS/MS in phase 3 studies. Method validation and sample analysis were acceptable and met acceptance criteria as described in FDA Guidance for Industry *Bioanalytical Method Validation* (May 2018).[25]

14.1.4. Formulations

The commercial formulations of CAB IM and RPV IM were administered in phase 2b and phase 3 studies.

A (b) (4) CAB tablet formulation was used in phase 2b studies. The commercial CAB 30 mg (b) (4) tablet formulation was used in phase 3 studies.

Approved RPV tablets were used in phase 2b and phase 3 studies.

14.2. Pharmacometrics Review

14.2.1. Pharmacometrics Review: CAB

Introduction

The Applicant developed a CAB popPK model for orally and IM-administered CAB (cabotegravir popPK report). Objectives of the popPK analysis included the following:

- Characterize the PK of CAB based on data from healthy and HIV-infected subjects following oral or IM administration of CAB.
- Provide PK parameters for the overall population and subgroups.
- Evaluate the association between intrinsic and extrinsic factors and CAB exposure.
- Perform simulations to support dosing strategies under various scenarios (dosing errors, dosing delays, use of concomitant medications, treatment discontinuation).

Our review of the CAB popPK model will focus on the following:

- Acceptability of the model
- Exposure-response relationships for efficacy and safety
- The need for dose adjustments based on intrinsic and extrinsic factors
- Dosing recommendations for missed injections

Methods

Studies Included in the PopPK Dataset

The Applicant modeled data from 16 studies; ten for orally administered CAB only and six studies contributed data for both orally and IM-administered CAB.

Excluded Data

CAB dosing or concentration records were excluded for the following reasons:

- Missing dosing and/or sampling time
- Duplicate dosing record
- Nonzero baseline concentration
- Records containing no concentration or dose
- Negative time
- Subjects whose entire dosing history was missing
- Peak concentration where time of sampling appeared before dosing
- Trough concentrations where time of sampling appeared after dosing

Outliers were identified by visual inspection of individual and pooled data and by weighted residuals. In subjects with potential outliers (|CWRES >5|), all samples were evaluated in an

attempt to determine if potential outliers were erroneous versus due to interindividual variability in PK. Concentrations identified as outliers were excluded.

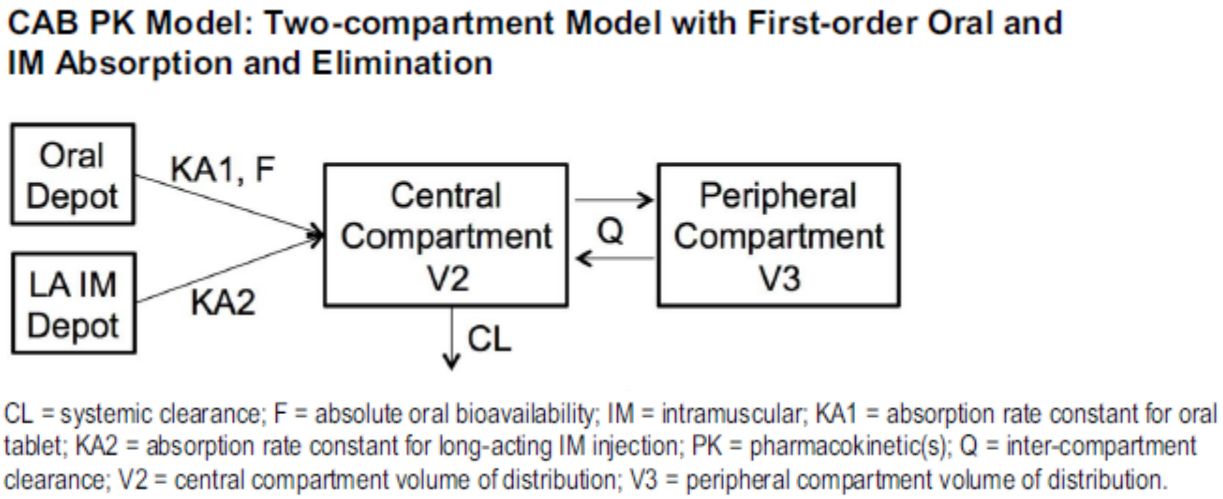
Imputation of demographic or laboratory covariate values were performed if values were missing for <15% of subjects. If values of a covariate were missing for >15% of subjects, the covariate was evaluated in exploratory analyses but not in the population analyses.

Concentrations BQL were to be excluded if the fraction of BQL values were small. If necessary, BQL values were to be included in the model using a likelihood-based method.

PopPK Modeling

PopPK models were developed using NONMEM software version 7.2 or higher. The starting point of the popPK analysis was the base model from previous CAB popPK analyses. This was a two-compartment model with first-order oral and IM absorption and elimination (Figure 29). Body size was included as a covariate for clearance (CL/F), volume of the central compartment (V2/F), intercompartmental clearance (Q/F), and volume of the peripheral compartment (V3/F).

Figure 29. Cabotegravir Base PopPK Model Structure Used in Previous PopPK Analyses



CL = systemic clearance; F = absolute oral bioavailability; IM = intramuscular; KA1 = absorption rate constant for oral tablet; KA2 = absorption rate constant for long-acting IM injection; PK = pharmacokinetic(s); Q = inter-compartment clearance; V2 = central compartment volume of distribution; V3 = peripheral compartment volume of distribution.

Source: Cabotegravir popPK report, page 26.

Numerous covariates were evaluated. Continuous covariates included age, ALT, albumin, alkaline phosphatase, AST, total bilirubin, creatinine, direct bilirubin, gamma glutamyl transferase, lactate dehydrogenase, urea, and HIV-1 viral load. Categorical covariates included gender, race, baseline HIV status and category (various categories according to viral load), concomitant medications, PGx data, route of administration, needle length, needle gauge, injection volume, injection type, smoker status, and exercise type. Standard forward addition (p-value<0.01) and backward elimination (p-value<0.001) procedures were used to identify significant covariates. For statistically significant continuous covariates, if the PK parameter estimate of a typical subject changed <15% when using the 10^{th} versus 90^{th} percentile value of the covariate, the covariate was removed from the model.

The final model was qualified through diagnostic goodness of fit plots, bootstrap analysis and visual predictive check (VPC).

Results

Data Summary

The oral and IM CAB popPK dataset available for analysis contained 24,039 samples from 1,650 subjects. The majority of subjects were male and of white race. The number of excluded samples was 113 of 24,039 (0.5%). The final analysis dataset contained 23,926 observations from 1,647 subjects. The number of BQL samples was 555 of 24,039 (2.3%). BQL samples were included in the model (M3 method).

PopPK Modeling

The base model from previous CAB popPK analyses (two-compartment model with first-order oral and IM absorption and elimination) was utilized as the base model in this analysis. Effects of body weight on clearance and volume parameters were implemented as exponents. The model was run with exponents estimated and also with exponents fixed to 0.75 for clearance and 1 for volume. As model fit was better with estimated exponents, modeling proceeded using estimated exponents. According to the Applicant, fixed and random effect parameters were estimated with good precision, and diagnostic plots indicated adequate base model performance.

The covariate analysis lead to a final model which included additional covariates on IM absorption (KA2) and clearance (Table 125). Diagnostic plots for the final model are shown below (Figure 30, Figure 31).

Table 125. Parameter Estimates for the Cabotegravir Final PopPK Model

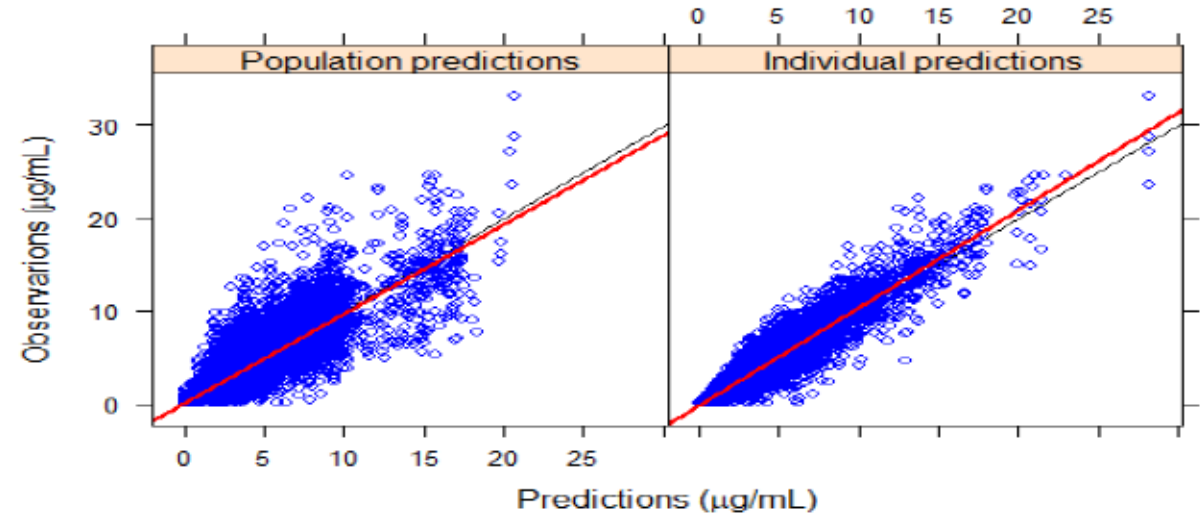
Parameter	Estimate	RSE (%)	90% CI (Bootstrap) 5th, 95th Percentile	IIV (%)	RSE of IIV (%)	Shrinkage (%)	Equation Expression
KA1 (hr^{-1})	1.41	4	1.23,1.52	89.4	4.34	69.1	
KA2 (hr^{-1})	0.000733	2.3	0.000705, 0.000761	57.9	2.46	17.9	$KA2 = 0.00073 \times (1 - 50.9\% \text{ if female}) \times (1 + 47.8\% \text{ if split}) \times \left(\frac{BMI \text{ in } \frac{kg}{m^2}}{25.4}\right)^{-0.766} \times \left(\frac{NDL \text{ in inch}}{1.5}\right)^{0.478}$
CL/F (L/hr)	0.151	0.9	0.148, 0.153	23.3	2.58	10.3	$CL/F = 0.151 \times \left(\frac{BWT}{76.6}\right)^{0.618} \times (1 + 17.4\% \text{ if current smoker})$
V2/F (L)	5.27	2	5.07, 5.45	20.3	9.38	31.1	$V2/F = 5.27 \times \left(\frac{BWT}{76.6}\right)^{0.702}$
Q/F (L/hr)	0.507	6.6	0.455, 0.579				$Q/F = 0.507 \times \left(\frac{BWT}{76.6}\right)^{0.618}$
V3/F (L)	2.43	4.8	2.26, 2.66				$V3/F = 2.43 \times \left(\frac{BWT}{76.6}\right)^{0.702}$
F1	0.756	0.9	0.744, 0.768	17.4	5.70	40	
Add Err (µg/mL)	0.0319	19.4	0.0202, 0.0496				
Prop Err	27.3%	1.1	26.7%, 27.8%				
BWT on CL/F and Q/F	0.618	5.6	0.562, 0.68				
BWT on V2/F and V3/F	0.702	7.1	0.622, 0.79				
Smoke on CL/F	17.4%	9.3	14.7%, 20%				
BMI on KA2	-0.766	13	-0.922, -0.611				
Needle length on KA2	0.478	36.2	0.184, 0.747				
Gender [a] on KA2	-50.9%	4.4	-54.1%, -47.1%				
Split on KA2	47.8%	14.2	36.9%, 60.2%				

Add Err = additive component of residual variability; BMI = body mass index; BWT =baseline body weight; CI = confidence interval; CL/F = apparent central clearance; F1 = relative bioavailability of the oral relative to IM formulation; IIV = inter-individual variability; IM = intramuscular; KA1 = absorption rate constant for oral tablet; KA2 = absorption rate constant for IM injection; NDL = needle length; PK = pharmacokinetic(s); Prop Err = proportional component of residual variability; Q/F = apparent inter-compartmental clearance; RSE = relative standard error; Smoke = current smoker status; Split = split injection; V2/F = apparent central compartment volume of distribution; V3/F = apparent peripheral compartment volume of distribution.

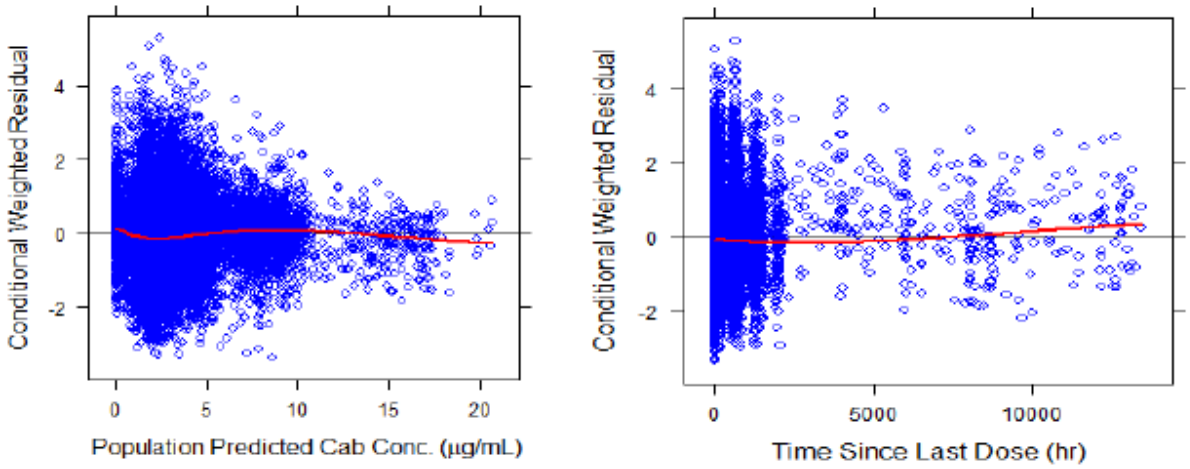
[a] Biological gender only (i.e., male or female).

Source: Cabotegravir popPK report, page 64.

Figure 30. Final Cabotegravir Model Goodness-of-Fit Plots



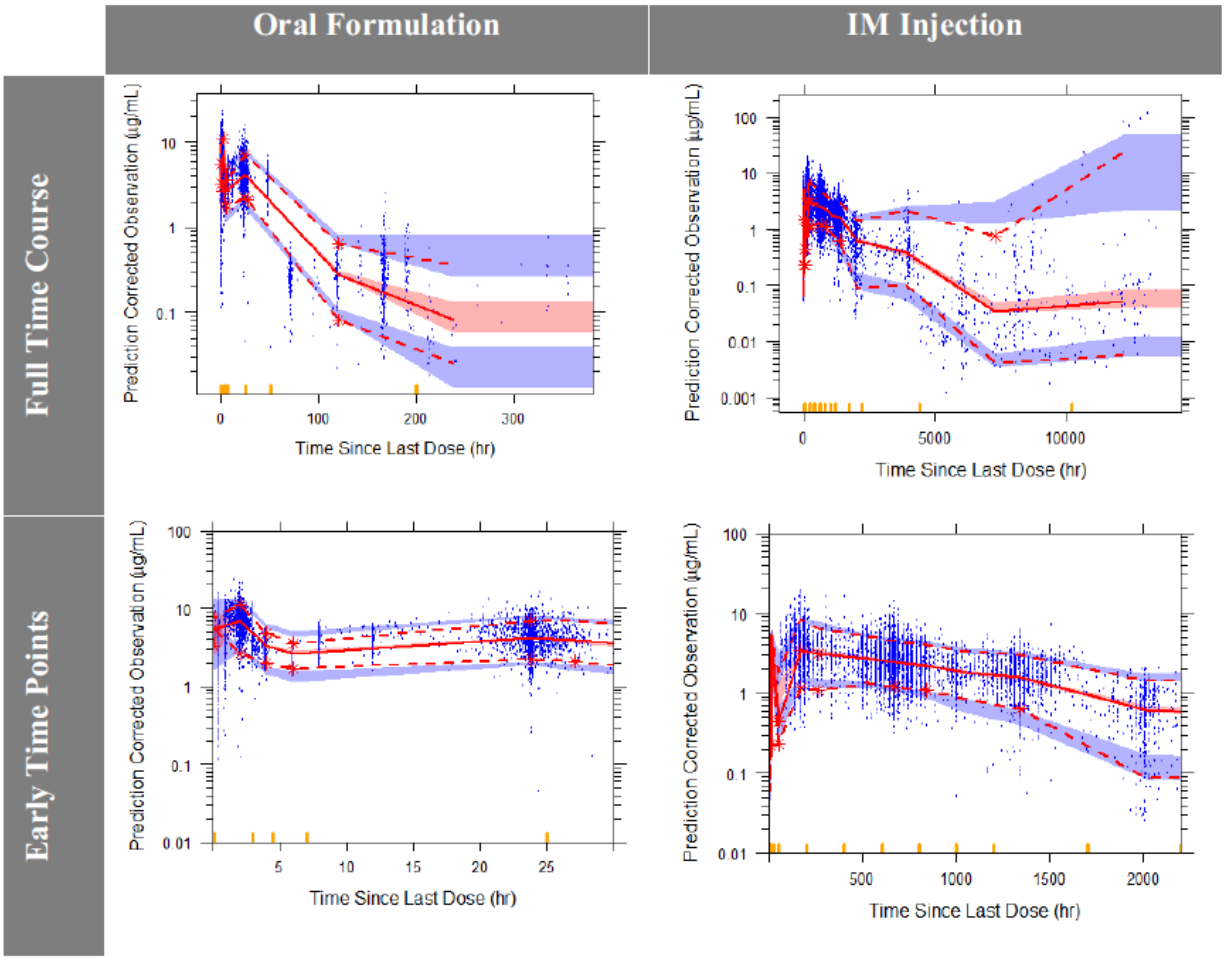
Note: Black line represents the identity line; red line represents the loess smoother.



Conc = concentration.
Note: Red line represents the loess smoother.

Source: Cabotegravir popPK report, page 68.

Figure 31. Prediction-Corrected VPC of the Cabotegravir Final PopPK Model



IM = intramuscular; VPC = visual predictive check.
Notes: Solid line corresponds to observed median; dashed lines correspond to the 5th and 95th percentiles of prediction-corrected observations; shaded regions correspond to 95% of the simulated (n = 500) values of the predicted median (pink), 5th, and 95th percentiles (blue). Red asterisks highlight where prediction-corrected observation lines were not contained within the shaded region. Blue dots correspond to prediction-corrected observed data. Yellow bars on the x axis indicate the boundaries between bins.

Source: Cabotegravir popPK report, page 70.

CAB exposures were estimated following administration of CAB plus RPV in HIV-infected subjects (Table 126).

Table 126. Model-Predicted Post Hoc Cabotegravir Exposures Following Administration of Cabotegravir Plus Rilpivirine in HIV-Infected Subjects

CAB Regimen	Dose	Statistics	Plasma CAB Exposure			
			$AUC_{(0-\tau)}$ (μg × h/mL)	C_{max} (μg/mL)	$C\tau$ (μg/mL)	T_{max} (hour)
30 mg PO QD	Steady-state	Geometric mean (95% CI)	145.7 (142.7,148.7)	8.1 (7.9,8.2)	4.7 (4.6,4.8)	2.0 [a] (2.0,4.0)
		Median [5th-95th percentile]	145.4 [92.5-234.0]	8.0 [5.3-12.6]	4.7 [2.8-7.8]	2.0 [a] [2.0-2.0]
600 mg IM initial dose + 400 mg IM monthly	Initial dose	Geometric mean (95% CI)	1574.1 (1521.9,1628.1)	8.1 [b] (7.9,8.2)	1.5 (1.4,1.5)	0.0 [a,b] (0.0,48.0)
		Median [5th-95th percentile]	1615.4 [730.0-3209.1]	8.0 [b] [5.3-12.6]	1.5 [0.7-2.8]	0.0 [a,b] [0.0-0.0]
	Steady-state	Geometric mean (95% CI)	2460.6 (2412.6,2509.6)	4.2 (4.1,4.3)	2.9 (2.9,3.0)	5.0 [a,c] (4.0,7.0)
		Median [5th-95th percentile]	2502.3 [1533.9-3675.4]	4.3 [2.5-6.5]	3.0 [1.8-4.6]	5.0 [a,c] [4.0-6.0]

$AUC_{(0-\tau)}$ = area under concentration-versus-time curve from time 0 to the end of the dosing interval; $C\tau$ = plasma concentration at the end of the dosing interval; C_{max} = maximum plasma concentration; CAB = cabotegravir; CI = confidence interval; HIV = Human Immunodeficiency Virus; IM = intramuscular; PK = pharmacokinetic(s); PO = oral; PopPK = population pharmacokinetics; QD = daily; RPV = rilpivirine; T_{max} = time to reach maximum plasma concentration.

Note: Simulation PK sampling schedule is one sample every 2 hours following PO doses, one sample every 24 hours following IM injections. PK parameter values were calculated based on individual post-hoc estimates of Studies 201584 (FLAIR) and 201585 (ALTAS) from the final PopPK model.

[a] Median (minimum, maximum).

[b] The C_{max} and T_{max} following the first CAB LA injection is likely determined by the last oral dose instead of the initial LA dose.

[c] The unit is day.

Source: Cabotegravir popPK report, page 67.

14.2.1.1. Effect of Intrinsic and Extrinsic Factors on Cabotegravir Exposure

The Applicant conducted analyses to evaluate the impact of intrinsic and extrinsic factors on CAB exposure. This analysis utilized the phase 3 study population and model-predicted exposures at week 8, week 48 or steady-state.

Note the impact of UGT inhibitors or inducers on CAB exposure is discussed elsewhere (Sections II.8.2 and 14.3).

The 5th percentile of AUC and C_{min} after the initial injection in phase 3 studies were used as targets for efficacy. In other words, intrinsic or extrinsic factors resulting in a significant share of the subgroup having exposures below the target would be of concern. CAB 5th percentile values are 714 μg·h/mL for AUC and 0.65 μg/mL for C_{min}.

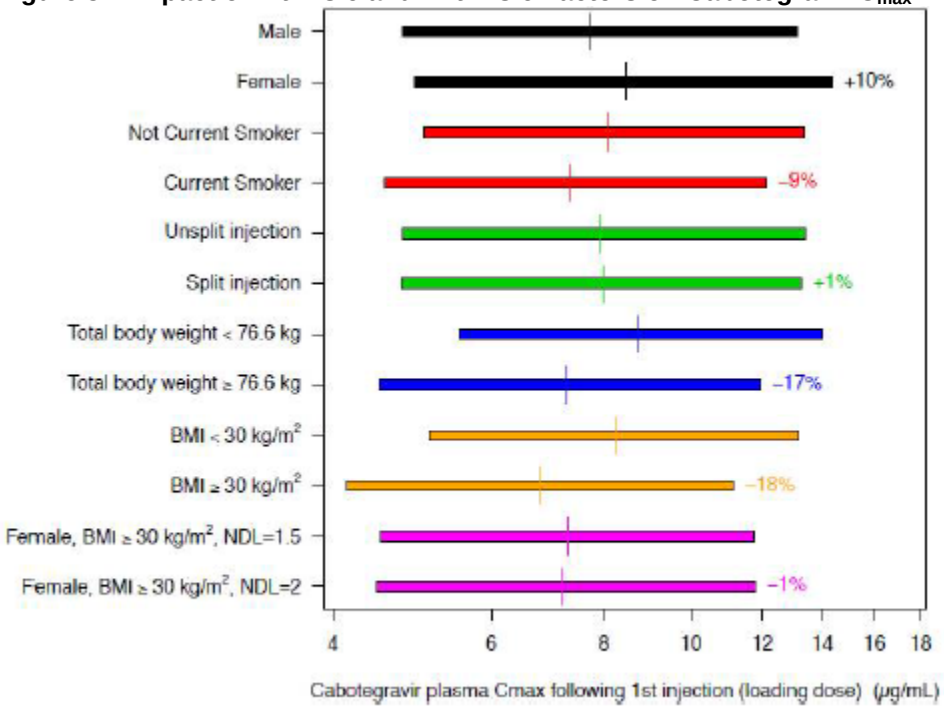
The CAB safety target was based on phase 2b study LAI116482 where CAB 60 mg orally daily was evaluated. Median CAB C_{max} of 13.1 µg/mL from the 60-mg dose in this study is used as the threshold for safety concerns. Note that the 95th percentile C_{max} value from CAB 30 mg orally or 600 mg IM in phase 3 studies was 12.6 µg/mL (Table 126).

The CAB popPK model contained covariates for IM absorption (gender, split injection, BMI, needle length), clearance (body weight, smoking status) and volume (body weight). After the first injection, subgroups with a sizable share of subjects with CAB AUC <714 µg·h/mL were females and those with BMI ≥30 kg/m^2 (Figure 23). At week 48, <5% of subjects have CAB AUC <714 µg·h/mL in any subgroup (Figure 23).

Similarly, after the initial injection a sizable fraction of females and those with BMI ≥30 kg/m^2 had CAB C_{min} <0.65 µg/mL, while <5% of subjects were below the target for any subgroup at steady-state (Figure 24).

After the first injection, C_{max} values were elevated due to the combination of oral therapy and the loading dose. In all subgroups ~5% of subjects were expected to exceed the CAB C_{max} threshold of 13.1 µg/mL (Figure 32). At steady-state, the 95th percentile of CAB C_{max} did not exceed ~7 µg/mL in any subgroups; thus <5% of subjects in each subgroup were expected to reach 13.1 µg/mL (Figure 33).

Figure 32. Impact of Intrinsic and Extrinsic Factors on Cabotegravir C_{max} After the Initial Injection



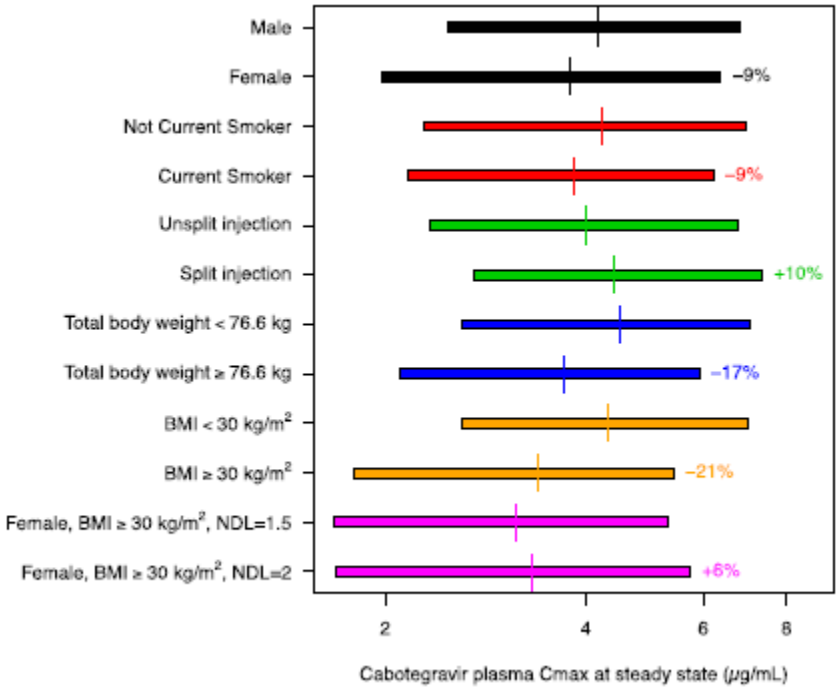
Note: Cmax following 1st injection reflects final oral dosing administered at the W4b visit

BMI = body mass index; Cmin = minimum concentration; NDL = needle length (inch); Each color represents a covariate or covariate combination. Each bar represents 5th to 95th percentile with median in each subgroup within the covariate (or covariate combination). Percentage numbers on the right side of each bar represent the percentage change in median versus the median of the reference subgroup within the same covariate or covariate combination (i.e. versus the other bar of the same color).

Note: Figure continues to next page.

Source: NDA 212888 SDN 19, page 7.

Figure 33. Impact of Intrinsic and Extrinsic Factors on Cabotegravir C_{max} at Steady State



BMI = body mass index; Cmin = minimum concentration; NDL = needle length (inch); Each color represents a covariate or covariate combination. Each bar represents 5th to 95th percentile with median in each subgroup within the covariate (or covariate combination). Percentage numbers on the right side of each bar represent the percentage change in median versus the median of the reference subgroup within the same covariate or covariate combination (i.e. versus the other bar of the same color).
Note: Figure continues to next page.

Source: Cabotegravir popPK report, page 77.

Reviewer comment:

CAB PopPK Model

The Applicant developed a two-compartment popPK model to describe the PK of CAB after oral or IM administration to healthy and HIV-infected adults. 16 studies were included in the analysis. The dataset contained 23,926 samples from 1647 subjects. Significant covariates included the following:

- ***KA2: Gender, split injection, BMI, needle length***
- ***CL/F: body weight and smoking status***
- ***V2/F, Q/F, V3/F: body weight***

Fixed and random effect parameters were estimated with good precision (relative standard error <20%) with the exception of the effect of needle length on KA2 (relative standard error =36%) (Table 125). Goodness of fit, bootstrap, and VPC results indicate adequate model performance. In addition, in individual subjects there is good general overlap between observed and individual predicted concentration-time profiles (cabotegravir popPK report, page 203 to 388). When popPK PK parameter estimates were compared to observed PK parameters from individual studies, CAB AUC after oral or LA administration was comparable (10% to 20% lower) (Table 127).

Table 127. Observed vs. Model-Predicted Cabotegravir (CAB) AUC After Oral or LA Dosing in HIV-Infected Subjects

CAB Regimen	Dose	Statistics	CAB $AUC_{0-\tau}$ (µg·h/mL)	Source
30 mg QD	Steady-state	Geometric mean	134	Observed data from study LAI116482
30 mg QD	Steady-state	Geometric mean	145.7	Model-predicted
400 mg IM monthly	Steady-state	Geometric mean	1,858	Observed data from study 200056
400 mg IM monthly	Steady-state	Geometric mean	2460.6	Model-predicted

Source: Prepared by reviewer.
Abbreviations: IM = intramuscular, LA = long-acting, QD = once daily

The final model had adequate performance. Model-predicted PK parameters can be used to evaluate exposure-response relationships, the effect of intrinsic and extrinsic factors on exposure, and dosing recommendations for missed injections.

The Effect of Intrinsic and Extrinsic Factors on CAB Exposure

For CAB efficacy, after the first injection there were two subgroups with a sizable fraction of subjects below the efficacy targets; these were females and obese subjects. However, at week 48 or steady-state, no subgroup had a sizable fraction of subjects below the efficacy targets. Due to the very low failure rate of 1.5% in phase 3 studies and the fact that CAB concentrations are relatively low only after the first injection, we think no CAB dose adjustment is warranted for females or obese patients.

Regarding CAB safety, after the first injection the fraction of subjects with C_{max} greater than the target was ~5% regardless of subgroup. At steady-state, <5% of subjects in each subgroup exceeded the target. No AEs of interest were found to be related to CAB concentrations. We do not recommend CAB dose adjustment based on membership in any of the subgroups evaluated.

14.2.2. Pharmacometrics Review: RPV

Introduction

The Applicant developed a RPV popPK model for IM-administered RPV using pooled data from seven studies; four in healthy adults and three in HIV-infected adults (rilpivirine popPK report). Objectives of the popPK analysis included the following:

- Obtain estimates of RPV typical PK parameters in the study populations and quantify their inter- and intra-individual variability.
- Provide a quantitative assessment of the effect of intrinsic and extrinsic factors on RPV exposure and the need for dose adjustments in specific populations.

Methods

Studies Included in the PopPK Dataset

Seven studies were included in the analysis; this includes four studies in healthy adults (single or multiple Q4W IM doses of 300 mg to 1200 mg) with intensive PK assessment and three studies in HIV-infected adults (OLI followed by multiple IM doses of 600 mg to 900 mg Q4W or 900 mg Q8W) where only predose samples were collected. Dataset A consisted of four studies in healthy adults with intensive PK assessment. Dataset B consisted of phase 2 study 200056 and phase 3 studies 201584 and 201585. Dataset C contained all seven studies.

Excluded Data

Aberrant data were excluded from the analysis. This includes samples collected before the first dose, subjects with incomplete dosing history, or samples where the concentration was inconsistent with the sampling time. Using dataset C, outliers were identified as samples where |conditional weighted residual| >6. Outliers were included in the analysis, and a sensitivity analysis was conducted to determine the effect of outliers on estimation of model parameters.

If missing for ≤10% of subjects, covariate values were imputed using the median (continuous covariates) or mode (categorical covariates) of nonmissing values.

Samples with concentration BQL (1 ng/mL) were excluded from the analysis.

PopPK Modeling

PopPK models were developed using NONMEM software version 7.2 or higher.

Initial model development utilized dataset A. Covariate effects were then included in the model. In a previous popPK analysis of RPV following oral administration (NDA 202022 SDN 95), no significant covariates were identified. Thus, in this covariate analysis for RPV following IM administration, only covariates for IM absorption were evaluated. Covariates evaluated included demographic factors (sex, age, weight, race), HIV-infection status, and needle length. Forward addition (p-value<0.005) and backward elimination (p-value<0.001) procedures were used to identify significant covariates. Model performance was verified using a VPC.

A previously developed popPK model for orally administered RPV was then combined with the present model to account for RPV concentrations from the OLI. Dataset B was then used for external validation of the model developed from Dataset A. Goodness of fit plots and VPC were used to evaluate the model. PK parameters were then updated using Dataset C, which resulted in the final model. VPC and bootstrap were used to evaluate the final model.

Results

Data Summary

The IM RPV popPK dataset available for analysis contained 19,225 samples (Table 128). The majority of subjects were male and of white race. The final analysis dataset contained 18,261 observations from 986 subjects. Five percent of available samples were excluded; the number of

BQL samples was 555 of 24,039 (2.3%) (Table 128). Thirteen outlier samples were identified; due to a minimal impact on parameter estimates (<12%) they were not excluded from the analysis.

Table 128. Summary of Rilpivirine Samples Included and Excluded in the PopPK Analysis by Dataset

Reason for exclusion	Dataset A N (%[a])	Dataset B N (%[a])	Dataset C N (%[a])
Oral bridging, long-term follow-up	.	253 (31.4)	253 (26.2)
Subjects randomized to IM treatment in extension period from ATLAS study	.	474 (58.9)	474 (49.2)
Pre-treatment sample	36 (22.6)	.	36 (3.73)
BQL samples[b]	109 (68.6)	15 (1.86)	124 (12.9)
Sample/dose date/time incomplete	.	36 (4.47)	36 (3.73)
Sample not analyzed by bioanalytical	.	15 (1.86)	15 (1.56)
Aberrant data	14 (8.81)	12 (1.49)	26 (2.7)
Total number of samples before exclusion	3061	16164	19225
Excluded	159 (5.19)	805 (4.98)	964 (5.01)
Included in the population pharmacokinetic analysis	2902	15359	18261

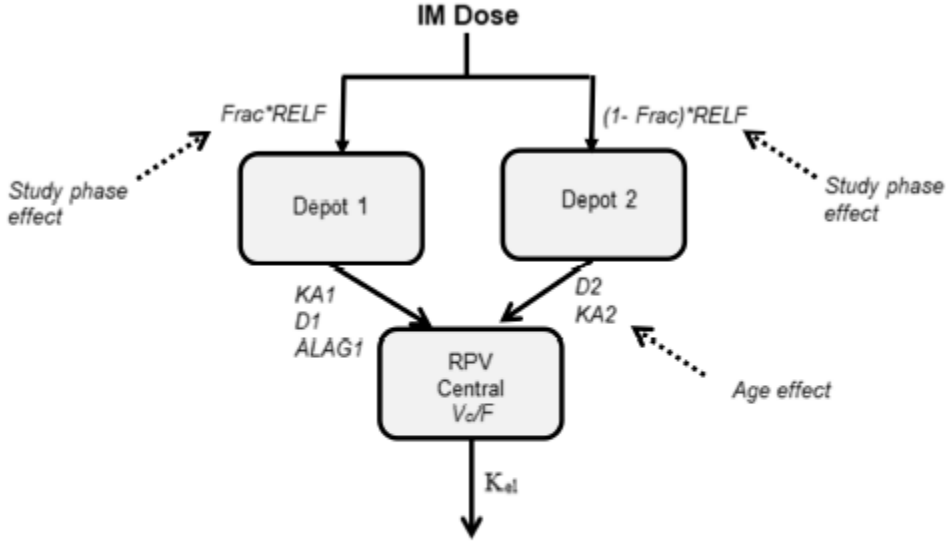
BQL, below the quantification limit.
[a] calculated based on the total number of excluded samples.
[b] BQL after dosing.

Source: Rilpivirine popPK report, page 47.
Abbreviations: IM = intramuscular

PopPK Modeling

The final model consisted of a one-compartment model with two parallel absorption pathways and linear elimination. The absorption pathways consisted of a fast pathway describing the initial peak and a second slow pathway describing the decline of the concentration-time profile (Figure 34). Covariate effects include the effect of study phase (phase 2 or phase 3) on slow and fast absorption (via an effect on relative bioavailability) and the effect of age on the fast absorption pathway (Figure 34, Table 129).

Figure 34. Final Rilpivirine PopPK Model Structure



ALAG1 (h), lag time before the slow first-order absorption starts; age effect, age-dependent fast first-order absorption rate; *D1* (h), zero-order absorption duration via the slow absorption pathway; *D2* (h), zero-order absorption duration via the fast absorption pathway; *Frac*, fraction of the IM dose absorbed via a fast absorption pathway; IM, intramuscular; *KA1* (1/h), slow first-order absorption rate constant; *KA2* (1/h), fast first-order absorption rate constant; K_{el}, elimination rate constant; LA, long acting; *RELF*, relative bioavailability; RPV, rilpivirine; V_c/F (L), apparent volume of distribution of the central compartment.

Source: Rilpivirine popPK report, page 105.

Table 129. Parameter Estimates for the Final Rilpivirine PopPK Model

Structural Model Parameters		*Inter-individual Variability (CV%)*	
Parameter	**Estimate (RSE%)**	**Parameter**	**Estimate (RSE%)**
Frac	0.396 (2.32)	ω *Frac*	0.168 (8.29)[d]
KA1 (1/d)	0.00346 (5.25)		
KA2 (1/d)	0.0322 (2.55)	ω *KA2*	36.6 (17.2)
D2 (h)	2.68 (2.82)	ω *D2*	107.7 (13.3)
ALAG1/D1 (d)	14.8 (2.30)		
K (1/d)	0.922 (3.75)		
K_{el} (1/d)[a]	0.924	ω K_{el}	25.2 (17.0)
V_c/F (L)	132 (3.76)		
RELF	1 FIX	ω *RELF*	23.5 (21.0)
F4	1.14 (1.68)		
Age on KA2[b]	-0.594 (10.8)		
Phase 2 on RELF[c]	-0.185 (17.7)		
Phase 3 on RELF[c]	-0.346 (8.79)		
Objective Function Value	-25413.50	***Residual Variability (CV%)***	
		σ_1	24.3 (1.23)

ALAG1 (h), lag time before the slow first-order absorption starts and equal to the zero-order duration of the slow absorption pathway; age effect, age-dependent fast first-order absorption rate; CV, coefficient of variation; *D2* (h), zero-order absorption duration via the fast absorption pathway; *F4*, relative bioavailability after oral administration; *Frac*, fraction of the IM dose absorbed via a fast absorption pathway; IM, intramuscular; *K* (1/h), first-order elimination rate constant; *KA1* (1/d), slow first-order absorption rate constant; *KA2* (1/d), fast first-order absorption rate constant; K_{el}, elimination rate constant; *RELF*, relative bioavailability with Phase 1 as reference (ie, 1 or 100%); RPV, rilpivirine; RSE, relative standard error; V_c/F (L), apparent volume of distribution of the central compartment.

[a] K_{el}=*KA1*+*K* with *K* >0.

[b] Power function on *KA2*: $(Age/37)^{-0.594}$.

[c] Implemented as EXP (Study Phase), with Phase 1 studies as reference.

[d] Standard deviation of *Frac* calculated as SQRT(ω².*Frac*.(1-*Frac*)).

Source: Rilpivirine popPK report, page 13.

Goodness of fit and diagnostic plots for the final model are shown below (Figure 35, Figure 36, Figure 37, Figure 38).

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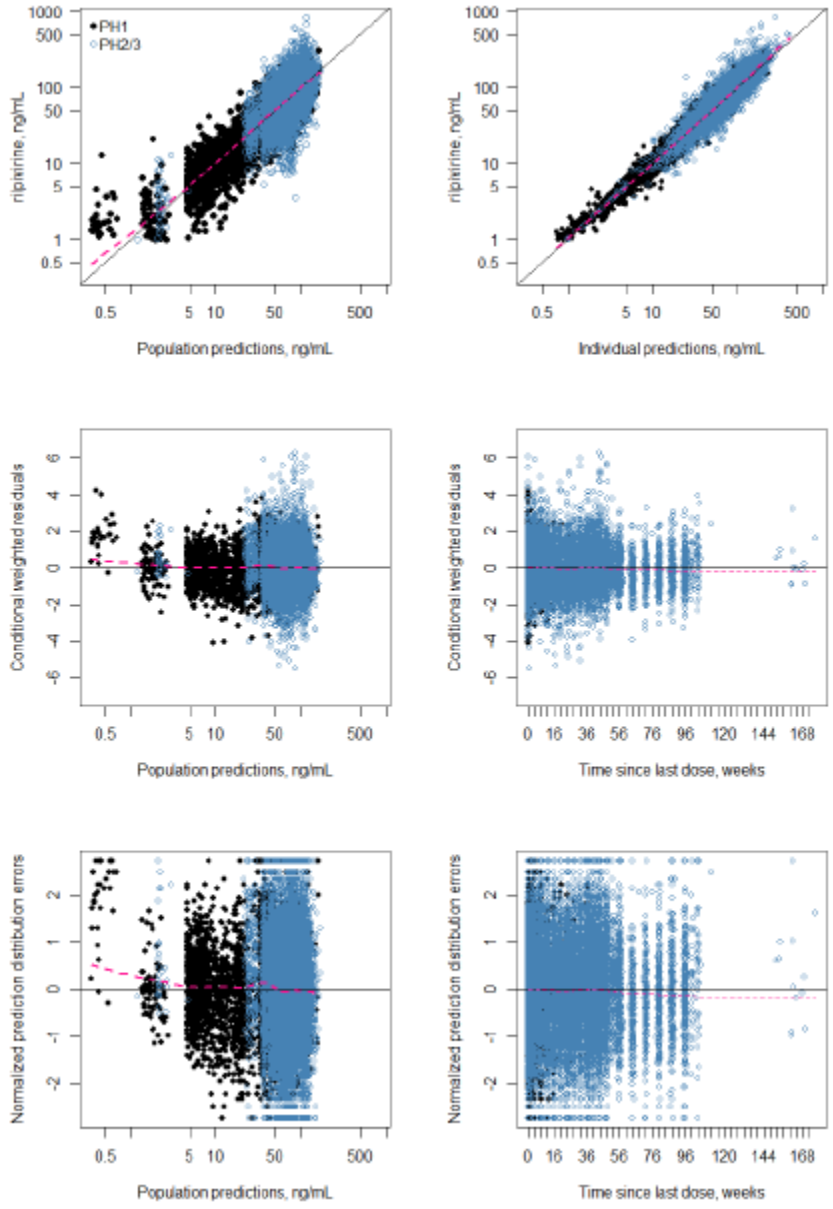
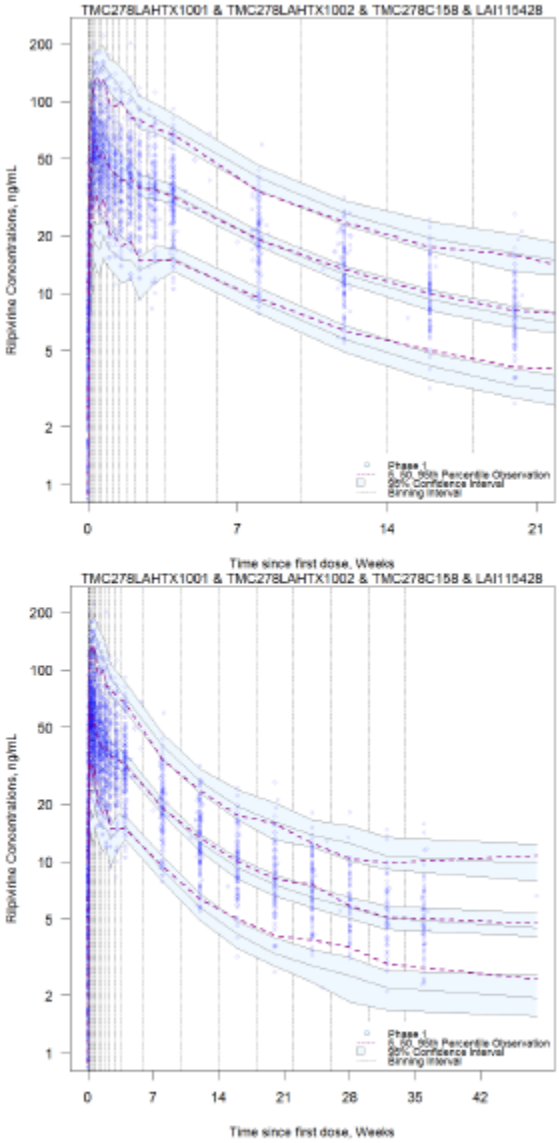
Figure 35. Goodness of Fit Plots for the Final Rilpivirine PopPK Model After IM Administration



Source: Rilpivirine popPK report, page 106.
Abbreviations: IM = intramuscular

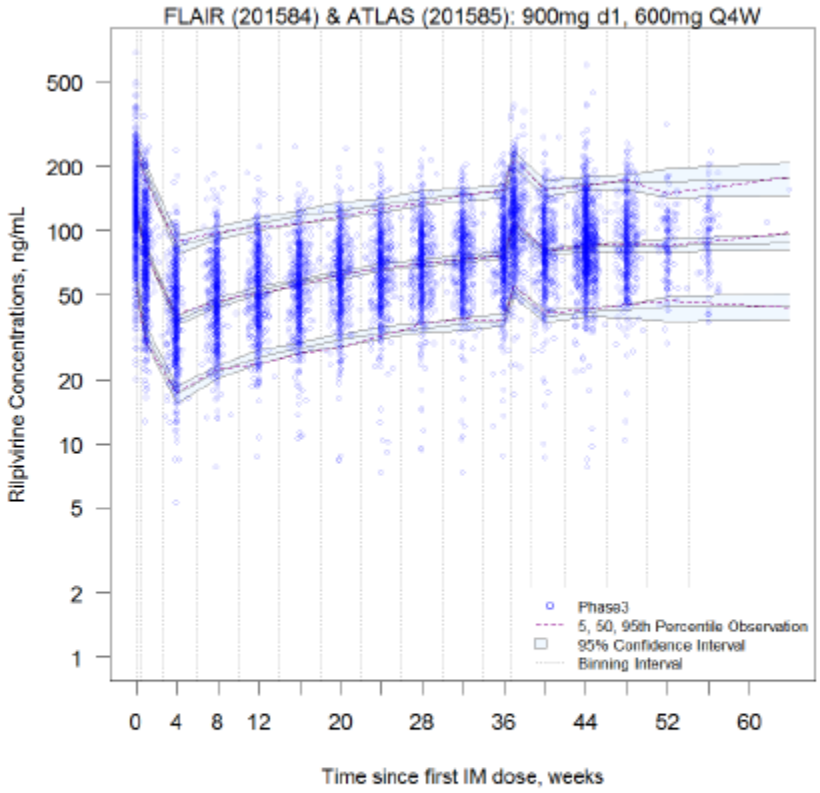
Figure 36. Prediction-Corrected VPC of the Final Rilpivirine PopPK Model for Phase 1 Studies



IM, intramuscular; LA, long acting; RPV, rilpivirine; VPC, visual predictive check.
The upper panel represents the VPC profile up to 21 weeks after the last IM administration of RPV LA and the lower panel represents the full VPC profile after the last IM administration of RPV LA. Solid lines represent the median, 2.5th, and 97.5th percentiles of the simulated data with its 95% confidence interval (blue shaded area). Purple dashed lines represent the median, 2.5th, and 97.5th percentiles of the observed data for RPV. Dotted vertical lines represent the binning interval to compute the statistics for the observed and simulated data.

Source: Rilpivirine popPK report, page 16.

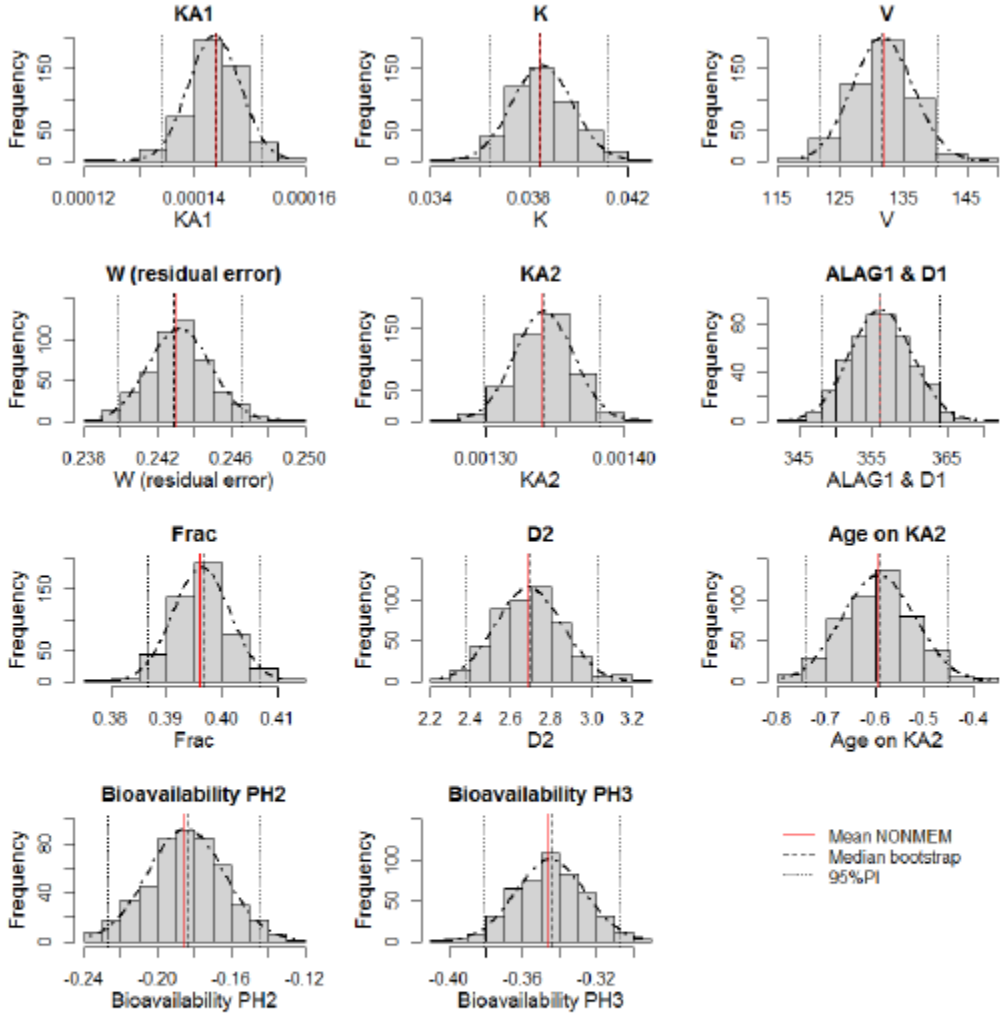
Figure 37. Prediction-Corrected VPC of the Final Rilpivirine PopPK Model for Phase 3 Studies



d1, day 1; IM, intramuscular; LA, long acting; Q4W, every 4 weeks; RPV, rilpivirine; VPC, visual predictive check.
The panel represents the full VPC profile after the first IM administration of RPV LA in the Phase 3 studies. Solid lines represent the median, 2.5th, and 97.5th percentiles of the simulated data with its 95% confidence interval (blue shaded area). Purple dashed lines represent the median, 2.5th, and 97.5th percentiles of the observed data for RPV. Dotted vertical lines represent the binning interval to compute the statistics for the observed and simulated data.

Source: Rilpivirine popPK report, page 17.

Figure 38. Bootstrap Results of the Final Rilpivirine PopPK Model



ALAG1 (h), lag time before the slow first-order absorption starts; age effect, age-dependent fast first-order absorption rate; *D1* (h), zero-order absorption duration via the slow absorption pathway; *D2* (h), zero-order absorption duration via the fast absorption pathway; *Frac*, fraction of the intramuscular dose absorbed via a fast absorption pathway; *K* (1/h), first-order elimination rate constant; *KA1* (1/h), slow first-order absorption rate constant; *KA2* (1/h), fast first-order absorption rate constant; PI, prediction interval; PH2, Phase 2; PH3, Phase 3; V, volume of distribution.

Dashed black line: median of the bootstrap; solid red line: NONMEM population mean; dotted black line: 95% PI of the bootstrap

Source: Rilpivirine popPK report, page 109.

RPV exposures were estimated following administration of CAB plus RPV in HIV-infected subjects (Table 130).

Table 130. Model-Predicted Rilpivirine Exposures Following Administration of Cabotegravir Plus Rilpivirine in HIV-Infected Subjects

Drug	Dosing Phase	Dose Regimen	Plasma RPV PK Parameter		
			$AUC_{0\text{-}tau}$ (ng•h/mL)	C_{max} (ng/mL)	C_{tau} (ng/mL)
RPV	Oral lead-in	25 mg PO once daily	2,227 (1,872, 2,649)	148 (128, 173)	78.8 (75.5, 82.2)
	Initial injection	900 mg IM initial dose	39,196 (37,893, 40,543)	139 (136, 142)	37.5 (36.3, 38.8)
	Monthly injection	600 mg IM monthly	65,603 (63,756, 67,503)	116 (113, 119)	82.2 (79.9, 84.6)

$AUC_{0\text{-}tau}$, area under the plasma concentration-time curve 4 weeks after IM dosing; C_{max}, maximum concentration; C_{tau}, RPV plasma concentration 4 weeks after IM dosing; HIV, human immunodeficiency virus; IM, intramuscular; PK, pharmacokinetic; PO, per os (oral); RPV, rilpivirine.

Oral lead-in PK parameter values represent steady state, monthly injection PK parameter values represent Week 48, and initial injection $AUC_{0\text{-}tau}$ and C_{max} values reflect a combination of RPV long acting + oral dosing because the initial injection was administered on the same day as the last oral dose.

PK parameter values were based on individual post-hoc estimates from the final population PK model for subjects enrolled in the Phase 3 Studies FLAIR (201584) and ATLAS (201585); data are presented as geometric mean (95% confidence interval)

For oral RPV 25 mg once daily, C_{tau} values are observed data from Phase 3 Studies FLAIR (201584) and ATLAS (201585), and $AUC_{0\text{-}tau}$ and C_{max} values are observed data from drug-drug interaction Study LAI116181.[19]

Source: Rilpivirine popPK report, page 14.

14.2.2.1. Effect of Intrinsic and Extrinsic Factors on RPV Exposure

The Applicant conducted analyses to evaluate the impact of intrinsic and extrinsic factors on RPV exposure. This analysis utilized the phase 3 study population and model-predicted exposures at week 8 and week 48.

The 5th percentile of AUC and C_{min} after the initial injection in phase 3 studies were used as targets for efficacy. In other words, intrinsic or extrinsic factors resulting in a significant share of the subgroup having exposures below the target would be of concern. RPV 5th percentile values are 20062 ng·h/mL for AUC and 17.3 ng/mL for C_{min}.

The Applicant proposed a RPV safety threshold C_{max} value of (b) (4) ng/mL. This is based on the observation that RPV was associated with QT prolongation at a supratherapeutic dose of 75 mg orally, where mean steady-state C_{max} was 635.7 ng/mL (TMC278-TiDP6-C131 CSR, page 100). RPV was not associated with QT prolongation at a therapeutic dose of 25 mg orally, where mean steady-state C_{max} was 229.4 ng/mL (TMC278-TiDP6-C151 CSR, page 82). Based on modeling the concentration-QT relationship from the two QT studies, no effect on QT was predicted if C_{max} increases 1.85-fold (and with 30% CV) compared to RPV 25 mg daily orally. The Applicant's calculations used (b) (4) (NDA 212888 SDN 19, page 5).

The only covariate in the RPV popPK model other than study phase was age. Study phase was not evaluated because this analysis is limited to the phase 3 population. The Applicant did not evaluate the fraction of subjects by age subgroup with exposure values below the efficacy target or above the safety target. In our analysis of RPV week 8 (end of dosing interval after the first injection) and week 48 (timepoint of the assessment of the primary virologic endpoint) model-

predicted PK parameters for phase 3 subjects, the fraction of subjects below efficacy targets or above the safety target did not significantly vary by age category (Table 131, Table 132).

Table 131. Fraction of Rilpivirine Phase Three Subjects With Week 8 Exposure Values Below the Efficacy Target or Above the Safety Target by Subgroup

Subgroup	Subjects With C_{max} >551 ng/mL	Subjects With AUC <20062 ng·h/mL	Subjects With C_{min} <17.3 ng/mL
Age <40 years	0/328 (0%)	21/328 (6.4%)	7/328 (2.1%)
Age 40– ≥60 years	0/235 (0%)	8/235 (3.4%)	7/235 (3.0%)
Age ≥60 years	0/18 (0%)	0/18 (0%)	0/18 (0%)
Total phase 3 population	0/581 (0%)	29/581 (5.0%)	14/581 (2.4%)

Source: Prepared by reviewer using phase 3 popPK parameter dataset (NDA 212888 SDN 20).

Table 132. Fraction of Rilpivirine Phase 3 Subjects With Week 48 Exposure Values Below the Efficacy Target or Above the Safety Target by Subgroup

Subgroup	Subjects With C_{max} >551 ng/mL	Subjects With AUC <20062 ng·h/mL	Subjects With C_{min} <17.3 ng/mL
Age <40 years	0/328 (0%)	3/328 (0.91%)	1/328 (0.43%)
Age 40– ≥60 years	0/235 (0%)	1/235 (0.43%)	1/235 (0.43%)
Age ≥60 years	0/18 (0%)	0/18 (0%)	0/18 (0%)
Total phase 3 population	0/581 (0%)	4/581 (0.69%)	2/581 (0.30%)

Source: Prepared by reviewer using phase 3 popPK parameter dataset (NDA 212888 SDN 20).

Reviewer comments:

RPV PopPK Model

The Applicant developed a two-compartment popPK model to describe the PK of RPV after IM administration to healthy and HIV-infected adults. Seven studies were included in the analysis. The dataset contained 18,261 samples from 986 subjects. Significant covariates included the effect of study phase on the slow and fast absorption pathways and the effect of age on the fast absorption pathway. While 5% of available samples were denoted as excluded by the Applicant, 727/964 (75%) were excluded because they were not intended for the analysis. A very small fraction (26 of 19,225 samples [~0.1%]) were excluded due to aberrant results and thus the number of excluded samples is not a concern.

Goodness of fit, VPC, and bootstrap results indicate adequate model performance. In addition, in individual subjects there is good general overlap between observed and individual predicted concentration-time profiles (RPV popPK report, pages 198 to 247).

Compared to observed PK parameters from individual studies, the RPV popPK AUC values appear comparable (Table 133).

Table 133. Rilpivirine AUC After Oral or LA Dosing in Selected Studies

RPV Regimen	Dose	Population	Statistics	RPV $AUC_{0-\tau)}$ (ng·h/mL)	Study/Source
25 mg QD orally	Steady-state	HIV-infected	Mean	2235	Edurant® labeling
600 mg LA Q4W×3	Steady-state	Healthy volunteers	Mean	52810	TMC278-C158

Source: Prepared by reviewer.
Abbreviations: LA = long-acting, QD = once daily, RPV = rilpivirine

The final model had adequate performance. Model-predicted PK parameters can be used to evaluate exposure-response relationships, the effect of intrinsic and extrinsic factors on exposure, and dosing recommendations for missed injections.

We disagree with the proposed RPV safety target of (b) (4) ng/mL. Reported RPV mean steady-state C_{max} from the thorough QT study was 229.4 ng/mL; when multiplied by 1.85 and 1.3 this results in a safety target of 551 ng/mL.

Effect of Intrinsic and Extrinsic Factors on RPV Exposure

Age was the only covariate identified as being associated with RPV exposure in the popPK model. No RPV dose adjustment is warranted based on age.

14.2.3. Exposure-Response Relationships for Efficacy

The Applicant conducted analyses of the phase 3 population to evaluate relationships between quartile (Q) of CAB and/or RPV exposure at week 8 (end of dosing interval after first IM injections) and week 48 (timepoint of the assessment of the primary virologic endpoint) and fraction of subjects with virologic failure (HIV-1 RNA ≥50 copies/mL) at week 48. Five hundred eighty-one subjects in phase 3 studies were included in the analysis dataset; of these, nine (1.5%) had virologic failure.

In univariate analyses, there was generally a numerical increase in failure rate with decreasing quartile of CAB and RPV exposure. For example, for each week 8 and week 48 CAB and RPV PK parameter (C_{max}, AUC, C_{min}), failure rate in Q1 was greater than failure rate in Q4 (Table 134). In a combined analysis taking into account both CAB and RPV exposure, the same pattern was observed. Specifically, for both week 8 and week 48 exposures, subjects with Q1 exposures for both drugs had a higher numerical failure rate than subjects with >Q1 exposures for both drugs. It is important to note that although higher proportions of subjects with HIV RNA ≥50 copies/mL were observed in Q1 of week 8 and week 48 CAB and RPV AUC and C_{min}, there does not appear to be a clear exposure-response relationship with greater than 90% of the subjects in the same quartile showing virologic success, suggesting that factors other than CAB and RPV exposures may also play a role.

The Applicant identified several limitations to these analyses:

- Exposures at the time of virologic failure were not used for this analysis because exposures after IM administration gradually increase to near steady-state by the week 48 efficacy endpoint. For this reason, subjects who discontinue prematurely due to virological failure would inherently have lower exposures than subjects who continued to week 48. This would confound any association between exposure and failure rate. Thus, predicted week 48 exposures were used for all subjects.
- The analysis does not account for ARV susceptibility at baseline.

Table 134. Week 48 Virologic Outcomes in Pooled Phase 3 Studies by Cabotegravir and PK Timepoint (Week 8)

		Cmax (µg/mL)			AUC (µg.h/mL)			Cmin (µg/mL)		
	n	Median	≥50 c/mL	<50 c/mL	Median	≥50 c/mL	<50 c/mL	Median	≥50 c/mL	<50 c/mL
Q1	146	6.06	2.1%	93.8%	911.14	4.8%	93.8%	0.85	4.8%	93.8%
Q2	145	7.36	2.8%	94.5%	1402.86	0.7%	95.2%	1.32	0	96.6%
Q3	145	8.64	0.7%	95.2%	1893.98	0	97.2%	1.80	0.7%	95.9%
Q4	145	10.51	0.7%	95.2%	2800.66	0.7%	92.4%	2.45	0.7%	92.4%

Source: Appendix Table 5.1

Source: NDA 212888 SDN 19, page 3.
Abbreviations: PK = pharmacokinetic

Table 135. Week 48 Virologic Outcomes in Pooled Phase 3 Studies by Cabotegravir and PK Timepoint (Week 48)

		Cmax µg/mL			AUC µg.h/mL			Cmin µg/mL		
	n	Median	≥50 c/mL	<50 c/mL	Median	≥50 c/mL	<50 c/mL	Median	≥50 c/mL	<50 c/mL
Q1	146	3.02	3.4%	95.2%	1776.51	2.7%	95.2%	1.99	2.7%	93.2%
Q2	145	3.91	2.1%	92.4%	2234.65	2.1%	93.1%	2.60	1.4%	95.9%
Q3	145	4.56	0	97.9%	2679.34	1.4%	95.2%	3.14	2.1%	93.1%
Q4	145	5.75	0.7%	93.1%	3258.50	0	95.2%	4.07	0	96.6%

Source: Appendix Table 5.1

Source: NDA 212888 SDN 19, page 3.
Abbreviations: PK = pharmacokinetic

Table 136. Week 48 Virologic Outcomes in Pooled Phase 3 Studies by Rilpivirine and PK Timepoint (Week 8)

	Cmax ng/mL				AUC ng.h/mL				Cmin ng/mL			
	n[1]	Median	≥50 c/mL	<50 c/mL	n	Median	≥50 c/mL	<50 c/mL	n	Median	≥50 c/mL	<50 c/mL
Q1	147	104	2.7%	91.2%	146	25271.5	4.1%	91.1%	147	23.4	4.8%	90.5%
Q2	146	131	2.1%	92.5%	145	36722	1.4%	93.8%	144	33.4	0.7%	95.8%
Q3	149	153	1.3%	96.0%	145	47948	0.7%	96.6%	145	42.0	0	96.6%
Q4	139	189	0	99.3%	145	64595	0	97.2%	145	57.8	0.7%	95.9%

Source: Appendix Table 5.1
1. Repeated parameter values (i.e., 'ties' in the data) at break points resulted in uneven distribution of subjects across quartiles

Source: NDA 212888 SDN 19, page 3.
Abbreviations: PK = pharmacokinetic

Table 137. Week 48 Virologic Outcomes in Pooled Phase 3 Studies by Rilpivirine and PK Timepoint (Week 48)

	Cmax ng/mL				AUC ng.h/mL				Cmin ng/mL			
	n	Median	≥50 c/mL	<50 c/mL	Median	≥50 c/mL	<50 c/mL	Median	≥50 c/mL	<50 c/mL
Q1	146	79.10	4.8%	91.8%	45037.5	4.8%	91.8%	56.16	3.4%	93.8%
Q2	145	106.98	0.7%	95.2%	60327	0.7%	95.2%	74.57	2.1%	92.4%
Q3	145	130.03	0	95.9%	73935	0	96.6%	91.81	0	95.9%
Q4	145	169.75	0.7%	95.9%	97320	0.7%	95.2%	122.25	0.7%	96.6%

Source: NDA 212888 SDN 19, page 3.
Abbreviations: PK = pharmacokinetic

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Table 138. Week 48 Virologic Outcomes in Pooled Phase 3 Studies by Quartile of Cabotegravir (CAB) and Rilpivirine and PK Timepoint (Week 8)

Cmax				AUC				Cmin			
	CAB (µg/mL)				CAB (µg.h/mL)				CAB (µg/mL)		
RPV (ng/mL)	Q1 (≤6.71)	>Q1 (>6.71)	Total	RPV (ng.h/mL)	Q1 (≤1181)	>Q1 (>1181)	Total	RPV (ng/mL)	Q1 (≤1.09)	>Q1 (>1.09)	Total
Q1 (≤119)	2/ 70 (2.9%)	2/ 77 (2.6%)	4/147 (2.7%)	Q1 (≤31623)	5/64 (7.8%)	1/82 (1.2%)	6/146 (4.1%)	Q1 (≤28.9)	6/67 (9.0%)	1/ 80 (1.3%)	7/147 (4.8%)
>Q1 (>119)	1/ 76 (1.3%)	4/358 (1.1%)	5/434 (1.2%)	>Q1 (>31623)	2/82 (2.4%)	1/353 (0.3%)	3/435 (0.7%)	>Q1 (>28.9)	1/ 79 (1.3%)	1/355 (0.3%)	2/434 (0.5%)
Total	3/146 (2.1%)	6/435 (1.4%)	9/581 (1.5%)	Total	7/146 (4.8%)	2/435 (0.5%)	9/581 (1.5%)	Total	7/146 (4.8%)	2/435 (0.5%)	9/581 (1.5%)

Source Appendix Table 5.3

Source: NDA 212888 SDN 19, page 4.
Abbreviations: PK = pharmacokinetic, RPV = rilpivirine

Table 139. Week 48 Virologic Outcomes in Pooled Phase 3 Studies by Quartile of Cabotegravir (CAB) and Rilpivirine and PK Timepoint (Week 48)

Cmax				AUC				Cmin			
	CAB (µg/mL)				CAB (µg.h/mL)				CAB (µg.h/mL)		
RPV (ng/mL)	Q1 (≤3.53)	>Q1 (>3.53)	Total	RPV (ng.h/mL)	Q1 (≤2040)	>Q1 (>2040)	Total	RPV (ng/mL)	Q1 (≤2.31)	>Q1 (>2.31)	Total
Q1 (≤93.74)	4/ 77 (5.2%)	3/ 69 (4.3%)	7/146 (4.8%)	Q1 (≤52811)	3/ 76 (3.9%)	4/ 70 (5.7%)	7/146 (4.8%)	Q1 (≤66.31)	2/ 70 (2.9%)	3/ 76 (3.9%)	5/146 (3.4%)
>Q1 (>93.74)	1/ 69 (1.4%)	1/366 (0.3%)	2/435 (0.5%)	>Q1 (>52811)	1/ 70 (1.4%)	1/365 (0.3%)	2/435 (0.5%)	>Q1 (>66.31)	2/ 76 (2.6%)	2/359 (0.6%)	4/435 (0.9%)
Total	5/146 (3.4%)	4/435 (0.9%)	9/581 (1.5%)	Total	4/146 (2.7%)	5/435 (1.1%)	9/581 (1.5%)	Total	4/146 (2.7%)	5/435 (1.1%)	9/581 (1.5%)

Source: NDA 212888 SDN 19, page 4.
Abbreviations: PK = pharmacokinetic, RPV = rilpivirine

Reviewer's comments: While we acknowledge the numerical association between exposure quartile and virologic failure rate in the univariate and two-drug analyses, response rates were >90% in all exposure quartile subgroups and the overall failure rate in the pooled phase 3 studies was 1.5%. Thus the association between exposure and failure rate is not clinically significant.

We also acknowledge a general limitation to exposure-response analyses, which is that subjects were not randomized by exposure and thus we cannot conclude that exposure is a causative factor for virologic failure rate.

Conclusion

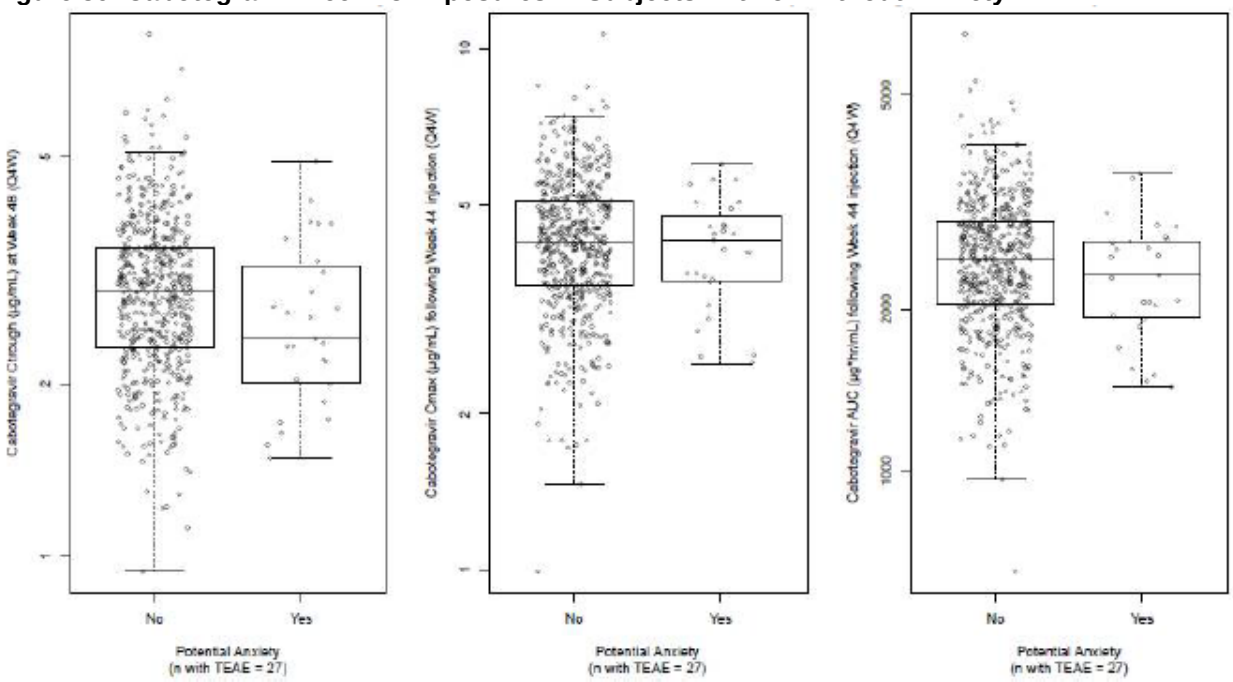
The overall failure rate in pooled phase 3 studies was 1.5% and response rate was >90% in all CAB and/or RPV exposure quartile subgroups. The observed numerical association between lower CAB and/or RPV exposure quartile and higher virologic failure rate is not clinically significant.

14.2.4. Exposure-Response Relationships for Safety

During the review, various AEs of interest were investigated to determine if CAB or RPV exposures differed in subjects with or without the AE. Investigated AEs included anxiety, depression, pancreatitis, pyrexia, sleep disorder and weight gain. The study population included subjects enrolled in phase 3 studies. The Applicant's analyses (all events except weight gain)

evaluated week 48 PK parameters in subjects with or without each event. Our analysis of weight gain compared concentration-time data stratified by subjects with or without weight gain (defined as increase of ≥5% from baseline to week 48). No exposure differences were observed between subjects with or without each AE (representative Figure 39 is shown for the relationship between CAB exposure and anxiety; plots for CAB and RPV for other AEs were similar and are not shown).

Figure 39. Cabotegravir Week 48 Exposures in Subjects With or Without Anxiety



Source: NDA 212888 SDN 17, page 27.
Abbreviations: Q4W = every 4 weeks, TEAE = treatment-emergent adverse event

14.2.5. Simulations to Support Dosing Recommendations for Missed Injections

Proposed labeling states the following:

- CAB and RPV injections should be taken monthly ±7 days. If a patient plans to miss an injection by >7 days, oral CAB and RPV can be used to replace up to two consecutive missed injections.
- If the time since last injection is <2 months, continue maintenance IM dosing
- If the time since last injection is ≥2 months, re-initiate IM therapy with loading doses

PK simulations were used to evaluate the proposed dosing for missed injections under two scenarios:

- No oral dosing between missed injections (unplanned missed injections)
- Oral dosing between missed injections (planned missed injections)

Missed CAB Injections

Dosing recommendations for missed injection were based on ensuring that most subjects exceed the 5th percentile of C_{min} after the initial injection in phase 3 studies (0.65 µg/mL) and that most subjects do not exceed the median CAB C_{max} value associated with CAB 60 mg orally in study LAI116482 (13.1 µg/mL).

Reviewer's comments: In exposure-response analyses for efficacy, the relationship between exposure quartile and virologic response rate was approximately the same for both C_{min} and AUC (Section 14.2.3). For this reason, it is acceptable that missed dosing scenarios evaluated C_{min} only as an efficacy target.

The lowest CAB concentrations was observed at the end of the dosing interval after the loading dose. Therefore, a missed second injection was used to determine general recommendations for any missed injection.

Planned Missed Injection (Oral Dosing to Replace Up to Two Consecutive Monthly Injections)

When oral dosing is used between planned missed injections, excessive exposures to CAB during oral bridging is a concern as oral exposures are added to residual exposures from previous injections. The simulations evaluating oral bridging between injections evaluated oral bridging when an injection was missed by 4 or 8 weeks. After 600 mg IM on week 0 and 400 mg IM every 4 weeks on weeks 0 through 12, oral bridging on weeks 12 through 16, and a maintenance dose of 400 mg IM on week 16, <5% of subjects exceeded 13.1 µg/mL during oral bridging. Similarly, when the proposed regimen was given on weeks 0 through 12, oral bridging on weeks 12 to 20, and a loading dose of 600 mg IM given on week 20, <5% of subjects exceeded 13.1 µg/mL during oral bridging (Figure 4, Figure 5).

Unplanned Missed Injection

When a loading dose injection (600 mg) was given on week 0, and a second injection of 400 mg (maintenance dose) was given on week 8 (four week delay), C_{min} at week 12 (C_{min} following the second injection) in <5% of subjects were below 0.65 µg/mL. When a loading dose injection (600 mg) was given on week 0, and a second injection of 600 mg was given on week 12 (eight week delay), C_{min} at week 16 (C_{min} following the second injection) in <5% of subjects were below 0.65 µg/mL (Figure 8, Figure 9).

Missed RPV Injections

Dosing recommendations for missed injection were based on ensuring that most subjects exceed the 5th percentile of C_{min} after the initial injection in phase 3 studies (17.3 ng/mL) and that most subjects do not exceed the highest RPV C_{max} value predicted to have no effect on the QT interval (551 ng/mL).

Reviewer's comments: In exposure-response analyses for efficacy, the relationship between exposure quartile and virologic response rate was approximately the same for both C_{min} and AUC (Section 14.2.3). For this reason, it is acceptable that missed dosing scenarios evaluated C_{min} only as an efficacy target.

Planned Missed Injection (Oral Dosing to Replace Up to 2 Consecutive Monthly Injections)

The simulations evaluated oral bridging when an injection was missed by 4 or 8 weeks. After 900 mg IM on week 0 and 600 mg IM every 4 weeks on weeks 4 through 16, oral bridging on weeks 16 through 20, and a maintenance dose of 400 mg IM on week 20, <5% of subjects exceeded 551 ng/mL during oral bridging. Similarly, after 900 mg IM on week 0 and 600 mg IM every 4 weeks on weeks 4 through 16, oral bridging on weeks 16 through 24, and a loading dose of 900 mg IM on week 24, <5% of subjects exceeded 551 ng/mL during oral bridging (Figure 6, Figure 7).

Unplanned Missed Injection

The lowest RPV concentrations were observed at the end of the dosing interval after the loading dose. Therefore, a missed second injection was used to determine general recommendations for any missed injection. When a loading dose injection (900 mg) was given on week 0, and a second injection of 600 mg (maintenance dose) was given on week 8 (four-week delay), <5% of subjects were below 17.3 ng/mL at week 12 (C_{min} following second injection). When 900 mg was given on week 0, and a second injection of 900 mg was given on week 12 (eight-week delay), <5% of subjects were below 17.3 ng/mL at week 16 (C_{min} following second injection) (Figure 10, Figure 11.

Reviewer's comments

We agree with proposed labeling for missed CAB or RPV injections:

- ***CAB and RPV injections should be taken monthly ±7 days. If a patient plans to miss an injection by >7 days, oral CAB and RPV can be used to replace up to two consecutive missed injections.***
- ***If the time since last injection is <2 months, continue maintenance CAB and RPV IM dosing***
- ***If the time since last injection is ≥2 months, re-initiate CAB and RPV IM therapy with loading doses followed by CAB and RPV monthly injection schedule.***

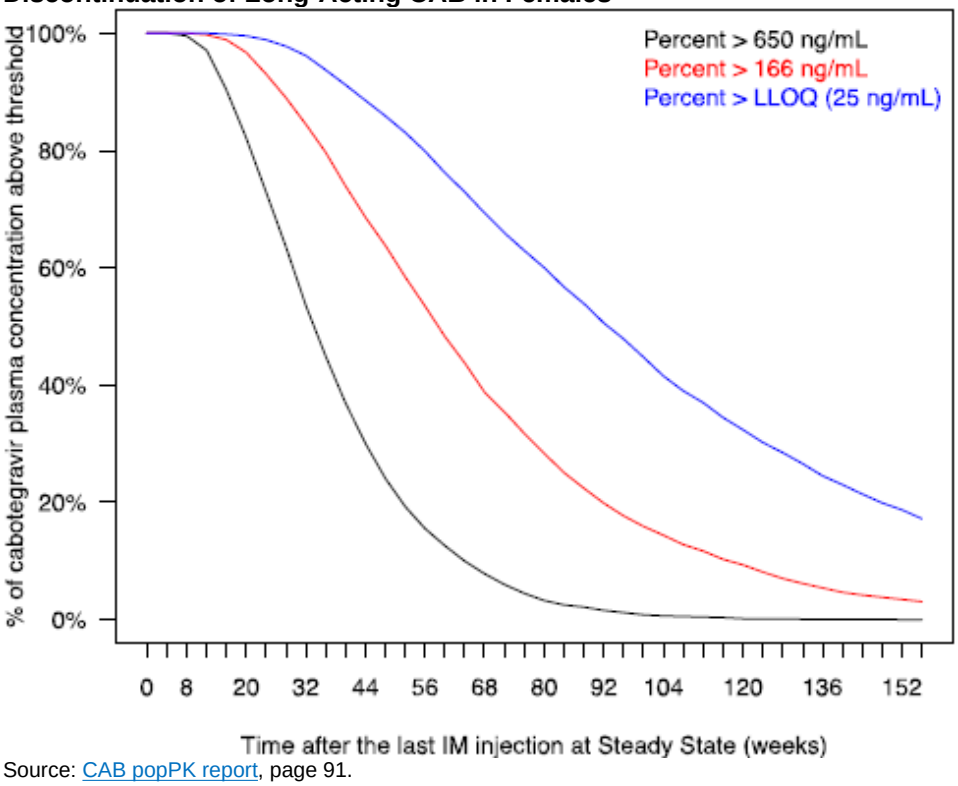
14.2.6. Residual CAB and RPV Exposures After Discontinuation

Due to slow absorption following IM administration, residual CAB and RPV exposures following discontinuation of the regimen are expected to be detectable in the systemic circulation for more three years after the last injections (Section II.7.7.2).

The predicted median time to CAB concentrations BQL after discontinuation is ~96 weeks for females (Figure 40), ~44 weeks for males (Figure 41) and ~182 weeks (42 months) for RPV regardless of sex (Figure 42). Observed concentrations from clinical studies were modeled and simulations of the model were used to predict the time to undetectable concentrations after discontinuation. The underlying observed concentrations used for model-building included a sizable number of observed concentrations from samples taken 6 to <18 months postdose for CAB and 6 to <12 months postdose for RPV (Table 45, Table 46). At timepoints greater than 6 months postdose, the fraction of samples with detectable concentrations of CAB ranged from

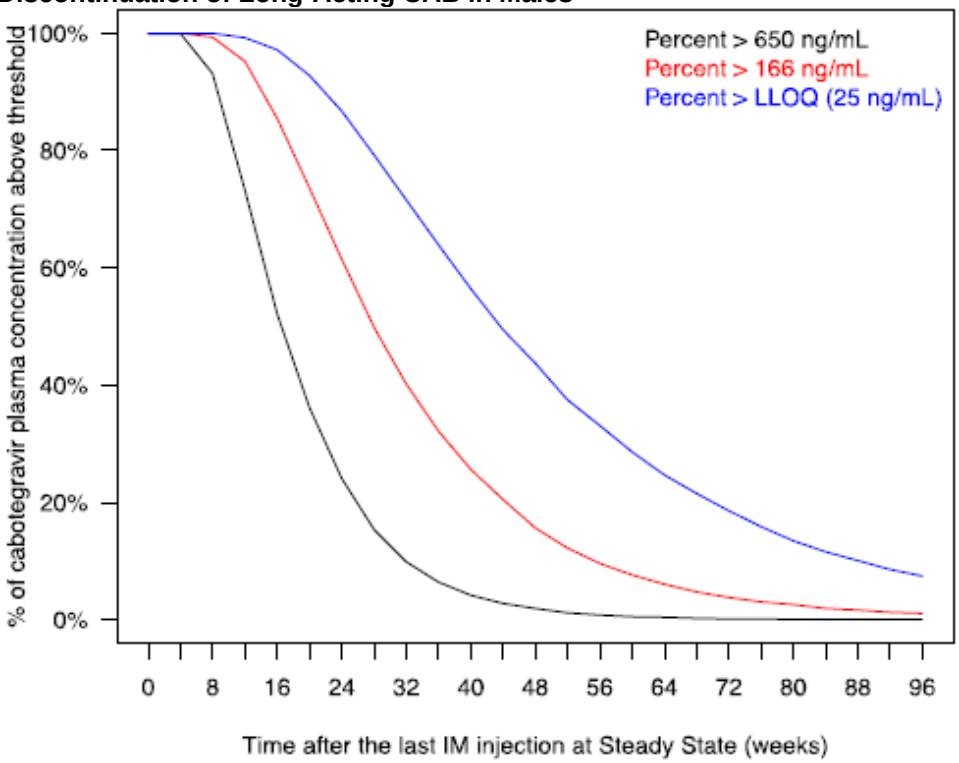
43% to 83% in females and 18% to 34% in males (Table 45). All observed RPV concentrations collected up to 12 months postinjection were detectable (Table 46).

Figure 40. Predicted Time to Undetectable Cabotegravir (CAB) Exposure Following Discontinuation of Long-Acting CAB in Females



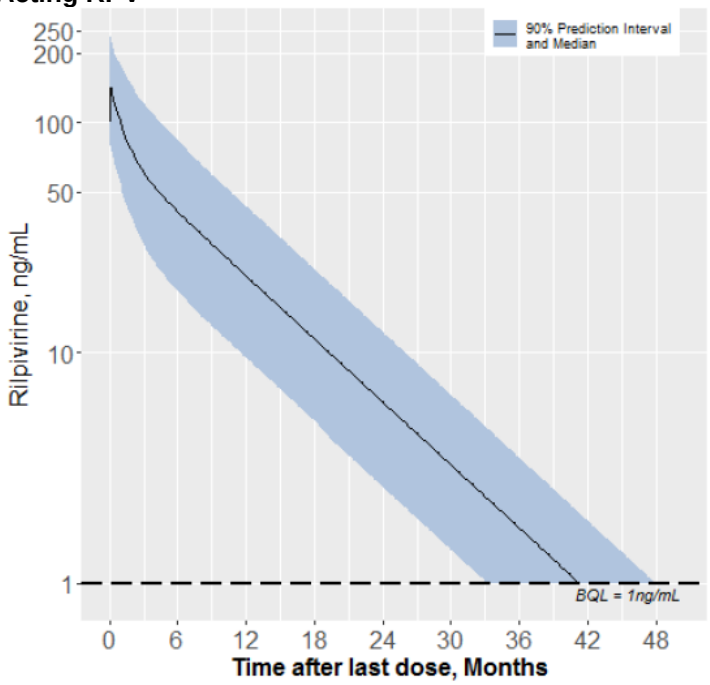
Source: CAB popPK report, page 91.
Abbreviations: IM = intramuscular, LLOQ = lower limit of quantification

Figure 41. Predicted Time to Undetectable Cabotegravir (CAB) Exposure Following Discontinuation of Long-Acting CAB in Males



Source: CAB popPK report, page 148.
Abbreviations: IM = intramuscular, LLOQ = lower limit of quantification

Figure 42. Predicted Time to Undetectable Rilpivirine (RPV) Exposure Following Discontinuation of Long-Acting RPV



BQL, below the quantification limit; Q4W, every 4 weeks; RPV, rilpivirine.
Source: RPV popPK report, page 137.

14.3. Physiologically-Based Pharmacokinetics Review

14.3.1. Executive Summary

CAB is primarily metabolized by UGT1A1 with a secondary contribution by UGT1A9. In vitro, CAB is an inhibitor of transporters OAT1 and OAT3. Based on results of basic static and mechanistic static models, further investigation of CAB as an OAT1/3 inhibitor was warranted. In lieu of human DDI studies, the Applicant conducted PBPK modeling to evaluate 1) the effect of CAB on the PK of OAT1/3 substrates and 2) the effect of UGT1A1/9 inhibitors on the PK of CAB.

PBPK modeling was verified for interactions mediated by OAT1/3 or UGT1A1 by comparing simulated versus observed results from DDI studies. PBPK modeling could not be verified for interactions mediated by inhibition of UGT1A9.

In PBPK modeling using measured CAB K_i values for inhibition of OAT1 and OAT3, no significant impact on the PK of OAT1/3 substrates was predicted. However, there is inherent uncertainty in vitro K_i values for transporter inhibition. Using sensitivity analyses, the review team predicted that CAB may increase exposures of OAT1/3 substrates (geometric mean AUC ratios of up to 1.8-fold when CAB K_i for OAT1/3 inhibition is reduced by 15-fold to account for the uncertainty typically associated with estimating Ki in vitro). Final labeling in section 12.3 states “cabotegravir may increase the AUC of OAT1/3 substrates up to approximately 80%”.

Using measured values and sensitivity analysis for atazanavir (ATV, known UGT1A1 inhibitor) K_i for inhibition of UGT1A1 and CAB fraction metabolized by UGT1A1, no significant impact of ATV on CAB is expected (CAB geometric mean AUC ratio of ≤1.9). We agree with proposed labeling which states that no clinically relevant interaction is expected between CAB and a UGT1A1 inhibitor.

14.3.2. Background

In vitro, CAB inhibited renal transporters OAT1 (K_i =0.405µM) and OAT3 (K_i =0.205µM). Based on the draft FDA guidance for industry *In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies* (December 2017),[26] the $I_{max,u}/IC_{50}$ values for OAT1 and OAT3 transporters exceeded 0.1 (values were 0.23 and 0.45, respectively, using phase 3 geometric mean CAB C_{max} =18.7µM and f_u =0.01), therefore a mechanistic static model (report 2015N258625) was used to quantify the potential drug interaction. This model showed CAB has low risk of perpetrator drug interactions with OAT substrates (predicted AUC change <1.26-fold). However, in sensitivity analyses where CAB fraction unbound was increased 5-fold or CAB C_{max} was increased 5-fold, predicted substrate AUC ratios were 2.0. The Applicant decided to further investigate CAB OAT1/3 inhibition using PBPK.

The Applicant conducted PBPK modeling to predict 1) the effect of CAB on the PK of OAT1/3 substrates and 2) the effect of UGT1A1/9 inhibitors on the PK of CAB. For both applications, the ability of PBPK modeling to recover the results of clinical DDI studies not involving CAB was evaluated firstly. PBPK modeling was then used to prospectively assess the interaction potential with CAB.

This review evaluates the adequacy of the PBPK modeling and the Applicant's proposed labeling statements that (b) (4)

14.3.3. Methods

Model Development

PBPK analysis was conducted using Simcyp® version 17 release 1 by both the Applicant and FDA reviewer.

CAB

The CAB PBPK model was developed and verified using in vitro, human PK and mass balance data. The Advanced Dissolution, Absorption, and Metabolism model was used to predict CAB absorption. A minimal PBPK model with single adjusting compartment was selected based on the ability to recover the PK profile of CAB after oral administration of a 30-mg dose. The CAB fraction unbound was determined from ex vivo and in vitro data. UGT1A1/9 intrinsic clearance values for metabolism of CAB were obtained from incubations of CAB with recombinant enzymes. In a mass balance study, renal elimination of unchanged CAB was <1% of the dose administered. CAB final model parameters and their sources are summarized in Table 140. CAB K_i values for inhibition of OAT1 and OAT3 were obtained from in vitro studies where IC_{50} was

measured (K_i was assumed to be equal to $IC_{50}/2$). CAB unbound fraction in the in vitro cell systems was not determined.

Table 140. Cabotegravir (CAB) PBPK Model Parameters

Parameter	Value	Source
Phys Chem and Blood Binding		
Molecular Weight (g/mol)	405.4	$C_{19}H_{17}F_2N_3O_5$ 2015N258625_00
Log P	1.58	Measured value; ELNB N8561-30
Compound type	Monoprotic Acid	Measured value; ELNB N8561-30
pKa1	7.71	
Blood/Plasma ratio (B/P)	0.54	RH2009/00003/07
Fraction unbound (Fu)	0.006	Measured value (Average value from Clinical and in vitro reports); RH2009/00003/07
Absorption		**ADAM**
Papp MDCK (10^{-6} cm/s)	25.6	RH2009/00003/07
Dissolution profile	For (b) (4) tablet formulation	Measured value: (b) (4) experiment EXP173305
Distribution		
Distribution model	Minimal PBPK model	
SAC kin (1/h)	0.03	Optimized
SAC kout (1/h)	0.07	
Vss (L/kg)	(Predicted) 0.12	Vss predicted by Simcyp® using Method 2

Parameter	Value	Source
Scalar	1.5	
Elimination		**Enzymatic**
UGT1A1 CL_{int} (µL/min/mg)	4.5	Bowers et al. 2016
UGT1A9 CL_{int} (µL/min/mg)	2.2	
Fu,mic	0.5	Optimized
Interaction		
OAT1 Ki (µM)	0.405	RH2009/00003/07
OAT3 Ki (µM)	0.205	
UGT1A1 Ki (µM)	6.0	
(b) (4)		

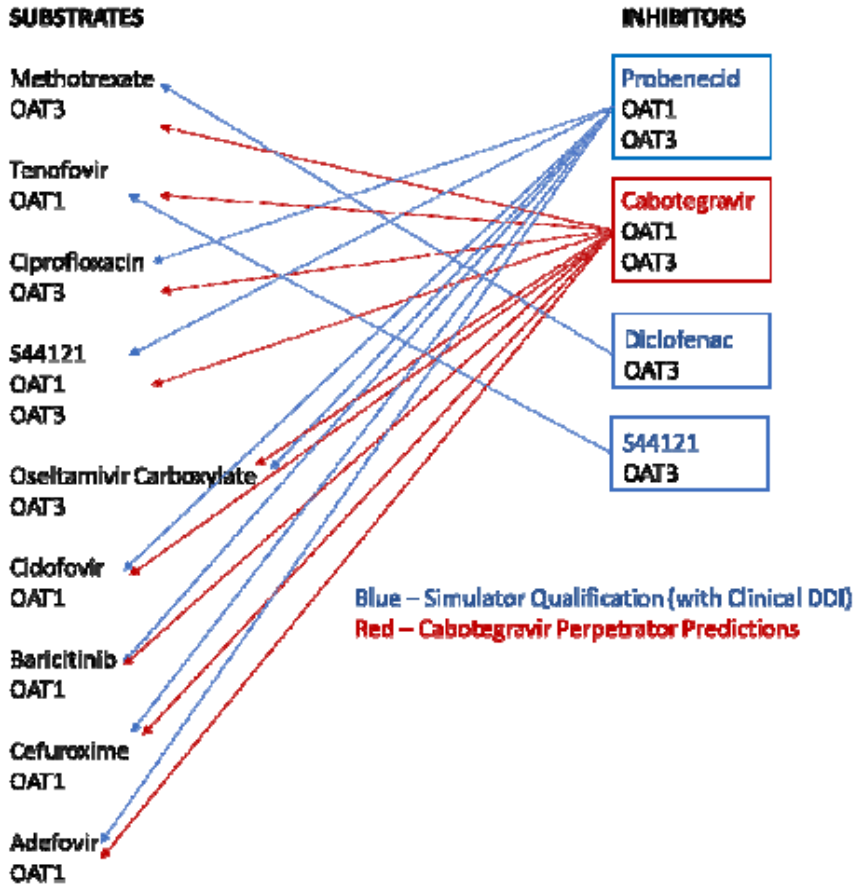
Source: Page 25, CAB PBPK report.

Of note, model parameters from CAB compound file V17 2018 were reported in the Applicant's PBPK report and this file was used for most simulations. For unknown reasons, a different CAB compound file (named V17 KST) was used by the Applicant for simulations of CAB repeat dose study (study 205712) and for DDI studies with baricitinib and oseltamivir. The reviewer verified the model files and used CAB compound file V17 2018 for all simulations.

OAT1/3 Substrates and Inhibitors

In order to qualify the substrate models for OAT1/3, the Applicant retrospectively predicted interactions between nine OAT1 and/or OAT3 substrates (methotrexate, tenofovir, ciprofloxacin, S44121, oseltamivir, cidofovir, baricitinib, cefuroxime and adefovir) and three OAT1 and/or OAT3 inhibitors (ibuprofen, diclofenac and probenecid)) for which observed clinical DDI data were available (Figure 43). The Applicant relied on PBPK models for OAT1/3 substrates and inhibitors described in published literature. The reviewer evaluated whether sufficient information regarding the source of model parameters were published and/or available from a Simcyp® compound file report. Using the literature, the reviewer also evaluated the specificity of compounds for OAT1 versus OAT3.

Figure 43. OAT1/3 Interactions Evaluated by the Applicant

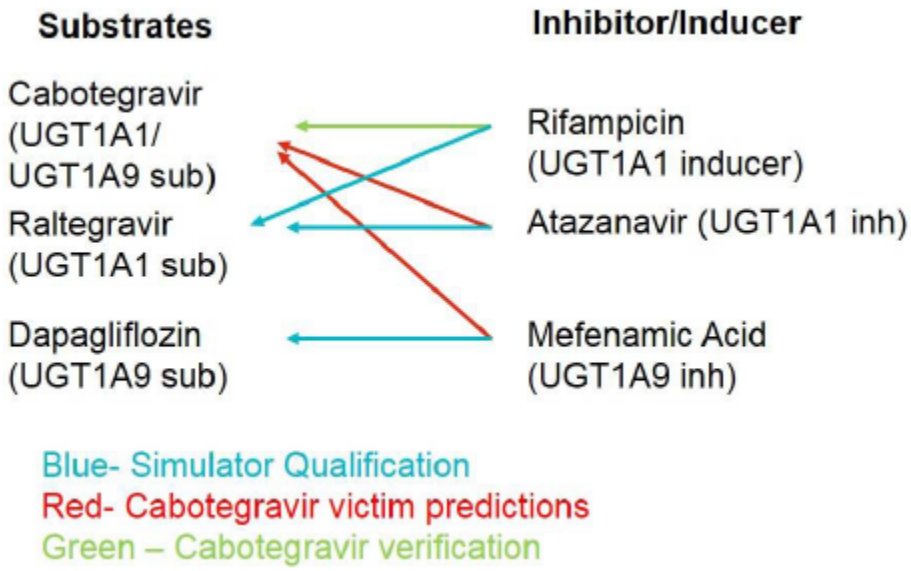


Source: page 39, CAB PBPK report.
Abbreviations: DDI = drug-drug interaction

UGT1A1/9 Substrates and Inhibitors

In order to qualify the perpetrator models for UGT1A1/9, the Applicant retrospectively predicted interactions between UGT1A1/9 substrates RAL and dapagliflozin and UGT1A1/9 inhibitors (ATV and mefenamic acid) and inducers (rifampicin) for which observed clinical DDI data were available (Figure 44).

Figure 44. UGT1A1/9 Interactions Evaluated by the Applicant



Source: page 40, CAB PBPK report.

The reviewer evaluated whether sufficient information regarding the source of model parameters were published and/or available from a Simcyp® compound file report. Using the literature, the reviewer also evaluated the specificity of compounds for UGT1A1 versus UGT1A9.

Model Verification

Compound files were verified by comparing simulated substrate AUC ratios with those observed in clinical DDI studies (CAB PK: Table 141; OAT1/3 substrates and inhibitors: Table 142; UGT1A1/9 substrates and inhibitors: Table 143). Note tables Table 142 and Table 143 are limited to the subset of compounds where we could verify the source of model parameters.

Table 141. Clinical Study Designs of Studies Used for Cabotegravir (CAB) Model Verification

Drug	N (No. of Subjects in trial)	Age Range Mean (SD)	Ratio of Females in study	Dose Regimen	Reference – Clinical study report
Cabotegravir	15	48.5 (14.11)	0.33	Single oral dose of 30 mg Cabotegravir in healthy volunteers	LAI117010 control arm
	8	56.9 (6.17)	0.25	Single oral dose of 30 mg Cabotegravir in healthy volunteers	201479
	8	52.3 (11.27)	0.25	Single oral dose of 30 mg Cabotegravir in healthy volunteers	201480
	8	55.6 (11.12)	0.25	Single oral dose of 30 mg Cabotegravir in severe renally impaired patients	201480
	15	43.7 (10.51)	0	Multiple dose of CAB 30 mg QD for 14 days in healthy adult male volunteers	205712
	20	26.5 (5.64)	1	Cabotegravir 30 mg QD dosed daily for 11 days in healthy adult female volunteers co-administered with microgynon.	LAI117011
Cabotegravir-Rifampin	15	48.5 (14.11)	0.33	Rifampin was administered once a day daily at 600 mg orally and single oral dose of 30 mg CAB was co-administered on day 14.	LAI117010 DDI arm
Cabotegravir in UGT1A1 Poor metabolisers	10	20 – 50 years (range)	0.5	Single oral dose of 30 mg Cabotegravir in healthy volunteers with Normal Metabolisers UGT1A1(Simcyp® default) or Poor Metabolizers	Clinical data for comparison from Clinical study 2016N297524_00 (205162)

Source: CAB PBPK report, page 27.
Abbreviations: DDI = drug-drug interaction, QD = once daily, SD = standard deviation

Table 142. Study Designs for Clinical OAT1/3 DDI Studies Considered in the FDA Analyses

Study (Substrate-Inhibitor)	Population	Substrate Dosing	Inhibitor Dosing	Reference
Adefovir-probenecid	Japanese healthy adults	Single dose 10 mg PO 2h after inhibitor	Single dose 1500 mg PO	PMID 24747579[27]
Baricitinib-probenecid	Healthy adults	Single dose 4 mg PO 1h after AM inhibitor dose on day 3	1000 mg PO Q12h for 5 days	PMID 28749581[28]
Methotrexate-probenecid (MTX)	Adult cancer patients	200 mg/m^2 IV bolus	500 mg PO before and 1h and 5h after MTX **or** 500 mg IV 15 min before MTX **or** 1000 mg IV 1h before MTX	PMID 638616[29]
Oseltamivir-probenecid	Healthy adults	Single dose 150 mg 1h before inhibitor on day 2	500 mg PO Q6h for 4 days	PMID 11744606[30]

Source: Prepared by reviewer from CAB PBPK report, page 27.
Abbreviations: DDI = drug-drug interaction, IV = intravenous, Q6h = every 6 hours, Q12h = every 12 hours, PO = by mouth

Table 143. Study Designs for Clinical UGT1A1/9 DDI Studies Considered in the FDA Analyses

Study (Substrate-Inhibitor)	Population	Substrate Dosing	Inhibitor Dosing	Reference
Raltegravir-atazanavir	Healthy adults	Single dose 1200 mg PO on day 7	400 mg PO QD for 9 days	PMID 27696440[31]

Source: Prepared by reviewer from CAB PBPK report, page 21.
Abbreviations: DDI = drug-drug interaction, PO = by mouth, QD = once daily

Model Application

Predicted Effect of CAB on the PK of Substrates of OAT1/3

DDI studies were simulated to evaluate the effect of CAB on OAT1/3 substrates. All of these simulations used the Sim-Healthy Volunteers population, an age range of 20 to 50 years, and 50% female population (Table 144). Due to uncertainty in CAB K_i values for inhibition of OAT1/3, the reviewer conducted sensitivity analyses using K_i values up to 15-fold lower than the measured values.

Table 144. Study Designs for Simulated DDIs Between OAT1/3 Substrates and Cabotegravir (OAT1/3 Inhibitor).

Substrate	Substrate Dosing	CAB Dosing	Population Size
Adefovir	Single dose 10 mg PO 2h after CAB on day 7	30 mg PO daily for 9 days	200
Baricitinib	Single dose 4 mg PO 1h after CAB on day 7	30 mg PO daily for 9 days	100
Methotrexate	Single dose 0.156 mg/kg PO 2h after CAB on day 10	30 mg PO daily for 14 days	100
Oseltamivir	Single dose 150 mg PO 1h before CAB on day 7	30 mg PO daily for 9 days	100

Source: Prepared by Reviewer
Abbreviations: CAB = cabotegravir, DDI = drug-drug interaction, PO = by mouth

Predicted Effect of UGT1A1/9 Inhibitors on the PK of CAB

DDI studies were simulated to evaluate the effect of UGT1A1/9 inhibitors on CAB. All of these studies used the Sim-Healthy Volunteers population with 50% of the population being female (Table 145).

The reviewer performed sensitivity analyses to evaluate the impact of a 10-fold reduction in ATV UGT1A1 inhibition (measured K_i =1.9µM) on the DDI with CAB. Unbound fraction of ATV in the incubation ($f_{u,inc}$ =0.406) was unchanged.

The reviewer also evaluated the impact of altered CAB fraction metabolized by UGT1A1 ($f_{m,UGT1A1}$) on the DDI with ATV. This was done by altering intrinsic clearance values for UGT1A1 ($CL_{int,UGT1A1}$) and UGT1A9 ($CL_{int,UGT1A9}$) to compare $f_{m,UGT1A1}$ values of 0.62 and 0.96.

Table 145. Simulated DDIs Between Cabotegravir (UGT1A1/9 Substrate) and UGT1A1/9 Inhibitors

CAB Dosing	Inhibitor	Inhibitor Dosing	Population Size	Age Range (Years)
Single dose 30 mg PO on day 7	Atazanavir	400-mg PO daily for 9 days	140	19-55
Single dose 30 mg PO on day 2	Mefenamic acid	500-mg loading dose on day 1 then 250 mg Q6h for 4 days	320	25-55

Source: Prepared by Reviewer
Abbreviations: CAB = cabotegravir, DDI = drug-drug interaction, PO = by mouth

14.3.4. Results

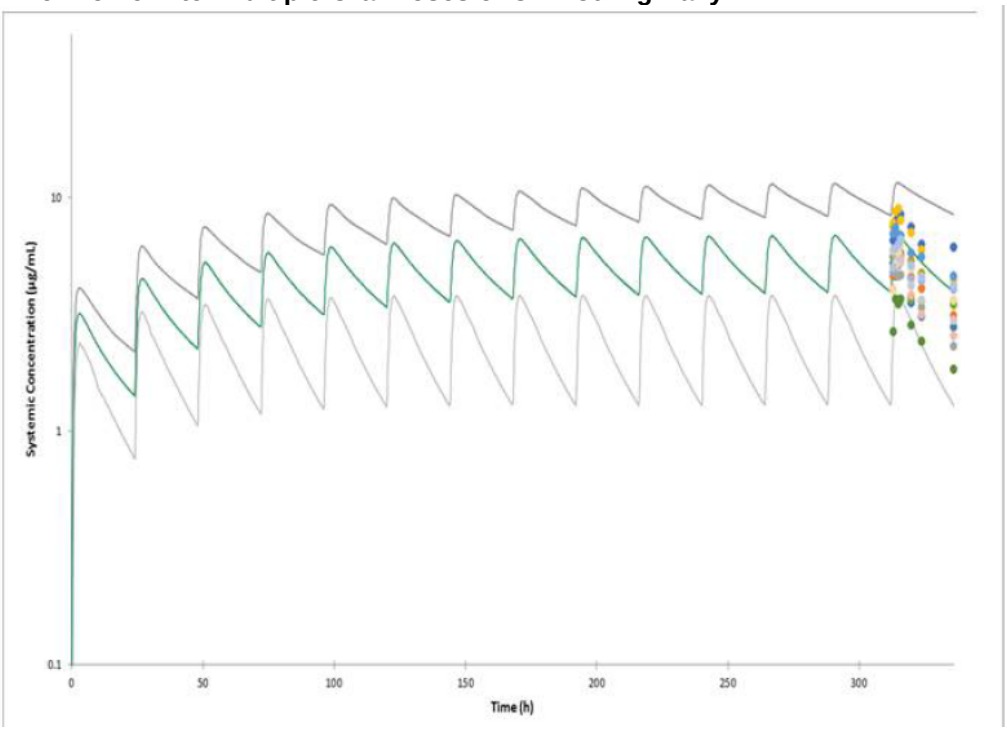
Q1. Can PBPK Analyses Provide a Reasonable Description of the PK of CAB?

Yes, PBPK simulations reasonably described the PK profile of CAB following single (data not shown) and multiple oral dose administration (30 mg) in healthy subjects (Figure 45).

In vitro UGT reaction phenotyping study showed that relative contributions (f_m) of UGT1A1 and UGT1A9 to the overall metabolism of CAB were 67% and 23%, respectively. In vitro UGT intrinsic clearance (CL_{int}) values of 4.5 µL/min/mg and 2.2 µL/min/mg, for UGT1A1 and UGT1A9, respectively, were directly incorporated in CAB PBPK model. The model accounts for the relative contribution for hepatic UGT1A1 and UGT1A9 to be 58% and 34%, respectively, to the systemic clearance of CAB. Since UGT metabolism also occurs in the kidney, the relative contribution of UGT1A1 and UGT1A9 clearance in the kidney was predicted to be 4% and 3%, respectively, using the software default scaling factor.

The relative contribution of UGT1A1 to CAB clearance was verified against clinical PK data available from UGT1A1 poor metabolizer phenotype subjects (study 2016N297524_00). Following a 30 mg single oral dose of CAB, the CAB PBPK model accurately predicted the 41% increase in CAB exposure in the UGT1A1 poor metabolizer population compared to UGT1A1 wild-type subjects, (observed and predicted AUC geometric mean ratio =1.41); C_{max} was predicted less well (predicted to observed of 0.81).

Figure 45. Simulated (Lines) and Observed (Symbols) Cabotegravir (CAB) Plasma Concentration-Time Profile After Multiple Oral Doses of CAB 30 mg Daily



Source: CAB PBPK report, page 43.

There was generally good agreement between observed and predicted CAB PK parameters. The ratio of predicted to observed PK parameters ranged from 0.78 to 1.33 (Table 146, Table 147).

Table 146. Simulated vs. Observed Oral Cabotegravir (CAB) PK Parameters in Single Dose Clinical Studies

Study Ref	AUC (0-inf) h.ug/mL Geometric Mean (5th-95th percentile)		Cmax (µg/mL) Geometric Mean (5th-95th percentile)		CL (L/h) Geometric Mean (5th-95th percentile)		T-half (h) Geometric Mean (5th-95th percentile)		Vd/F (L/Kg) Geometric Mean (5th-95th percentile)	
	Observed	Simulated	Observed	Simulated	Observed	Simulated	Observed	Simulated	Observed	Predicted
LAI117010 30 mg PO SD Healthy Volunteers	146 (128, 167)	114 (56, 238)	3.6 (3.3, 4.0)	3.2(2.5, 4.3)	0.21 (0.18, 0.23)	0.28 (0.15, 0.54)	39 (36, 42)	34 (20, 66)	NR	0.12 (0.11, 0.13)
201479 30 mg PO SD Healthy Volunteers	127 (95, 170)	132 (68, 276)	3.6 (2.9, 4.3)	3.2 (2.4, 4.2)	0.24 (0.18, 0.32)	0.24 (0.13, 0.45)	37 (33, 42)	39 (24, 72)	0.15	0.12 (0.11, 0.14)
201480 30 mg PO SD Healthy Volunteers	140 (116, 170)	122 (60, 247)	3.4 (3.0, 3.8)	3.2 (2.4, 4.3)	0.21 (0.18, 0.26)	0.26 (0.14, 0.50)	42 (37, 45)	36 (21, 70)	0.15	0.12 (0.11, 0.14)

Source: CAB PBPK report, page 29.
Abbreviations: PK = pharmacokinetic, PO = by mouth, SD = standard deviation

Table 147. Simulated vs. Observed Oral Cabotegravir (CAB) PK Parameters in Multiple Dose Clinical Studies

Study	AUC (0-t) h.µg/mL		Cmax (µg/mL)		CL (L/h)	
Geometric Mean (5th-95th percentile)	Observed[1]	Simulated	Observed	Simulated	Observed	Simulated
205712 Cab 30 mg QD Repeat Dose PK from day 14 in healthy adults	104 (87, 124)	109 (54, 230)	6.4 (5.5, 7.4)	6.2 (3.7, 11.0)	0.29 (0.24, 0.34)	0.28 (0.13, 0.55)
LAI117011 Cab 30 mg QD Repeat Dose PK from Day 11 in healthy female adults	133 (121, 148)	120 (59, 261)	7.8 (7.1, 8.6)	7.0 (4.2, 12.8)	NR	0.25 (0.11, 0.50)

NR – Not Reported.

1. Geometric Mean (95% CI)

Source: CAB PBPK report, page 31.
Abbreviations: CL = Clearance, PK = pharmacokinetic, QD = once daily

Q.2. Can PBPK Analysis be Used to Predict the Inhibitory Potential of CAB on OAT1/3 Substrates?

Yes, PBPK analysis can be used predict the effect of CAB inhibition on the exposure of OAT1/3 substrates.

The Applicant did not adequately document internal verification of model development and qualification of the compounds used in the submission. In a literature search to verify the source of model parameters, the reviewer found insufficient information from publications and/or a Simcyp® report for tenofovir, ciprofloxacin, S44121, cidofovir, cefuroxime and diclofenac. Therefore, our analyses focused on the compounds with sufficient information, which were adefovir, baricitinib, methotrexate, oseltamivir and probenecid (Table 148).

With the exception of baricitinib, the reviewer was able to verify the specificity of substrates for OAT1 versus OAT3 (Table 148) For baricitinib, we conducted simulations of clinical DDI studies with transport assigned to OAT3 (the Applicant's analyses (b) (4) based on the reasoning provided in the table below.

Table 148. Specificity of OAT1/3 Substrates and Inhibitors Considered in the PBPK Analyses

Compound	Type (Applicant's Analysis)	Source	Notes	Conclusions
Adefovir	OAT1 substrate	PMID 28738449[32]	Applicant obtained adefovir model parameters from this FDA publication. Publication assigns clearance via OAT generally and does not specify OAT1 vs. OAT3.	We agree with assignment of adefovir transport to OAT1 (b) (4) OAT1 predominates.
		PMID 17372702[33]		
		PMID 28179375[34]	In vitro studies where adefovir was determined to be a substrate of OAT1 and OAT3, with OAT1 being the primary transporter	
		PMID 24747579[27]		
		PMID 25448811[35]	In vitro study where adefovir was determined to be a substrate of OAT1 and OAT3	
Baricitinib	(b) (4)			We do not accept the Applicant's analyses with baricitinib (b) (4) . We repeated the simulations of clinical studies with baricitinib as an OAT3 substrate.
		NDA 207924	PBPK model with baricitinib as an OAT3 substrate (b) (4) was previously accepted by an FDA reviewer	
Methotrexate	OAT3 substrate	PMID 12130730[36]	In vitro studies where methotrexate affinity was much greater for OAT3 vs. OAT1	We agree with assignment of methotrexate transport to OAT3 (b) (4) because OAT3 predominates.
		PMID 28179375[34]		
		2018 Simcyp® compound file report	PBPK model with methotrexate as an OAT3 substrate (b) (4) was previously accepted by an FDA reviewer	
		NDA 211192		

Compound	Type (Applicant's Analysis)	Source	Notes	Conclusions
Oseltamivir	OAT3 substrate	PMID 28179375[34]	In vitro study where oseltamivir was determined to be a substrate of OAT3 and not a substrate of OAT1	We accept the model
		PMID 24214317[37] PMID 28738449[32]	Applicant obtained oseltamivir model parameters from these FDA publication. In these publications, transport was not assigned specifically to OAT1 vs. OAT3.	
Probenecid	OAT1 inhibitor OAT3 inhibitor	PMID 28749581[28] 2019 Simcyp® compound file report (b) (4)		We accept the model

Source: Reviewer.
Abbreviations: PBPK = physiologically-based pharmacokinetic

The PBPK modeling was able to adequately recover results of DDI studies of OAT1/3 substrates and inhibitors, with predicted to observed AUC ratios ranging from 0.90 to 1.1 (Table 149).The results support the use of the PBPK modeling to predict unstudied OAT1/3-mediated interactions involving CAB.

Table 149. Observed and Simulated Substrate AUC Ratios in the Presence/Absence of OAT1/3 Inhibitor

Study (Substrate-Inhibitor)	Observed AUC or CL Ratio	Simulated AUC or CL Ratio (FDA Analysis)
Adefovir-probenecid[1]	1.8	1.8 (1.4-2.3)
Baricitinib-probenecid[2]	2.0 (1.9, 2.2)	1.8 (1.3-2.8)
Methotrexate-probenecid[3]	0.64	0.68
Oseltamivir-probenecid[2]	2.5 (2.3, 2.8)	2.2 (1.6-3.1)

Source: Reviewer
[1]mean AUC ratio (5th, 95th percentile)
[2]AUC GMR (5th-95th percentile)
[3]Observed ratio of mean clearance from four subjects. Simulated ratio of mean clearance from one subject×20 trials.
Abbreviations: CL = clearance

Predicted Effect of CAB on the PK of Substrates of OAT1/3

At measured CAB K_i values for inhibition of OAT1/3, a minimal (AUC geometric mean ratio of ~1.1) increase in substrate AUC is predicted when co-administered with CAB.

At K_i values for inhibition of OAT1/3 that are 15-fold lower than measured, AUC geometric mean ratios ranged from 1.5 to 1.8. (Table 150).

Methotrexate is an OAT3 substrate with a narrow therapeutic index. As methotrexate has a relatively narrow therapeutic index, a small K_i lowering of 5-fold was investigated. A

statistically significant interaction was not detected at the measured K_i value but was detected at a 5-fold lower K_i value (Table 150).

Table 150. Simulated Effect of Cabotegravir (CAB) on OAT1/3 Substrates

Compound	Transporter	CAB K_i (μM)	K_i Source	Substrate AUC Ratio (5^{th}-95^{th} Percentile)
Adefovir	OAT1	0.405	Measured	1.1 (1.0-1.1)
Adefovir	OAT1	0.027	15-fold lower than measured	1.5 (1.3-1.9)
Baricitinib	OAT3	0.205	Measured	1.1 (1.1-1.3)
Baricitinib	OAT3	0.0137	15-fold lower than measured	1.6 (1.3-2.3)
Methotrexate	OAT3	0.205	Measured	1.1 (1.0-1.2)
Methotrexate	OAT3	0.041	5-fold lower than measured	1.3 (1.1-1.7)
Oseltamivir	OAT3	0.205	Measured	1.1 (1.1-1.2)
Oseltamivir	OAT3	0.0137	15-fold lower than measured	1.8 (1.5-2.3)

Source: FDA Reviewer's Analysis.
Abbreviations: CAB = cabotegravir, K_i = inh bitory constant

In sensitivity analyses of CAB K_i values for inhibition of OAT1 and OAT3, potentially clinically significant effects of CAB on the PK of OAT1/3 substrates are predicted. In vitro K_i values for a given transporter substrate-inhibitor pair can vary due to interlaboratory variation, choice of substrate, experimental conditions, etc.[38] For example, K_i and IC_{50} values for in vitro inhibition of OAT1 and OAT3 by probenecid varied by up to 41-fold (Table 151). Due to uncertainty in K_i values, our focus is on the DDI magnitude predicted when using CAB K_i values 15-fold lower than measured when formulating labeling recommendations for use of CAB with substrates of OAT1/3.

Table 151. Variation in Measured In Vitro K_i and IC_{50} Values for Inhibition of OAT1/3 by Probenecid

Substrate	K_i (μM)	IC_{50} (μM)
OAT1	9.49 (3.6-26) n=11	10.5 (3.9-160) n=30
OAT3	7.25 (1.3-32) n=16	4.62 (0.76-27.9) n=23

Source: UW DIDB (https://didb.druginteractionsolutions.org). Values are median (range).
Abbreviations: IC_{50} = half maximal inhibitory concentration, K_i = inhibitory constant

Proposed labeling states the following: "In vitro, cabotegravir inhibited renal OAT1 (IC_{50}=0.81μM) and OAT3 (IC_{50}=0.41μM). (b) (4) . Following label negotiations, final labeling in section 12.3 states "cabotegravir may increase the AUC of OAT1/3 substrates up to approximately 80%".

Q.3. Can PBPK Analysis be Used to Predict the Interaction Potential of an UGT1A1 Inhibitor on CAB?

Yes, PBPK analysis can be used to predict the lack of effect of a selective UGT1A1 inhibitor on CAB exposure.

Sufficient information regarding the source of model parameters were available from literature and/or a Simcyp® compound file report for ATV, RAL, and rifampicin (Table 152).

The RAL model assumed the drug is only metabolized by UGT1A1 (all nonrenal clearance assigned to UGT1A1) and 9% eliminated unchanged in urine. The relative contribution of UGT1A1 to RAL overall clearance was partially verified against clinical DDI ATV as an

UGT1A1 inhibitor. The Applicant did not perform verification of UGT1A1 contribution using reported pharmacogenetic data. While the RAL model did not account for known UGT1A9 metabolism,[39] the sensitivity analysis with ATV accounts for the higher inhibition potency of ATV required to recover the observed RAL-ATV interaction magnitude.

Predictive performance of the RAL-ATV interaction was acceptable (predicted to observed AUC ratio of 0.88) (Table 153).

Based on sufficient recovery of the RAL-ATV interaction, we consider the PBPK modeling verified for interactions mediated by UGT1A1 inhibition.

Clinically, there were a 60% decrease in CAB AUC and 2.5-fold increase in the apparent clearance in the presence of the UGT1A1 inducer rifampin [LAI17010]. The Applicant conducted an exploratory analysis to verify the clearance and exposure changes of CAB in the presence of UGT1A1 induction by rifampin. The default rifampin model ("SV_Rifampin_MD", V17) was modified to include UGT1A1 induction parameters available in the literature (PMID 29440451 and 15849716).[40,41] Four different in vitro UGT1A1 induction parameters (E_{max} and EC_{50}) from different donors were tested. The predicted AUC_{inf} ratio ranged from 0.21 to 0.66 compared to observed AUC_{inf} ratio of 0.41 (90% CI: 0.36 to 0.46); while the predicted clearance ratio ranged from 1.5 to 4.6 compared to observed value of 2.4. (Table 153)

Table 152. Summary of UGT1A1 Substrates, Inhibitors, and Inducers Used in the PBPK Analyses

Compound	Type (Applicant's analysis)	Sources	Notes	Conclusions
Raltegravir	UGT1A1 substrate	PMID 30804050[39] 2018 Simcyp® compound file report	In vitro study with recombinant enzymes where raltegravir was found to be a substrate of UGT1A1 and UGT1A9 with similar formation rates with both enzymes The Simcyp model assumes that raltegravir is only metabolized by UGT1A1 (all nonrenal clearance assigned to UGT1A1)	We accept the model. The model does not account for UGT1A9 metabolism. However, the sensitivity analysis around atazanavir K_i accounts for this limitation.
Atazanavir	UGT1A1 inhibitor	PMID 16118329[42] 2018 Simcyp® compound file report	In vitro study where atazanavir was found to inhibit UGT1A1 and not inhibit UGT1A9	We accept the model

Compound	Type (Applicant's analysis)	Sources	Notes	Conclusions
[redacted]	[redacted]	[redacted]	(b) (4)	We do not accept the model because UGT1A1 induction parameters are not verified.

Source: Reviewer.
Abbreviations: K_i = inhibitory constant, PBPK = physiologically-based pharmacokinetic,

Table 153. Observed and Simulated Substrate (Raltegravir) AUC Ratios in the Presence/Absence of UGT1A1 Inhibitor or Inducer

Study (Substrate-Inhibitor)	Observed AUC Ratio[1]	Simulated AUC Ratio (FDA Analysis)[2]
Raltegravir-rifampicin	0.60	0.2 (0.1-0.4)[3]
Raltegravir-atazanavir	1.7 (1.3-2.1)	1.5 (1.2-1.7)

[1]Observed GMR (90% CI). Simulated GMR (5th, 95th percentile).
[2]Simulated GMR (5th, 95th percentile).
[3]Exploratory analysis: Simulated ratio obtained from use of mean in vitro rifampicin UGT1A1 induction values from four donors (Ind_{max} =9.04, Ind_{C50}=0.350µM).

Predicted Effect of UGT1A1 Inhibition on the PK of CAB

PBPK simulations indicated that no clinically relevant interaction is expected between CAB and a specific UGT1A1 inhibitor such as ATV (Table 154). In sensitivity analyses, lowering ATV K_i for UGT1A1 inhibition 10-fold and/or increasing CAB $f_{m,UGT1A1}$ from 0.62 (default model) to 0.96 did not result in a geometric mean CAB AUC ratio of ≥1.9 (Table 154).

Table 154. Simulated Effect of UGT1A1 Inhibition on Cabotegravir (CAB) Exposure

Inhibitor	Enzyme	Inhibitor K_i (µM)	K_i Source	CAB $f_{m,UGT1A1}$	CAB AUC Ratio (5th-95th Percentile)
Atazanavir	UGT1A1	1.9	Measured	0.62	1.1 (1.0, 1.2)
Atazanavir	UGT1A1	0.19	10-fold lower than measured	0.62	1.5 (1.2, 1.8)
Atazanavir	UGT1A1	1.9	Measured	0.96	1.2 (1.1, 1.3)
Atazanavir	UGT1A1	0.19	10-fold lower than measured	0.96	1.9 (1.3, 2.4)

Source: FDA reviewer's analysis. Atazanavir $f_{u,inc}$ =0.406
Abbreviations: K_i = inhibitory constant

Q4. Can PBPK Analysis be Used to Predict the Interaction Potential of an UGT1A9 Inhibitor on CAB?

PBPK analysis cannot be used predict the interaction effect of a selective UGT1A9 inhibitor on CAB exposure.

[redacted] (b) (4) (Table 155).

Table 155. Summary of UGT1A9 Substrates and Inhibitors Used in the PBPK Analyses

Compound	Type (Applicant's analysis)	Sources	Notes	Conclusions
(b) (4)				Because (b) (4) is not a specific (b) (4) inhibitor, we do not accept the Applicant's analyses regarding the effect of (b) (4)
				We do not accept the model because (b) (4)

Source: Reviewer.
Abbreviations: IC_{50} = half maximal inhibitory concentration, PBPK = physiologically-based pharmacokinetic

14.3.5. Conclusions

CAB may increase concentrations of OAT1/3 substrates and patients should be monitored for toxicities associated with the OAT1/3 substrates, based on the following:

- The PBPK modeling was verified for a DDI mediated by OAT1 and/or OAT3 inhibition by comparing simulations with the reported DDIs between probenecid (OAT1/3 inhibitor) and OAT1 (adefovir) and OAT3 substrates (baricitinib, methotrexate, and oseltamivir).
- Sensitivity analyses were conducted for the predicted CAB DDI with OAT1/3 substrates by varying CAB K_i for inhibition of OAT1 and OAT3 where the predicted increase in geometric mean AUC ratio of OAT1/3 substrate ranges from 1.3 to 1.8.

No clinically relevant interaction is expected between CAB and the UGT1A1 inhibitor ATV, based on the following:

- The PBPK modeling was verified for a DDI mediated by UGT1A1 inhibition by comparing simulations with the reported DDIs between ATV and UGT1A1 substrate RAL.
- Sensitivity analyses were conducted for the predicted ATV-CAB DDI by varying ATV K_i for inhibition of UGT1A1 and CAB $f_{m,UGT1A1}$ where the predicted CAB geometric mean ratio was ≤1.9.

The FDA do not accept the Applicant's analysis regarding interactions mediated by inhibition of UGT1A9, (b) (4)

15. Protocol Overview and Conduct

The FLAIR and ATLAS trials had a lot of similarities in design, yet they were different in terms of the enrolled population, duration of follow-up, inclusion and exclusion criteria, etc. Therefore, the review team listed the protocol overview and conduct separately for the two trials. The review team agreed that the protocols and the conduct of the FLAIR and ATLAS trials were satisfactory. An overview of the protocols and conduct is summarized below.

15.1. Protocol 201584 - FLAIR

Table 156. Protocol Overview: 201584

Applicant	**ViiV Healthcare**
Drug name	Cabotegravir + rilpivirine
Indication	Treatment of HIV-1 infection
Protocol title	A Phase III, Randomized, Multicenter, Parallel-group, Open-Label Study Evaluating the Efficacy, Safety, and Tolerability of Long-Acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch from an Integrase Inhibitor Single Tablet Regimen in HIV-1 Infected Antiretroviral Therapy Naïve Adult Participants
Source of information	Protocol amendment 04 dated 24-Sep-2018, week 48 CSR dated 05-MAR-2019
Trial identifiers	
Protocol number:	201584
Clinical phase:	III
EudraCT number:	2016-001646-25
Other codes:	Not applicable
IND number:	109,678
ClinicalTrial.gov identifier:	NCT02938520
Ethics	The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the ICH GCP and applicable country-specific requirements, including US 21 CFR 312.3(b) for constitution of independent ethics committees.
Trial centers	This was a multicenter study conducted at 108 centers in 11 countries: Canada (6 centers), France (8 centers), Germany (11 centers), Italy (5 centers), Japan (3 centers), Netherlands (4 centers), Russia (13 centers), South Africa (8 centers), Spain (18 centers), United Kingdom (7 centers) and the USA (25 centers).

Abbreviations: CFR = Code of Federal Regulations, CSR = clinical study report, GCP = good clinical practice, ICH = International Council for Harmonisation

15.1.1. Design

Table 157. Design of Protocol 201584

Study Features and Methods	Details
Planned duration of main phase	120 weeks
Planned duration of extension phase	Until regulatory approval and commercial availability within country.
Trial status	Ongoing
Date of database lock	19-Sep-2018 Database release for week 48 primary endpoint.
Other important dates	Primary completion last subject last visit achieved: 30-Aug-2018 Primary database release: 19-Sep-2018 Week 48 CSR (primary endpoint analysis): 27-Nov-18 Week 48 CSR: 05 Mar 2019

Abbreviations: CSR = clinical study report

This was a 120-week phase 3, multiphase, randomized, open label, active-controlled, multicenter, parallel-group, noninferiority study in HIV-1, ART-naïve adult subjects.

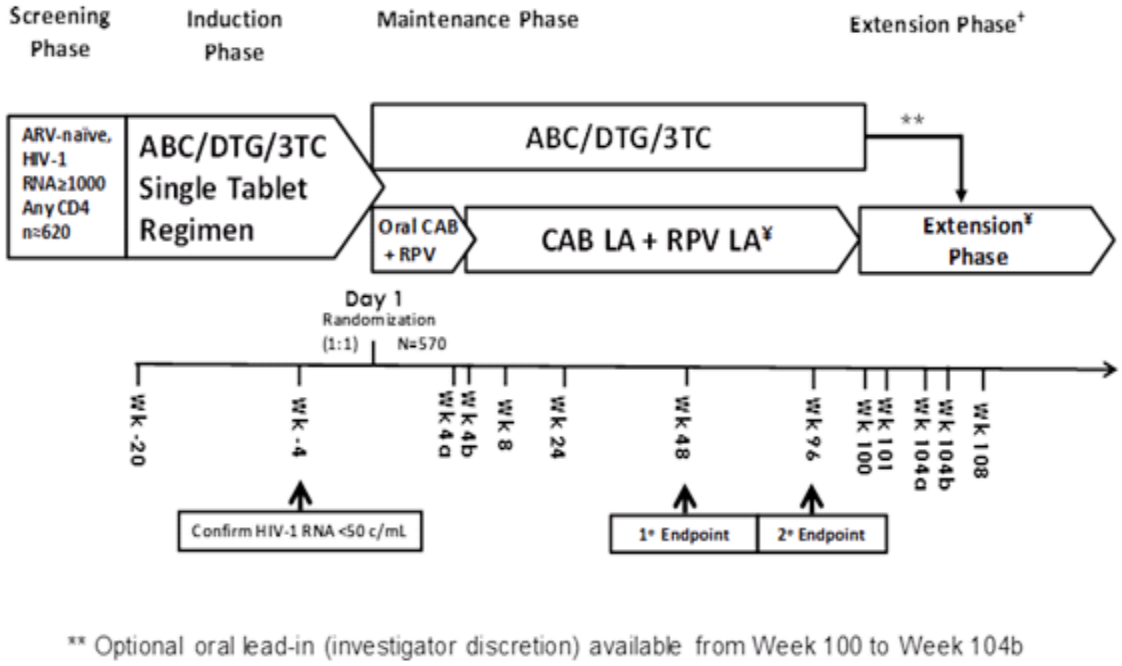
All subjects completed the screening phase of up to 35 days prior to induction baseline (week -20). Eligible subjects were enrolled into the induction phase of the study and received ABC/DTG/3TC for 20 weeks (week -20 to day 1). For subjects who were HLA-b*5701 positive, DTG was taken with a non-ABC nucleoside reverse transcriptase inhibitor (NRTI) backbone, chosen per investigator.

Subjects who had an HIV 1 RNA <50 c/mL at the week -4 visit were eligible to enter the maintenance phase. Eligible subjects were randomized (1:1) to receive either oral CAR (ABC/DTG/3TC or the alternative non-ABC backbone) or oral CAB◦30◦mg+RPV 25 mg once daily for a minimum of 4 weeks (OLI) followed by CAB LA+RPV LA every 4 weeks thereafter. Randomization was stratified by subject's induction baseline (week -20) HIV-1 RNA (<100,000 c/mL, ≥100,000◦c/mL) and sex at birth.

Subjects randomized to CAR during the maintenance phase will continue CAR for at least an additional 100 weeks. Subjects who successfully complete week 100 (without meeting study defined withdrawal criteria and who remain virologically suppressed at week 96: HIV-1 RNA <50 c/mL) will be given the option to switch to the CAB LA+RPV LA arm in the extension phase or be withdrawn from the study. The transition from CAR to CAB LA+RPV LA within the extension phase can be completed with or without an OLI prior to commencement of injectable treatment. The OLI decision will be made by the subject in consultation with the investigator;.

All subjects randomized to CAB+RPV during the maintenance phase will continue CAB LA+RPV LA for at least an additional 96 weeks and will continue to have access to CAB LA+RPV LA in the extension phase. Any subject who received at least a single dose of CAB LA and/or RPV LA and discontinued the regimen for any reason entered a 52-week LTFU phase. Subjects were to be put on oral highly active ART (HAART) as soon as possible after discontinuing CAB LA+RPV LA and were to remain on HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA.

Figure 46. 201584 Study Schematic



¥ Subjects who withdraw from CAB LA+RPV LA must enter the 52-week Long Term Follow-Up Phase
Abbreviations: 3TC = lamivudine, ABC = abacavir, CAB = cabotegravir, DTG = dolutegravir, LA = long-acting, RPV = rilpivirine

15.1.2. Objectives in Base Study

The primary objective of this study was to demonstrate the noninferior antiviral activity of switching to IM CAB LA+RPV LA (every 4 weeks) compared to remaining on an IN-based CAR regimen (ABC/DTG/3TC or the alternative non-ABC backbone) over 48 weeks in HIV-1–infected ART naïve subjects. The study will also allow for characterization of long-term antiviral activity, safety, tolerability, and subject satisfaction of the regimens through week 96.

15.1.2.1. Primary Objective

To demonstrate the noninferior antiviral activity of switching to CAB LA+RPV LA every 4 weeks compared to continuation of CAR over 48 weeks in HIV 1 ARV naïve subjects.

15.1.2.2. Secondary Objective

- To demonstrate the antiviral and immunologic activity of switching to IM CAB LA+RPV LA every 4 weeks compared to continuation of CAR.
- To evaluate the safety and tolerability of switching to CAB LA+RPV LA every 4 weeks compared to continuation of CAR over time.
- To evaluate the effects of CAB LA+RPV LA every 4 weeks on fasting lipids over time compared to continuation of CAR over time.
- To assess the development of viral resistance in subjects experiencing CVF.
- To characterize CAB and RPV concentrations and Population PK and identify important determinants of variability.

- To assess the acceptance of pain and ISRs following injections.
- To assess degree of health-related quality of life (HR QoL).
- To assess treatment satisfaction of CAB LA+RPV LA compared to continuation of CAR.
- To assess health status.
- To assess treatment acceptance.
- To assess tolerability of injections.
- To evaluate the antiviral and immunologic effects, safety and tolerability, and viral resistance of CAB LA+RPV LA at week 124 and over time for subjects switching from ABC/DTG/3TC in the extension phase, with and without OLI.
- To evaluate the PK of CAB and RPV in the setting of no OLI for subjects switching from ABC/DTG/3TC in the extension phase.

15.1.2.3. Exploratory Objectives

- To explore the effect of subject characteristics on the virologic and immunologic response of CAB LA and RPV LA compared to continuation of CAR.
- To explore relationship(s) between plasma concentrations of CAB and RPV and pharmacodynamic endpoints.
- To evaluate renal and bone biomarkers in subjects receiving CAB LA and RPV LA compared to continuation of CAR over time.
- To assess preference for CAB LA+RPV LA compared to oral ART using a single dichotomous preference question.

15.1.3. Selection of Trial Population

15.1.3.1. Key Inclusion Criteria

1) HIV-1–infected, ART-naïve men or women aged 18 years or greater at the time of signing the informed consent.
2) HIV-1 infection as documented by screening plasma HIV-1 RNA ≥1000 c/mL.
3) ARV-naïve (≤10 days of prior therapy with any ARV agent following a diagnosis of HIV-1 infection). Any previous exposure to an HIV INI or NNRTI will be exclusionary.
4) Female subjects were to be nonpregnant, nonlactating and had to be either of non-reproductive potential or of reproductive potential and agree to follow one of the options of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential.

Capable of giving signed informed consent.

French subjects only: In France, a subject was eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

15.1.3.2. Key Exclusion Criteria

1) Women who are pregnant, breastfeeding, or plan to become pregnant or breastfeed during the study.
2) Evidence at screening of active CDC stage 3 disease, except cutaneous Kaposi's sarcoma not requiring systemic therapy or historic or current CD4+ cell count <200 cells/mm^3 are not exclusionary (local guidelines dictate).
3) Subjects with known moderate to severe hepatic impairment.
4) Pre-existing physical or mental condition (including substance abuse disorder) which, in the opinion of the Investigator, may interfere with the subject's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the subject.
5) Subjects determined by the Investigator to have a high risk of seizures, including subjects with an unstable or poorly controlled seizure disorder.
6) Subject who, in the investigator's judgment, posed a significant suicide risk.
7) Tattoo or other dermatological condition overlying the gluteus region which may interfere with interpretation of ISRs.
8) Evidence of HBV infection based on the results of testing at screening for HbsAg, anti-HBc, anti-HBs and HBV DNA as follows:
   - Subjects positive for HbsAg were excluded;
   - Subjects negative for anti-HBs but positive for anti-HBc (negative HbsAg status) and positive for HBV DNA were excluded.
9) Asymptomatic individuals with chronic HCV infection were not excluded, however Investigators were to carefully assess if therapy specific for HCV infection was required; subjects who were anticipated to require HCV treatment prior to week 48 of the maintenance phase were excluded.

   Subjects with HCV co-infection were allowed entry into phase 3 studies if:

   - Liver enzymes met entry criteria.
   - HCV disease had undergone appropriate work-up, HCV was not advanced, and did not require treatment prior to the week 48 visit.
   - In the event that recent biopsy or imaging data was not available or was inconclusive, the Fib-4 score was used to verify eligibility.
     - A Fib-4 score >3.25 was exclusionary
     - Fib-4 scores 1.45 to 3.25 required medical monitor consultation.

Fibrosis 4 Score Formula:

$$(\text{Age} \times \text{AST}) / (\text{Platelets} \times (\sqrt{\text{ALT}}))$$

10) Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's

syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).

11) History of liver cirrhosis with or without hepatitis viral co-infection.

12) Ongoing or clinically relevant pancreatitis.

13) All subjects were screened for syphilis (rapid plasma reagin [RPR]). Subjects with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, were excluded. Subjects with a positive RPR test who had not been treated could be rescreened at least 30 days after completion of antibiotic treatment for syphilis.

14) Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, noninvasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; other localized malignancies required agreement between the Investigator and the study Medical Monitor for inclusion of the subject prior to enrolment.

15) Any condition which, in the opinion of the Investigator, may interfere with the absorption, distribution, metabolism or excretion of the drug or render the subject unable to receive study medication.

16) History or presence of allergy or intolerance to the study drugs or their components or drugs of their class. In addition, if heparin was used during PK sampling, subjects with a history of sensitivity to heparin or heparin-induced thrombocytopenia were excluded.

17) Current or anticipated need for chronic anticoagulation.

18) ALT ≥3× ULN.

19) Clinically significant cardiovascular disease, as defined by history/evidence of congestive heart failure, symptomatic arrhythmia, angina/ischemia, CABG surgery or PTCA or any clinically significant cardiac disease.

20) Exposure to an experimental drug and/or experimental vaccine within 28 days or five half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of study drug.

21) Treatment with any of the following agents within 28 days of screening:

- radiation therapy
- cytotoxic chemotherapeutic agents
- TB therapy, with the exception of treatment of latent TB with isoniazid
- immunomodulators that alter immune responses (such as chronic systemic corticosteroids, interleukins, or interferons).

22) Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of screening.

23) Treatment with any agent, except recognized ART as allowed above, with documented activity against HIV-1 within 28 days of the first dose of study drug.

24) Use of medications which are associated with Torsades de Pointes

25) Any evidence of primary resistance to NNRTIs (except for K103N which was allowed), or any known resistance to integrase inhibitor (INSTIs) from historical resistance test results.

26) Subjects who were HLA-B*5701 positive and unable to use an NRTI backbone that does not contain ABC (subjects who are HLA-B*5701 positive may be enrolled if they use a NRTI backbone that does not contain ABC).

27) Any verified grade 4 laboratory abnormality.

28) Any acute laboratory abnormality at screening

29) Estimated creatinine clearance <50 mL/min/1.73m^2 via the Chronic Kidney Disease Epidemiology Collaboration equation.

30) Participation in other interventional study.

15.1.4. Hypotheses

This study was designed to show that the antiviral effect of oral ABC/DTG/3TC (CAR) followed by IM CAB LA+RPV LA regimen was noninferior to continuation of CAR at week 48 of maintenance treatment.

For this study, noninferiority in the proportion of subjects with HIV-1 RNA ≥50 c/mL at week 48 for the ITT-E population (per FDA's snapshot algorithm) was concluded if the upper bound of a two-sided 95% CI for the difference in the proportion of subjects with HIV-1 RNA ≥50 c/mL between the two treatment arms ([CAB+RPV]–CAR) is less than 6%.

If f_{la} is the proportion of subjects with HIV-1 RNA ≥50 c/mL for the CAB+RPV arm and f_c is the proportion of subjects with HIV-1 RNA ≥50 c/mL (per FDA snapshot algorithm) for the CAR arm, then the hypotheses can be written as follows:

$$H_o: f_{la} - f_c \geq 6\% \qquad H_1: f_{la} - f_c < 6\%$$

The data from this study, together with data from a separate study, 201585, were combined to assess noninferiority in the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL at week 48. Noninferiority was concluded if the upper bound of a 2 sided 95% CI for the difference in the proportion between the 2 treatment groups ([CAB+RPV] – CAR) was not more than 4%.

15.1.5. Treatment Groups

All subjects received ABC/DTG/3TC (TRIUMEQ) during the induction phase (unless the subject was HLA-b*5701 positive at screening in which case a non-ABC containing DTG regimen was chosen). At the end of the induction phase, eligible subjects were randomized 1:1 into the maintenance phase to receive either:

- Oral CAB 30 mg + RPV 25 mg once daily for a minimum of 4 weeks followed by IM injections of CAB + RPV (CAB 600 mg + RPV 900 mg at week 4b, CAB LA 400 mg + RPV LA 600 mg at week 8 and every 4 weeks thereafter. Subjects were to receive IM injections of CAB LA+RPV LA for at least 96 weeks, or;

- Oral CAR (ABC/DTG/3TC or DTG + the alternative non-ABC backbone) for at least 100 weeks.

15.1.6. Endpoints and Definitions

15.1.6.1. Primary Efficacy Endpoint

Proportion of subjects with a "virologic failure" endpoint (HIV-1 RNA ≥50) as per FDA snapshot algorithm at week 48 (missing, switch, or discontinuation = failure, ITT-E population).

15.1.6.2. Secondary Efficacy Endpoint

- Proportion of subjects with plasma HIV-1 RNA <50 copies/mL at week 48 using the FDA snapshot algorithm (ITT-E population).
- Proportion of subjects with plasma HIV-1 RNA <200 c/mL at week 48 using the FDA snapshot algorithm (ITT-E population).
- Proportion of subjects with plasma HIV-1 RNA <200 c/mL and HIV-1 RNA <50 c/mL at week 96 using the FDA snapshot algorithm (ITT-E population).
- Proportion of subjects with a 'virologic failure' endpoint as per FDA snapshot algorithm at week 96.
- Proportion of subjects with CVF at week 48 and week 96.
- Absolute values and change from baseline in plasma HIV-1 RNA (log_{10} copies/mL) at week 48 and week 96.
- Absolute values and changes from baseline in CD4+ cell count over time including week 48 and week 96.
- Incidence of disease progression (HIV-associated conditions, AIDS, and death).
- Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on-study ART at week 48 and week 96.
- Proportion of subjects with HIV-1 RNA ≥ 50 c/mL at week 124, with and without OLI (FDA snapshot algorithm, extension switch population).
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL and HIV-1 RNA <200 c/mL over time.
- Proportion of subjects with CVF over time.
- Incidence of treatment emergent genotypic and phenotypic resistance to CAB and RPV over time.
- Absolute values and change from baseline in CD4+ cell count over time.

15.1.6.3. Exploratory Efficacy Endpoints

- Proportion of subjects by subject subgroup(s) (e.g., by age, gender, BMI, race, HIV-1 subtype, baseline CD4+ cell count) with virologic failure over time including week 48, and 96 using the snapshot algorithm for the ITT-E population.

- Proportion of subjects by subgroup(s) (e.g., by age, gender, BMI, race, HIV-1 subtype, baseline CD4+ cell count) with plasma HIV-1 RNA <50 c/mL at week 48 and week 96.
- Change from baseline in CD4+ cell count by subgroups at week 48 and week 96.

15.1.6.4. Primary (Tier 1) Safety Endpoints

There were no primary safety endpoints.

15.1.6.5. Secondary (Tier 2) Safety Endpoints

- Incidence and severity of AEs and laboratory abnormalities over time including week 48 and week 96.
- Proportion of subjects who discontinue treatment due to AEs over time including week 48 and week 96.
- Absolute values and changes in laboratory parameters over time including week 48 and week 96.
- Change from baseline in fasting lipids over time including week 48 and week 96.

15.1.6.6. Virology/Microbiology Endpoint

- Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on-study ART at week 48 and week 96.

15.1.6.7. Pharmacokinetic Endpoints

- Plasma PK parameters for CAB LA and RPV LA (when evaluable, C_{trough}. Concentrations postdose [~C_{max}], and AUC).
- Demographic parameters including, but not limited to age, sex, race, body weight, BMI, and relevant laboratory parameters will be evaluated as potential predictors of inter- and intrasubject variability for pharmacokinetic parameters.

15.1.6.8. Value Evidence and Outcomes Endpoints

- Change from week 5 in dimension scores (e.g., “bother of ISRs”, “leg movement”, “sleep”, and “injection acceptance”) and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the PIN questionnaire .
- Proportion of subjects considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using the PIN questionnaire.
- Change from baseline in total “treatment satisfaction” score, and individual item scores of the HIVTSQs at week 4b, week 24, week 44, week 96 (or withdrawal).
- Change in treatment satisfaction over time (using the HIVTSQc) at week 48 (or withdrawal).
- Change from baseline in treatment acceptance at weeks 8, 24, 48, 96 (or withdrawal from the study) using the “General acceptance” dimension of the ACCEPT questionnaire.

- Change from baseline in health status at weeks 24, 48, 96 (or withdrawal) using the 12-item short form survey (SF-12).
- Change from baseline in HR QoL (using the HAT-QoL short form) at weeks 24, 48, 96 (or withdrawal from the study).
- Change from week 4b in the tolerability of injections (using the NRS) at weeks 5, 40, 41, 96.

15.1.7. Interim Analysis

No interim analyses beyond the IDMC analyses were conducted.

15.1.8. Data Monitoring Committee

An independent data monitoring committee (IDMC) was instituted to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of subjects and to protect the scientific validity of this study (201584) and study 201585.

An ad hoc review of data by the IDMC was triggered whenever the number of CVFs in the CAB LA+RPV LA arm exceeded thresholds prespecified in the IDMC charter. Further, an interim futility analysis was performed for the IDMC to evaluate the efficacy and safety of CAB LA+RPV LA when approximately 50% of subjects had completed their visit at week 24; the Applicant remained blinded to this analysis. In addition, the IDMC also monitored the incidence of subjects meeting CVF criteria through week 48 to ensure that subjects are not being suboptimally treated in the CAB LA+RPV LA arm.

15.1.9. Endpoint Adjudication Committee

For the CAB LA+RPV LA group only, cases meeting LSC were evaluated by an independent hepatic adjudication committee operating under an adjudication committee charter.

15.1.10. Sample Size Considerations

15.1.10.1. Sample Size Assumptions

This study planned to randomize approximately 285 subjects per treatment group. Assuming the true proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL was 3% for the CAB LA+RPV LA treatment group and 2% for the CAR group, a noninferiority margin of 6%, and a 2.5% one-sided significance level, this provided approximately 97% power to show noninferiority for the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL at week 48.

The sample size of 285 subjects per arm also provides at least 90% power to show non-inferiority in the proportion of subjects with plasma HIV-1 RNA <50 c/mL (per FDA's snapshot algorithm) at week 48 over a range of true response rates, based on a -10% noninferiority margin and 2.5% one-sided significance level. Assuming true response rates for the CAB LA+RPV LA arm and CAR arm were both 87%, the power is at least 94% to show noninferiority for this key secondary endpoint.

The combined sample size from both studies (201585 and 201584; 570 pooled per group) provided 90% power, under the assumptions described, to show noninferiority for the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL at week 48.

15.1.11. Rationale for Noninferiority Margin

As this study (201584) and study 201585 were not sufficiently powered individually to rule out 4% virologic failure in excess, the 6% margin chosen in each study can be viewed as defining criteria for assessing the consistency acceptability of the study-specific results prior to integration of the studies in the pooled analysis. Assuming an observed control failure rate of 2%, then noninferiority would be shown in an individual study using a 6% margin if the observed CAB+RPV failure rate was less than 5% (that is, if the observed treatment difference was less than 3 percentage points). Accordingly, if the individual studies were successful in ruling out a 6% margin, the observed results were expected to be similar and reasonable to integrate for the purposes of the primary efficacy assessment based on the pooled analysis. In addition, a virologic failure rate in this range may be clinically tolerable given the CAB+RPV regimen may offer important advantages over standard 3-drug oral regimens such as better tolerability, as well as improved adherence and treatment satisfaction in virologically-suppressed subjects. Therefore, 6% was considered to be a reasonable noninferiority margin for the individual studies, with a more stringent 4% margin applied for the pooled analysis.

The noninferiority margin of 6% was chosen in consideration of the FDA's 2015 guidance document,[2] which is the most current regulatory guidance from either the EMA or FDA and includes specific recommendations regarding switch studies. It suggests that margins in the neighborhood of 4% are clinically tolerable, with typical observed rates of virological failure ranging from 1% to 3%.

15.1.12. Response Rate Assumptions

Assumption for Virologic Failure Rate (per FDA Snapshot Algorithm) at Week 48 (Primary Endpoint)

Based on recent stable switch studies and treatment-naïve studies with INSTI based regimens, reasonable assumptions for the true failure rates are 2% for the control arm and 3% for the CAB LA+RPV LA injectable regimen.

Assumption for Response Rate (per FDA Snapshot Algorithm) at Week 48 (Secondary Endpoint)

A reasonable assumption for the true success response rate (HIV-1 RNA <50 c/mL) for both arms was 87%.

15.1.13. Analysis Population and Time Point Description

- **All subjects screened population:** Comprised all subjects screened for inclusion in the study.
- **Randomized population:** Included all randomized subjects.

- **All subjects enrolled**: All enrolled subjects who received at least one dose of study drug in the induction phase. Secondary population for some analyses
- **ITT-E population:** The ITT-E population consisted of all randomly assigned subjects who received at least 1 dose of the study drug. Subjects were assessed according to their randomized treatment, regardless of the treatment they received. The population used in the primary efficacy analysis was the ITT-E population.
- **Per protocol (PP) population:** The PP population consisted of all subjects in the ITT-E population with the exception of those with important protocol deviations. The PP population was used for sensitivity analysis of the primary and key secondary efficacy endpoints.
- **PK population:** The PK population included all subjects who received CAB and/or RPV and underwent PK sampling during the study and provided evaluable CAB and/or RPV plasma concentration data. Subjects in this population were included in the PK analysis.
- **Safety population:** The safety population consisted of all randomly assigned subjects who received at least 1 dose of the study drug. Subjects were assessed according to the actual treatment received. Unless otherwise stated, the Safety population was used for safety analyses.
- **Confirmed virologic failure population:** The CVF population comprised all subjects in the ITT-E population who met CVF criteria.
- **Extension switch population:** This population consisted of all randomized subjects from the CAR group who received at least one dose of CAB and/or RPV during the extension phase of the study.
- **LTFU population:** Included all subjects receiving at least one dose of CAB LA and/or RPV LA who have discontinued the CAB LA+RPV LA regimen and have at least one LTFU phase clinic visit.

15.1.14. Analysis Description

15.1.14.1. Primary Efficacy Analysis Description

The primary analyses were based on the ITT-E population using the snapshot dataset. The primary comparison was made at a one-sided 2.5% level of significance. Treatment with CAB+RPV was to be declared noninferior to CAR if the upper end of a two-sided 95% CI for the difference between the two groups ([CAB+RPV] – CAR) in the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL at week 48 was below 6%.

For the primary comparison, adjusted estimates of the difference in the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL between the two treatment groups were presented along with CIs based on a stratified analysis using CMH weights. All CIs were two-sided, and the analyses were stratified according to the baseline HIV-1 RNA (<100,000, ≥100,000 c/mL) and sex at birth. The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in response rates between the two groups.

The weighted least squares chi-squared statistic was used to test for one-way homogeneity across the levels of each categorical variable, with each stratification factor considered separately. If the stratum-specific rate estimates of either f_{la} or f_c were 0 or 1, and tests were one-sided, 0.5 was added to each cell in that stratum. Any heterogeneity found to be statistically significant was explored and if necessary, results were reported for each level of the categorical variable. Investigation of heterogeneity was confined to the primary endpoint using the week 48 snapshot analysis. Tests of homogeneity were assessed at the one-sided 10% level of significance. On-treatment data collected from extra visits within a window were included in the derivation of the snapshot response/failure but summary tables using observed case datasets only used the data captured closest to the target visit date.

The analyses for primary comparison were also performed using the PP population, and the results were compared for consistency with the results from the ITT-E population.

The proportion of virologic failures (HIV-1 RNA ≥50 c/mL per snapshot algorithm) for each treatment group and the difference between the two groups at week 48 were also summarized within demographic and baseline characteristic subgroups. The 95% CIs for the differences were calculated using an unconditional exact method with two inverted one-sided tests.

15.1.14.2. Sensitivity and Supportive Statistical Analyses Description

A key secondary efficacy analysis evaluated the proportion of subjects with HIV-1 RNA <50 c/mL per snapshot at week 48 based on the ITT-E population using the same analysis method and stratification factors as specified for the primary endpoint. A noninferiority margin of -10% was used for this secondary comparison; where if the lower limit of the 95% CI of the difference in responder rate between the two treatment groups was greater than -10%, then noninferiority was demonstrated.

The analysis described above was also be performed using the PP population and the results were compared for consistency with the results from the ITT-E population.

Similar subgroup analyses (as described for the primary efficacy endpoint) were also performed for the key secondary efficacy endpoint.

15.1.15. Other Efficacy Analysis

Proportion of subjects in each treatment group with plasma HIV-1 RNA <200 c/mL and <50 c/mL, and HIV-1 RNA ≥200 c/mL and ≥50 c/mL, respectively, over time during the maintenance phase was summarized using the snapshot algorithm. The proportion of subjects with CVF during the maintenance phase was also be summarized over time.

Time-to-event analyses of failure were performed to estimate the proportion of subjects in each treatment group without efficacy-related (ERDF) or treatment-related failure (TRDF), respectively, using the Kaplan-Meier nonparametric method. To account for missing data, follow-up time for subjects who did not experience the event of interest were censored at time of early withdrawal or end of the week 48 analysis window. For the ERDF, events included CVF or discontinuation because of lack of efficacy. For the TRDF analysis, events included confirmed virology failure or discontinuation for treatment-related reasons, such as lack of efficacy, ADR, protocol-defined safety stopping criteria and intolerability of injections. The estimated

proportion of subjects without any of these events at week 48 for each treatment group, and the treatment difference with 95% CI were presented.

Absolute values and changes from maintenance (day 1) baseline in plasma HIV-1 RNA and CD4+ lymphocyte count were summarized over time using descriptive statistics (mean, median, interquartile range, min and max). The incidence of HIV-1 disease progression (AIDS and death) during the maintenance phase was presented. Data from low level of HIV-1 RNA quantification were summarized at maintenance (day 1) baseline and week 48.

15.1.15.1. Safety Analysis

The safety analyses were performed on the safety population. Safety data collected during the maintenance phase up to the analysis cut-off date for this week 48 analysis are including in data tabulations (unless stated otherwise), including data beyond week 48 for the majority of subjects.

The proportion of subjects reporting AEs was tabulated for each treatment group. The following summaries of AEs are provided:

- Incidence and severity of all AEs
- Incidence and severity of treatment related AEs
- Incidence and severity of AEs leading to withdrawal
- Incidence of SAEs
- ISR AEs at the event level and subject level, separately

The extent of exposure was summarized for each treatment group. The adherence to CAB+RPV dosing schedule in relation to the projected date was assessed.

Changes from maintenance (day 1) baseline in laboratory (including fasting lipids), vital signs and ECG data were summarized. In addition, the number and percentage of subjects with worsening in graded laboratory toxicities relative to maintenance (day 1) baseline (based on DAIDS categories) was summarized by treatment group.

Changes from baseline in renal and bone biomarkers were summarized by treatment and visit.

Treatment differences with respect to log-transformed bone biomarker parameters at week 48 were assessed using an analysis of covariance (ANCOVA) model, including treatment, Log-transformed bone marker value at maintenance baseline (day 1) and other prespecified baseline and demographic characteristic factors as fixed effects. Model adjusted treatment differences and associated 95% CIs, expressed as the geometric treatment ratio (CAB+RPV over CAR), and p-values were presented.

15.1.15.2. Viral Genotyping/Phenotyping Analyses

The incidence of treatment emergent genotypic and phenotypic resistance was summarized by treatment arm for subjects meeting CVF criteria.

15.1.15.3. Pharmacokinetic Analyses

Plasma CAB and RPV concentration data were listed and summarized by week, day, and planned sampling time in both tabular and graphical forms.

The statistical analysis of log-transformed plasma steady state concentration was performed for CAB and RPV separately using a mixed effects ANOVA model with week (continuous variable)

as a fixed effect and subject as a random effect. Steady state would be claimed it the coefficient for the slope of the week effect on the (natural) log scale was close to 0 or the 90% CI for the slope estimate included 0. If steady-state is not demonstrated, concentrations from early weeks (e.g., week 16, 20, 24, etc.) were dropped in sequence and the analysis repeated until either steady state is shown or only two timepoints remained.

15.1.15.4. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between the plasma CAB and RPV concentrations and snapshot HIV-1 RNA ≥50 c/mL at week 48, and predictors of efficacy failure, were explored using univariable and multivariable logistic regression analysis (using backwards covariate selection of predictors that were significant in the univariable analysis with $p<0.15$). Fisher's exact test was also used as post hoc analyses when the univariate logistic model could not converge. In addition, the relationship between plasma CAB and RPV concentrations and the following measures during maintenance phase were assessed graphically:

- Change from maintenance baseline (day 1) in 2 hours postdose QTc at week 4b and week 48
- Maximum change from maintenance baseline (day 1) in ALT/total bilirubin
- The maximum toxicity grades of the five most common non-ISR AEs.

15.1.15.5. Health Outcomes Analyses

The following endpoints were summarized for the observed case values by visit during the maintenance phase. In addition, these endpoints were also summarized by visit with missing values imputed by last observation carried forward (LOCF):

- Change from maintenance baseline (day 1) in HIVTSQs total treatment satisfaction score 24 and 44
- Treatment satisfaction score (HIVTSQs change version) at week 48
- Change from maintenance baseline (day 1) in ACCEPT general acceptance score at week 8, 24 and 48
- Change from maintenance baseline (day 1) in SF-12: Preclinical services and MCS at week 24 and 48
- Change from maintenance baseline (day 1) in HATQoL (life satisfaction, HIV medications, disclosure worries) at week 24 and 48
- Change from week 5 in the PIN acceptance score at week 41 and week 48 (CAB+RPV arm only)
- Change from week 4b in tolerability of injections using NRS (CAB+RPV arm only).

A statistical comparison between treatment groups was performed at each visit for HATQoL, HIVTSQs, HIVTSQc, ACCEPT, and SF-12 using an ANCOVA model with treatment, age, induction baseline (week -20) viral load, sex at birth, race and baseline score value (except for HIVTSQc) as fixed effects and LOCF imputation for missing data.

Changes from week 5 in PIN acceptance score to week 41 and week 48, respectively, based on LOCF imputation for missing data were evaluated using a Wilcoxon signed-rank test.

15.1.16. Changes in Conduct of the Study or Planned Analyses

PK/PD (pharmacodynamics) efficacy analyses exploring predictors of snapshot failure:

- HIV-1 subtype was dichotomized post hoc into a two-level factor of A1 versus other; subgroup categories for CDC category, visit of first HIV-1 RNA <50 c/mL, and baseline CD4+ cell count were also collapsed post hoc for the purposes of logistic modelling.
- Fisher's exact tests were performed post hoc because planned analyses using univariate logistic models could not converge for some subgroups due to sparse data.

Additional post hoc analyses included:

- Change from baseline for HIVTSTs individual item scores summarized by visit.
- HIVTSTc individual item scores at week 48.
- Interaction plot to examine the interaction between treatment and baseline for HIVTSTs total score.
- Subgroup analysis of selected bone biomarker parameters based on presence of treatment-by-subgroup interactions.
- Figures of QTcF change from maintenance baseline (day 1) versus PK concentrations at week 4b and week 48.
- Exploratory subgroup analyses of the primary and key secondary efficacy endpoint were performed according to post hoc grouping of countries into geographic region.

15.2. Protocol 201585 - ATLAS

Table 158. Protocol Overview: 201585

Applicant	**ViiV Healthcare**
Drug name	Cabotegravir + Rilpivirine
Indication	Treatment of HIV-1 Infection
Protocol title	A phase III, randomized, multicenter, parallel group, noninferiority, open label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current INI, NNRTI, or PI based antiretroviral regimen in HIV 1 infected adults who are virologically suppressed
Source of information	Protocol amendment 4 dated 02-Nov-2017; week 48 CSR dated 09-Jan-2019
Trial identifiers	
Protocol number:	201585
Clinical phase:	III
EudraCT number:	2016-001647-39
Other codes:	Not applicable
IND number:	109,678
ClinicalTrial.gov identifier:	NCT02951052

Applicant	ViiV Healthcare
Ethics	The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable country-specific requirements, including United States (US) 21 Code of Federal Regulations (CFR) 312.3(b) for constitution of independent ethics committees.
Trial centers	This trial was conducted at 115 sites: 4 in Argentina, 4 in Australia, 6 in Canada, 8 in France, 10 in Germany, 2 in Italy, 1 in Mexico, 5 in Republic of Korea, 13 in the Russian Federation, 9 in South Africa, 14 in Spain, 3 in Sweden, and 36 in the United States.

Abbreviations: CSR = clinical study report, INI = integrase inhibitor, NNRTI = Nonnucleoside reverse transcriptase inhibitor, PI = protease inh bitor

15.2.1. Design

Table 159. Design of Protocol 201585

Planned Duration of Maintenance Phase	52 Weeks
Planned duration of extension phase	Following the completion of week 52 maintenance visit, participants have options to: rollover to the 207966 (ATLAS-2M) study, continue to have access to both CAB LA and RPV LA in the Extension Phase until study treatment is locally approved and commercially available:
Trial status	Extension phase is ongoing Week 48 CSR available: Primary endpoint analysis
Date of database lock	Planned Database lock: 12-Apr-2022
Other important dates	Primary week 48 report achieved: DBF: 31-Aug-2018 SAC: 14-Sep-18 CSR: 09-Jan-2019 Planned week 96 report DBF: 20-Jun-2019 SAC: 09-Aug-2019 Planned end of study report Planned Last Subject Last Visit: 08-Feb-2022 Planned Database Freeze: 12-Apr-2022

Abbreviations: CSR = clinical study report, DBF = database freeze, INI = Integrase inhibitor, NNRTI = Nonnucleoside reverse transcriptase inh bitor, PI = Protease inhibitor, SAC = Statistical analysis completion

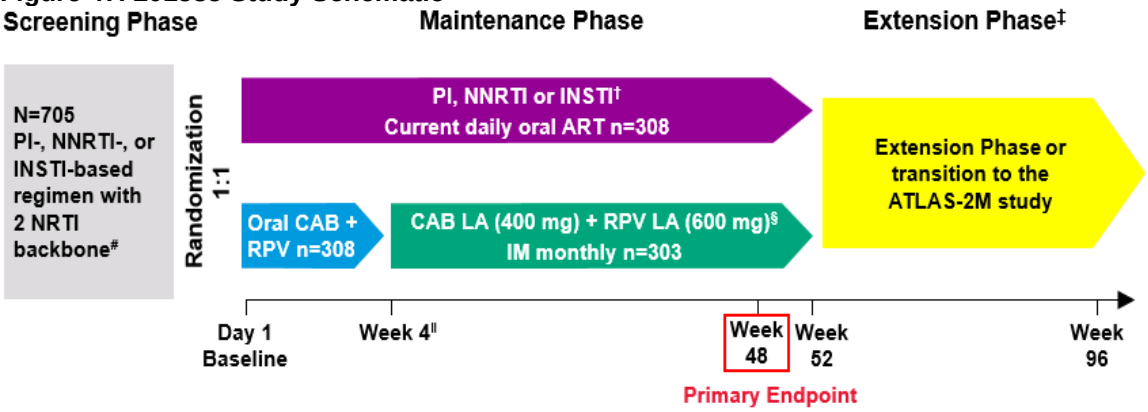
Study 201585 is a phase 3, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of a two-drug regimen of CAB plus RPV compared with maintenance of current first-line ARV regimen (CAR). A total of 618 adult HIV-1–infected patients who were on a stable ART regimen containing 2 NRTIs plus an INI, NNRTI, or PI were randomized 1:1 to continue CAR or were switched to the CAB+RPV regimen through 52 weeks (Figure 47). Following the week 52 visit, eligible subjects were given the option to transition to Study 207966 (comparing CAB+RPV every 4 weeks [Q4W] to CAB+RPV every 8 weeks [Q8W]) or to continue within the

Study 201585 extension phase. This study will continue (extension phase) until study treatment is locally approved and commercially available.

Randomization was stratified by baseline third agent class (PI, INI, or NNRTI), and sex at birth. The primary endpoint for the study was the proportion of subjects who met the snapshot virologic failure criteria, defined as plasma HIV-1 RNA ≥ 50 c/mL, at week 48. The proportion of subjects with plasma HIV-1 RNA <50 c/mL at week 48 using the snapshot algorithm for ITT-E population was a key secondary endpoint.

The planned sample size of 285 per group was such that the study had approximately 97% power to demonstrate noninferiority in the proportion of subjects with snapshot virologic failure at week 48 using a 6% margin, assuming a true 3% failure rate for CAB+RPV and a 2% failure rate for the CAR control group and using a 2.5% one-sided α level. This sample size was primarily chosen to accommodate the pooled analysis of data from this study and study 201584 (a phase 3, multiphase, randomized, open label, noninferiority study comparing CAB+RPV with oral ABC/DTG/3TC in HIV-1–infected, ART-naïve adult subjects). The combined sample size of 570 per treatment group for the pooled analysis would have 90% power to show noninferiority for the proportion of subjects with snapshot virologic failure at week 48 using a 4% non-inferiority margin, under the assumptions described. The randomized portion of the study continued for 52 weeks with an extension phase up to at least 96 weeks.

Figure 47. 201585 Study Schematic



Uninterrupted ART 6 months and VL <50 c/mL at screening, 2× VL <50 c/mL ≤12 months;
† INSTI-based regimen capped at 40% of enrollment; Triumeq excluded from study;
‡ Optional switch to CAB LA+RPV LA at week 52 for those on CAR;
§ Participants who withdraw/complete IM CAB LA+RPV LA must complete 52 weeks of follow-up;
‖ Participants received an initial loading dose of CAB LA (600 mg) and RPV LA (900 mg) at week 4b. From week 8 onwards, participants received CAB LA (400 mg) + RPV LA (600 mg) injections every 4 weeks.
Abbreviations: ART = antiretroviral therapy, CAB = cabotegravir, CAR = current antiretroviral, IM = intramuscular, INSTI = integrase strand transfer inhibitor, LA = long-acting, NNRTI = nonnucleoside reverse transcriptase inh bitor, NRTI = nucleoside RTI, PI = protease inh bitor, RPV = rilpivirine, VL = viral load

Maintenance Phase (Day 1 to Week 52)

Subjects were randomized (1:1) at day 1 to either continue on CAR or to discontinue CAR and begin oral therapy with CAB 30 mg+RPV 25 mg once daily for 4 weeks to determine individual safety and tolerability, prior to administration of CAB+RPV every 4 weeks. CAR dosing on day 1 was recommended to occur after randomization to avoid overlap of regimens (in the event that the subject was assigned to the CAB+RPV treatment group). At the week 4a visit, safety

assessments (e.g., clinical chemistries) were performed for those subjects randomized to receive CAB+RPV. At visit week 4b, subjects returned to the clinic, took the last dose of oral CAB+RPV, and received the first CAB LA [600 mg]+RPV LA [900 mg] injections (within 2 hours of the final oral dose of CAB+RPV). The first injection visit (week 4b) was performed once central lab results were available and safety parameters were reviewed. If a retest was required based on week 4a labs, the retest was performed as soon as possible (and preferably no later than 7 days following week 4a). Subjects remained on oral CAB 30 mg+RPV 25 mg until the week 4b injection visit, and until any required visit 4a retest results were available for review. The visit schedule following the OLI phase was based on timing of the first injection visit at week 4b such that the week 5 visit was performed approximately 7 days after the week 4b visit.

Extension Phase

Subjects who were randomized to continue CAR and successfully completed week 48 (without meeting study defined withdrawal criteria and remaining virologically suppressed: HIV-1 RNA <50 c/mL) were given the option at week 52 to switch to the CAB+RPV group in the extension phase or to complete the study. In addition, starting at week 52, subjects were given the option to transition to study 207966.

Long-Term Follow-Up Phase – CAB+RPV Only

Any subject who received at least a single dose of CAB LA and/or RPV LA and discontinues the CAB+RPV regimen for any reason must remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent the potential selection of INI- and/or NNRTI-resistant mutants. Investigators must discuss the choice of the follow-up HAART regimen with the Medical Monitor prior to initiating the new regimen with the subject. HAART therapy should be initiated within 4 weeks of the last injection. The long-term follow up will begin the day of the last CAB LA and/or RPV LA dose and continue for 52 weeks, or until CAB+RPV is locally approved and commercially available. Subjects will be assessed with clinic visits at months 1, 3, 6, 9 and 12 during the long-term follow-up (LTFU) phase.

15.2.2. Objectives in Base Study

The primary objective of this study was to demonstrate the non-inferior antiviral activity of switching to IM CAB LA+RPV LA compared to continuation of CAR over 48 weeks in HIV-1–infected ART-experienced subjects. The study will also provide important data regarding long-term antiviral activity, safety, tolerability, and patient satisfaction through week 96.

15.2.2.1. Primary Objective

To demonstrate the noninferior antiviral activity of switching to IM CAB+RPV every 4 weeks (monthly) compared to continuation of CAR over 48 weeks in HIV-1–infected ART-experienced subjects.

15.2.2.2. Secondary Objective

- To demonstrate the antiviral and immunologic activity of switching to IM CAB+RPV every 4 weeks (monthly) compared to continuation of CAR

- To evaluate the safety and tolerability of switching to CAB+RPV every 4 weeks (monthly) compared to continuation of CAR
- To evaluate the effects of CAB+RPV every 4 weeks on fasting lipids over time compared to continuation of CAR over time
- To assess viral resistance in subjects experiencing protocol-defined virologic failure
- To assess the impact of baseline third agent treatment class (INI, NNRTI, or PI) on efficacy, safety, tolerability, and viral resistance of CAB+RPV compared to continuation of CAR
- To characterize CAB and RPV concentrations and popPK and identify important determinants of variability
- To evaluate the antiviral and immunologic effects, safety, tolerability, and viral resistance of CAB+RPV for subjects during the extension phase
- For subjects randomized to CAB+RPV at day 1
- For subjects electing to transition to CAB+RPV in the extension phase
- To assess the acceptance of pain and ISRs following injections
- To assess the degree of HR QoL
- To assess health status
- To assess treatment satisfaction of CAB+RPV compared to continuation of CAR
- To assess treatment acceptance
- To assess tolerability of injections

15.2.2.3. Exploratory Objectives

- To explore the effect of patient characteristics (e.g., demographic factors, baseline CD4+ cell count) on the virologic and immunologic responses to CAB+RPV compared to continuation of CAR;
- To explore relationship(s) between plasma concentrations of CAB and RPV and pharmacodynamics endpoints;
- To evaluate renal and bone biomarkers in subjects treated with CAB+RPV compared to continuation of CAR;
- To assess preference for CAB+RPV compared to oral ARV using a single dichotomous preference question;
- To assess reason for switching using a single question.

15.2.3. Selection of Trial Population

15.2.3.1. Key Inclusion Criteria

- Males and nonpregnant, nonlactating females, aged 18 years or older (or ≥19 years where required by local regulatory agencies) at the time of signing the informed consent;

- Remained on uninterrupted current regimen (either the initial or second ARV regimen) for at least 6 months prior to screening. Any prior switch, defined as a change of a single drug or multiple drugs simultaneously, had to occur due to tolerability/safety, access to medications, or convenience/simplification, and must NOT have been done because of treatment failure (HIV-1 RNA ≥400 c/mL). Acceptable stable (initial or second) ARV regimens prior to screening included two NRTIs plus:
  - INI with the exception of ABC/DTG/ 3TC (either the initial or second CAR regimen);
  - NNRTI (either the initial or second CAR regimen);
  - Boosted PI (or ATV unboosted) (had to be either the initial CAR regimen or 1 historical within-class switch was permitted due to safety/tolerability);
- The addition, removal, or switch of a drug(s) that had been used to treat HIV based on ARV properties of the drug constituted a change in ART with the following limited exceptions:
  - Historical changes in formulations of ART drugs or booster drugs did not constitute a change in ART regimen if the data supported similar exposures and efficacy, and the change must have been at least 3 months prior to screening;
  - Historical perinatal use of an NRTI when given in addition to an ongoing HAART was not considered a change in ART regimen;
  - A change in dosing scheme of the same drug from twice daily to once daily was not considered a change in ART regimen if the data supported similar exposures and efficacy;
- Documented evidence of at least two plasma HIV-1 ribonucleic acid (RNA) measurements <50 c/mL in the 12 months prior to screening: 1 within the 6- to 12-month window and 1 within 6 months prior to screening;
- Plasma HIV-1 RNA <50 c/mL at screening.

15.2.3.2. Key Exclusion Criteria

- Any plasma HIV-1 RNA measurement ≥50 c/mL within 6 months prior to screening and after confirmed suppression to <50 c/mL on CAR regimen;
- Any plasma HIV-1 RNA measurement >200 c/mL, or two or more plasma HIV-1 RNA measurements ≥50 c/mL within the 6- to 12-month window prior to screening and after confirmed suppression to <50 c/mL;
- Any drug holiday during the window between initiating first HIV ART and 6 months prior to screening, except for brief periods (less than 1 month) where all ART was stopped due to tolerability and/or safety concerns;
- Any switch to a second-line regimen, defined as change of a single drug or multiple drugs simultaneously, due to virologic failure to therapy (defined as a confirmed plasma HIV-1 RNA measurement ≥400 c/mL after initial suppression to <50 c/mL while on first-line HIV therapy regimen);
- A history of use of any regimen consisting of only single NNRTI therapy (even if only for peri-partum treatment) or only single or dual NRTI therapy prior to starting CAR;

- Subjects who were currently participating in or anticipated being selected for any other interventional study;
- Any evidence of an active CDC stage 3 disease, except cutaneous Kaposi's sarcoma not requiring systemic therapy and historical or current CD4+ cell counts less than 200 cells/mm^3;
- Any pre-existing physical or mental condition (including substance use disorder) which, in the opinion of the Investigator, could interfere with the subject's ability to comply with the dosing schedule and/or protocol evaluations or which could compromise the safety of the subject;
- Subjects determined by the Investigator to have a high risk of seizures or posed a significant suicide risk.
- Tattoo or other dermatological condition overlying the gluteus region which could interfere with interpretation of ISRs.
- Evidence of HBV infection (based on the results of testing at screening for hepatitis B surface antigen [HbsAg], hepatitis B core antibody [anti-HBc], hepatitis B surface antibody [anti-HBs], and HBV DNA) or syphilis (based on RPR).
- Asymptomatic individuals with chronic HCV infection were not excluded. Subjects who were anticipated to require HCV treatment within 12 months were excluded (HCV treatment on study was permitted post week 48, following consultation with the medical monitor).
- Moderate to severe hepatic impairment; unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice or cirrhosis); known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment); or history of liver cirrhosis with or without hepatitis viral co-infection.
- Ongoing or clinically relevant pancreatitis, clinically significant cardiovascular disease, or any condition which, in the opinion of the Investigator, could interfere with the absorption, distribution, metabolism or excretion of the study drugs, or render the subject unable to receive study medication.
- Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, noninvasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localized malignancies required agreement between the investigator and the study medical monitor for inclusion of the subject prior to randomization.
- History or presence of allergy or intolerance to the study drugs or their components or drugs of their class. In addition, if heparin was used during PK sampling, subjects with a history of sensitivity to heparin or heparin-induced thrombocytopenia were not enrolled.
- Current or anticipated need for chronic anticoagulation with the exception of the use of low dose acetylsalicylic acid (≤325 mg).
- Any evidence of primary resistance based on the presence of any major known INI or NNRTI resistance-associated mutation, except for K103N.

- Any acute laboratory abnormality at screening, which, in the opinion of the investigator, precluded the subject's participation in the study of an investigational compound. Any grade 4 (verified) laboratory abnormality, estimated creatine clearance <50 mL/min per 1.73 m^2 via chronic kidney disease epidemiology collaboration method, ALT ≥3× ULN was excluded.
- Treatment with radiation therapy, cytotoxic chemotherapeutic agents, tuberculosis therapy with the exception of isoniazid (isonicotinylhydrazide), anticoagulation agents, or immunomodulators that alter immune responses within 28 days of screening:
- Current or prior history of etravirine (ETR) use.
- Current use of tipranavir/ritonavir, or fosamprenavir/ritonavir, or medications that were associated with Torsade de Pointes, or received any prohibited medication and were unwilling or unable to switch to an alternate medication.

15.2.4. Hypotheses

The study was designed to demonstrate that switching to CAB+RPV is noninferior to continuation of CAR at week 48 in HIV-1–infected ART-experienced subjects.

For this study, noninferiority in the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL at week 48 was concluded if the upper bound of a two-sided 95% CI for the difference in the proportion between the 2 treatment groups ([CAB+RPV] – CAR) was not more than 6%.

If f_{la} is the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL for CAB+RPV, and f_c is the proportion for CAR, then the hypotheses can be written as follows:

- Null hypothesis (H_0):: $f_{la} - f_c \geq 6\%$
- Alternative hypothesis (H_1): $f_{la} - f_c < 6\%$

The data from this study, together with data from a separate study, 201584, were combined to assess noninferiority in the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL at week 48. Noninferiority was concluded if the upper bound of a two-sided 95% CI for the difference in the proportion between the two treatment groups ([CAB+RPV] – CAR) was not more than 4%.

15.2.5. Treatment Groups

Subjects were randomly assigned to receive treatment with oral CAB 30 mg+RPV 25 mg once daily for approximately 4 weeks during the OLI period, followed by
CAB LA 600 mg+RPV LA 900 mg IM at week 4, CAB LA 400 mg+RPV LA 600 mg IM at week 8 and Q4 weekly thereafter for 52 weeks, or to remain on their CAR. The randomized portion of the study will continue with an extension phase up to at least 96 weeks. In addition, starting at week 52, subjects were also given the option to transition to study 207966.

15.2.6. Endpoints and Definitions

15.2.6.1. Primary Efficacy Endpoint

Proportion of subjects with a 'virologic failure' endpoint as per the snapshot algorithm at week 48 (ITT-E population).

15.2.6.2. Secondary Efficacy Endpoint

- Proportion of subjects with plasma HIV-1 RNA <50 copies/mL (c/mL) at week 48 using the snapshot algorithm (missing, switch or discontinuation = failure, ITT-E population).
- Proportion of participants with plasma HIV-1 RNA <50 c/mL over time including week 96 (observed case).
- Proportion of subjects with plasma HIV-1 RNA <200 c/mL at week 48 using the snapshot algorithm (ITT-E population).
- Proportion of subjects with CVF (2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) at week 48.
- Proportion of participants with CVF (two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) through week 96.
- Absolute values and change from baseline in plasma HIV-1 RNA (log_{10} c/mL) at week 48 and week 96.
- Absolute values and change from baseline in CD4+ lymphocyte count at week 48 and week 96.
- Incidence of disease progression (HIV-associated conditions, AIDS, and death over 48 weeks and 96 weeks, respectively.

15.2.6.3. Exploratory Efficacy Endpoints

- Proportion of subjects by subgroup(s) (e.g., by age, sex at birth, BMI, race, HIV-1 subtype, baseline CD4+ cell count) with virologic failure over time including week 48 using the snapshot algorithm for the ITT-E population.
- Proportion of subjects by subgroup(s) (e.g., by age, sex at birth, BMI, race, HIV-1 subtype, baseline CD4+ cell count) with plasma HIV-1 RNA <50 c/mL over time including week 48 using the snapshot algorithm for the ITT-E population.
- Change from baseline in CD4+ cell counts by subgroups at week 48.
- Relationship between plasma PK concentrations and virologic, immunologic responses, and/or occurrence of AEs over time may be explored.
- Absolute value and change from baseline in renal (in urine and blood), and bone (in blood) over time.
- For patients randomized to the "CAB LA+RPV LA" arm, preference for CAB LA+RPV LA compared to oral ARV regimen, at week 48

- For patients randomized to the "Current ART" arm who switched to the injectable treatment, preference for CAB LA+RPV LA compared to current ART regimen at week 96 (end of extension phase- secondary analysis)
- The reasons for willingness to switch ART at baseline and for patients randomized to the "Current ART" arm at week 52.

15.2.6.4. Primary (Tier 1) Safety Endpoints

There are no primary safety endpoints.

15.2.6.5. Secondary (Tier 2) Safety Endpoints

- Incidence and severity of AEs and laboratory abnormalities over time including week 48 and week 96.
- Proportion of participants who discontinue treatment due to AEs over time including week 48 and week 96.
- Absolute values and changes in laboratory parameters over time including week 48 and week 96.
- Change from baseline in fasting lipids over time including week 48 and week 96.

15.2.6.6. Virology/Microbiology Endpoint

Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV and other on-study ART at week 48 and week 96.

15.2.6.7. Pharmacokinetic Endpoints

To characterize CAB and RPV concentrations and pop-PK and identify important determinants of variability.

- Plasma PK parameters for CAB LA and RPV LA (when evaluable, C_{trough}, concentrations postdose [~C_{max}], and area under the curve [AUC])
- Demographic parameters including, but not limited to, age, sex, race, body weight, BMI, and relevant laboratory parameters will be evaluated as potential predictors of inter- and intraparticipant variability for pharmacokinetic parameters

15.2.6.8. Value Evidence and Outcomes Endpoints

- Change from week 5 in dimension scores ("bother of ISRs", "leg movement", "sleep", and "injection acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the PIN questionnaire.
- Proportion of participants considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using the PIN questionnaire.
- Change from baseline in HRQoL using the HIV/AIDS-targeted QoL questionnaire (HATQoL) short form at week 24, week 48, week 96 (or withdrawal).

- Change from baseline in health status at week 24, week 48, and week 96 (or withdrawal) using the 12-item Short Form Survey (SF-12).
- Change from baseline in total "treatment satisfaction" score, and individual items scores of the HIVTSQs at weeks 4b, 24, 44, 96 (or withdrawal)
- Change in treatment satisfaction over time using the HIVTSQc at week 48 (or withdrawal) for CAB LA+RPV LA arm only
- Change from baseline in treatment acceptance at week 8, week 24, week 48, week 96 (or withdrawal) using the "General acceptance" dimension of the ACCEPT questionnaire.
- Change from week 4b in tolerability of injection at week 5, week 40, week 41, and week 96 using the NRS within the CAB+RPV arm.

15.2.7. Interim Analysis (if Applicable)

No interim analyses beyond the IDMC purpose were conducted.

15.2.8. Data Monitoring Committee

An IDMC was instituted to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of subjects and to protect the scientific validity of this study (201585) and study 201584.

An ad hoc review of data by the IDMC was to be triggered whenever the number of CVFs in the CAB LA+RPV LA exceeds thresholds prespecified in the IDMC charter. An IDMC evaluated interim efficacy, tolerability, safety, and PK of CAB+RPV at predefined times during the study. An interim futility analysis was performed for the IDMC with approximately 50% of subjects who reached week 24 to allow this analysis to complete prior to any subjects transitioning to the extension phase at week 52. In addition, the IDMC also monitored the incidence of subjects meeting PDVF criteria to ensure that subjects were not being suboptimally treated in the CAB+RPV group. In addition, the IDMC also monitored the incidence of participants meeting CVF criteria through week 48 to ensure that participants are not being suboptimally treated in the CAB+RPV arm.

15.2.9. Endpoint Adjudication Committee

For the CAB+RPV group only, cases meeting LSC were evaluated by an independent hepatic adjudication committee operating under an Adjudication Committee Charter.

15.2.10. Sample Size Considerations

15.2.10.1. Sample Size Assumptions

This study planned to randomize approximately 285 subjects per treatment group. Assuming the true proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL was 3% for the CAB+RPV treatment group and 2% for the CAR group, a noninferiority margin of 6%, and a 2.5% one-sided significance level, this provided approximately 97% power to show noninferiority for the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL at week 48.

This sample size of 285 subjects per treatment group also provided at least 90% power to show noninferiority in the proportion of subjects with plasma HIV-1 RNA <50 c/mL (snapshot algorithm) at week 48 over a range of true response rates on the basis of a 10% noninferiority margin and 2.5% one-sided significance level. Assuming true response rates for the CAB+RPV group and the CAR group were both 87%, the power was at least 94% to show noninferiority for this key secondary endpoint.

The combined sample size from both studies (201585 and 201584; 570 pooled per group) provided 90% power, under the assumptions described, to show noninferiority for the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL at week 48.

15.2.11. Rationale for Noninferiority Margin

As this study (201585) and study 201584 were not sufficiently powered individually to rule out 4% virologic failure in excess, the 6% margin chosen in each study can be viewed as defining criteria for assessing the consistency acceptability of the study-specific results prior to integration of the studies in the pooled analysis. Assuming an observed control failure rate of 2%, noninferiority would be shown in an individual study using a 6% margin if the observed CAB+RPV failure rate was less than 5% (that is, if the observed treatment difference was less than 3 percentage points). Accordingly, if the individual studies were successful in ruling out a 6% margin, the observed results were expected to be similar and reasonable to integrate for the purposes of the primary efficacy assessment based on the pooled analysis. In addition, a virologic failure rate in this range may be clinically tolerable given the CAB+RPV regimen may offer important advantages over standard three-drug oral regimens, such as better tolerability, as well as improved adherence and treatment satisfaction in virologically-suppressed subjects. Therefore, 6% was considered to be a reasonable noninferiority margin for the individual studies, with a more stringent 4% margin applied for the pooled analysis.

The noninferiority margin of 6% was chosen in consideration of the FDA 2015 guidance document,[2] which was the most current regulatory guidance from either the EMA or FDA and included specific recommendations regarding switch studies. It suggested that margins in the neighborhood of 4% were clinically tolerable, with typical observed rates of virologic failure ranging from 1% to 3%.

15.2.12. Response Rate Assumptions

Assumption for Virologic Failure Rate (per FDA Snapshot Algorithm) at Week 48 (Primary Endpoint)

The control arm comprised of subjects whose viral load at time of randomization was suppressed (<50 c/mL) on INI-, NNRTI- or PI- based regimens. Based on these data, reasonable assumptions for the true failure rates are 2% for the control arm and 3% for the CAB LA+RPV LA injectable regimen.

Assumption for Response Rate (per FDA Snapshot Algorithm) at Week 48 (Secondary Endpoint)

A reasonable assumption for the true success response rate (HIV-1 RNA <50 c/mL) for both arms was 87%.

15.2.13. Analysis Population and Timepoint Description

- **All subjects screened population:** Comprised all subjects screened for inclusion in the study.
- **Randomized population:** Included all randomized participants.
- **ITT-E population:** The ITT-E population consisted of all randomly assigned subjects who received at least 1 dose of the study drug. Subjects were assessed according to their randomized treatment, regardless of the treatment they received. The population used in the primary efficacy analysis was the ITT-E population.
- **PP population:** The PP population consisted of all subjects in the ITT-E population with the exception of those with important protocol deviations which potentially affects primary or key secondary efficacy analysis. The PP population was used for sensitivity analysis of the primary and key secondary efficacy endpoints.
- **PK population:** The PK population included all subjects who received CAB and/or RPV and underwent PK sampling during the study and provided evaluable CAB and/or RPV plasma concentration data. Subjects in this population were included in the PK analysis.
- **Safety population:** The safety population consisted of all randomly assigned subjects who received at least one dose of the study drug. Subjects were assessed according to the actual treatment received. Unless otherwise stated, the Safety population was used for safety analyses.
- **Confirmed virologic failure population:** The CVF population comprised all subjects in the ITT-E population who met CVF criteria.
- **Extension switch population:** This population consisted of all randomized subjects from the CAR group who received at least one dose of CAB and/or RPV during the extension phase of the study.
- **LTFU population:** Included all subjects receiving at least one dose of CAB LA and/or RPV LA who have discontinued the CAB LA+RPV LA regimen and have at least one LTFU phase clinic visit.
- **Futility analysis population:** Included of all subjects in the ITT-E population and who started study treatment at least 169 days prior to the IDMC cut-off date (in order to account for subjects who withdrew early but would have achieved week 24)

15.2.14. Analysis Description

15.2.14.1. Primary Efficacy Analysis Description

The primary analyses were based on the ITT-E population using the snapshot dataset. The primary comparison was made at a one-sided 2.5% level of significance. Treatment with

CAB+RPV was to be declared noninferior to CAR if the upper end of a two-sided 95% CI for the difference between the two groups ([CAB+RPV] - CAR) in the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL at week 48 was below 6%.

For the primary comparison, adjusted estimates of the difference in the proportion of subjects with snapshot HIV-1 RNA ≥50 c/mL between the two treatment groups were presented along with CIs based on a stratified analysis using CMH weights. All CIs were two-sided, and the analyses were stratified according to the baseline third agent class (INI, NNRTI, or PI) and sex at birth. The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in response rates between the two groups.

The weighted least squares chi-squared statistic was used to test for one-way homogeneity across the levels of each categorical variable, with each stratification factor considered separately. If the stratum-specific rate estimates of either f_{la} or f_c were 0 or 1, and tests were one-sided, 0.5 was added to each cell in that stratum. Any heterogeneity found to be statistically significant was explored and if necessary, results were reported for each level of the categorical variable. Investigation of heterogeneity was confined to the primary endpoint using the week 48 snapshot analysis. Tests of homogeneity were assessed at the one-sided 10% level of significance. On-treatment data collected from extra visits within a window were included in the derivation of the snapshot outcome.

The analyses for primary comparison were also performed using the PP population, and the results were compared for consistency with the results from the ITT-E population.

The proportion of virologic failures (HIV-1 RNA ≥50 c/mL per snapshot algorithm) for each treatment group and the difference between the two groups at week 48 were also summarized by subgroups (baseline third agent class, sex at birth, age, race, and country, baseline CD4+ cell count, baseline CDC, and baseline viral load). The 95% CIs for the differences were calculated using both the normal approximation and an unconditional exact method with two inverted one-sided tests, separately.

15.2.14.2. Sensitivity and Supportive Statistical Analyses Description

A key secondary efficacy analysis evaluated the proportion of subjects with HIV-1 RNA <50 c/mL per snapshot at week 48 using a CMH test stratified by baseline third agent class (INI, NNRTI, or PI) and sex at birth. A noninferiority margin of -10% was used for this secondary comparison; if the lower limit of the 95% CI of the difference in responder rate between the two treatment groups was greater than -10%, then non-inferiority was demonstrated. Sensitivity analyses of the key secondary endpoint were also conducted.

Similar subgroup analyses (as described for the primary efficacy endpoint) were also performed for the key secondary efficacy endpoint.

15.2.15. Other Efficacy Analysis

The proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL, respectively, for the ITT-E population over time was summarized using the snapshot algorithm. The proportion of subjects with CVFs was also summarized over time.

The proportion of subjects without virologic (ERDF) or virologic/tolerability (TRDF) failure was estimated using the Kaplan-Meier nonparametric method based on the time to the event (events including CVF or TRDF/ERDF such as ADR, intolerability of injection, protocol defined safety stopping criteria, or lack of efficacy). Subjects without any of these events were censored. The estimate of the standard error used to derive CIs for the difference in proportions between treatment groups was based on Greenwood's formula. The estimated proportion of subjects without any of these events at week 48 for each group, the difference, and its 95% CI between two groups were presented. Absolute values and changes from baseline in plasma HIV-1 RNA and CD4+ lymphocyte count were summarized over time. The incidence of HIV-1 disease progression (AIDS and death) was presented. Data from low level of HIV-1 RNA quantification were summarized at baseline and week 48.

15.2.15.1. Safety Analysis

The safety analyses were performed on the safety population.

The proportion of subjects reporting AEs was tabulated for each treatment group. The following summaries of AEs were provided:

- Incidence and severity of all AEs
- Incidence and severity of treatment related AEs
- Incidence and severity of AEs leading to withdrawal
- Incidence of SAEs
- ISR AEs at the event level and subject level, separately

The incidence and severity of treatment-related AEs, SAEs, and AEs leading to withdrawal were also assessed by baseline third agent class.

The extent of exposure was summarized for each treatment group. The adherence to the monthly dosing schedule in relation to the projected date was assessed.

Changes from baseline in laboratory (including fasting lipids) and vital signs data were summarized by visit and treatment group. In addition, the number and proportion of subjects with graded laboratory toxicities (based on DAIDS categories) were summarized by treatment group. The number and proportion of subjects with graded laboratory toxicities and the change from baseline in fasting lipids were also assessed by baseline third agent class.

Change from baseline in renal and bone biomarkers was summarized by treatment and visit.

The change of each bone marker at week 48 from baseline was analyzed for the comparison between the 2 treatment groups, using an ANCOVA model. Baseline third agent class, use of tenofovir disoproxil fumarate (TDF) at baseline, baseline demographic characteristics, and log-transformed biomarker at baseline were included in the model. Interaction between treatment and ART third agent class and interaction between treatment and TDF at baseline were examined.

15.2.15.2. Viral Genotyping/Phenotyping Analyses

The incidence of observed genotypic and phenotypic resistance to CAR, CAB, or RPV was summarized for subjects meeting CVF criteria (i.e., CVF population).

15.2.15.3. Pharmacokinetics Analyses

Plasma CAB and RPV concentrations were summarized by visit for the subjects switching to CAB+RPV during the maintenance phase.

The statistical analysis of plasma steady state concentration was performed for CAB and RPV separately.

15.2.15.4. Pharmacokinetics/Pharmacodynamics Analyses

The relationship between plasma CAB and RPV concentrations and the efficacy measure (i.e., snapshot HIV-1 RNA ≥50 c/mL at week 48) was analyzed. In addition, the relationship between plasma CAB and RPV concentrations and the following safety measures during maintenance phase was assessed:

- Maximum change from baseline in ALT/total bilirubin;
- 2 hours postdose QTc at week 4B and week 48;
- The maximum toxicity grades of the top five most common non-ISR AEs.

15.2.15.5. Health Outcomes Analyses

The following endpoints were summarized for the observed case values by visit during the maintenance phase. In addition, these endpoints were also summarized by visit with missing values imputed by LOCF.

- Change from week 5 in dimension scores and proportion of subjects considering pain and local reactions following injection using PIN (CAB+RPV group only)
- Change from baseline in HR QoL using HATQoL
- Change from baseline in health status using SF-12
- Change from baseline in treatment acceptance using ACCEPT
- Change from week 4b in tolerability of injection [NRS] (CAB+RPV group only)
- Change from baseline in total treatment satisfaction score and individual item scores of the HIV treatment satisfaction status (HIVTSQs)
- Total treatment satisfaction score change and individual item scores of the HIV treatment satisfaction score change (HIVTSQc) for CAB+RPV group only
- Patients' treatment preference at week 48 (CAB+RPV group only)
- Patient reported reasons for willingness to switch therapies

A statistical comparison between the two treatment groups was performed at each visit for HATQoL, HIVTSQs, ACCEPT, and SF-12 using an ANCOVA model with covariates (treatment, age, baseline third agent class, sex at birth, and race and baseline score value) included in the model.

15.2.16. Changes in Conduct of the Study or Planned Analyses

No major changes were made to the formal statistical analysis of the primary or the secondary comparisons planned in the protocol and/or RAP. However, several additional displays after the randomization schedule had been released are included in the clinical study report. These summaries/analyses were not detailed in the RAP.

- Summary of non-ISR ADRs by SOC and maximum toxicity – maintenance phase
- Summary of non-ISR AEs by SOC and maximum toxicity – maintenance phase
- Summary of subject-level characteristics of ISR AEs – overall and common (maintenance phase) by baseline BMI group

The following displays used exact statistical method to derive 95% CIs for the efficacy treatment difference in all subgroup analyses. This method could be more appropriate when the number of events and/or sample sizes are small, which is the case in many of the subgroups in this study.

- Treatment by strata tests of homogeneity for proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at week 48 (maintenance phase) – exact CI – snapshot analysis
- Summary of analysis for proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at week 48 by subgroup (maintenance phase) – exact CI – snapshot analysis
- Treatment by strata tests of homogeneity for proportion of subjects with plasma HIV-1 RNA <50 c/mL at week 48 (maintenance phase) exact CI – snapshot analysis
- Summary of analysis for proportion of subjects with plasma HIV-1 RNA <50 c/mL at week 48 by subgroup (maintenance phase) – exact CI – snapshot analysis

The following summaries have been included in the protocol but were omitted in error from the RAP:

- Summary of HIVTSQs - Change from baseline in individual item score by visit - LOCF (maintenance phase)
- Summary of HIVTSQc - Individual item score at week 48 (maintenance phase)

The following displays cover the conditional use of expanded analysis windows for the snapshot over time displays (i.e., use the default window based on the midpoint rule between visits (e.g., ±2 weeks) in the first instance as described in the RAP; if there is no viral load within the default window, then the upper bound of analysis window was expanded to +6 weeks in this post hoc analysis. This expanded analysis was to address the different visit scheduling per protocol for the CAB+RPV group (relative to week 4b) versus CAR group (relative to day 1). The different scheduling between the 2 groups resulted in misleading snapshot analysis over time with the default window because some subjects in CAB+RPV group had a duration >2 weeks between week 4a and week 4b.

- Proportion (95% CI) of subjects with HIV-1 RNA ≥50 c/mL by visit – snapshot analysis with expanded analysis window

- Proportion (95% CI) of subjects with HIV-1 RNA <50 c/mL by visit – snapshot analysis with expanded analysis window
- Proportion (95% CI) of subjects with HIV-1 RNA ≥200 c/mL by visit – snapshot analysis with expanded analysis window
- Proportion of subjects with plasma HIV-1 RNA ≥50 c/mL by visit (maintenance phase) – snapshot analysis with expanded analysis window
- Proportion of subjects with plasma HIV-1 RNA ≥50 c/mL by subgroup and visit (maintenance phase) – snapshot analysis with expanded analysis window
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL by visit (maintenance phase) – snapshot analysis with expanded analysis window

16. Efficacy Assessment Additional Information and Assessment

16.1. Results From LATTE and LATTE-2 Trials

The dose selected for the phase 3 trials was based on the efficacy and safety from two phase 2b trials, LATTE and LATTE-2.

LATTE was conducted to support dose selection of oral CAB for use in combination with the marketed dose of oral RPV 25 mg. A total of 244 subjects were randomized 1:1:1:1 to CAB 10 mg + NRTIs, 30 mg + NRTIs, 60 mg + NRTIs, and control + NRTIs group. The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA <50 copies/mL at week 24. LATTE-2 was a dose finding study for the IM dosing. After 20 weeks of OLI using CAB + ABC/3TC, a total of 286 subjects were randomized 2:2:1 to CAB+RPV IM Q4W, Q8W, or oral CAB+ABC/3TC group. The primary efficacy endpoint was the proportion of subjects with HIV-1 RNA <50 copies/mL at week 32. The main efficacy results can be found in the following table:

Table 160. Results of Efficacy, LATTE and LATTE-2

Study	Treatment Arm	Completed Primary Endpoint/No Enrolled	Primary Efficacy Variable	Primary Endpoint Proportion of Subjects with HIV-1 RNA <50 c/mL at Week 24 n/N (%) (Snapshot Analysis)	Secondary Endpoint Proportion of Subjects with HIV-1 RNA <50 c/mL n/N (%) Snapshot Analysis		
					Week 48	Week 96	Week 144 [a]
LAI116482	CAB 10 mg	52/60	Viral Load HIV-1 RNA c/mL	52/60 (87)	48/60 (80)	41/60 (68)	-
	CAB 30 mg	53/60		51/60 (85)	48/60 (80)	45/60 (75)	122/181 (67)
	CAB 60 mg	55/61		53/61 (87)	53/61 (87)	51/61 (84)	-
	EFV 600 mg	46/62		46/62 (74)	44/62 (71)	39/62 (63)	-
200056	CAB Q4W IM	105/115	Viral Load HIV-1 RNA c/mL	108/115 (94)	105/115 (91)	100/115 (87)	95/115 (83)
	CAB Q8W IM	112/115		109/115 (95)	106/115 (92)	108/115 (94)	104/115 (90)
	Oral CAB + ABC/3TC	50/56		51/56 (91)	50/56 (89)	47/56 (84)	-
	Optimized CAB Q4W IM	-		-	-	-	10/10 (100)
	Optimized CAB Q8W IM	-		-	-	-	33/34 (97)

Source: Applicant's summary of clinical efficacy, Appendix Table 2
Abbreviations: 3TC = lamivudine, ABC = abacavir, CAB = cabotegravir, EFV = efavirenz, IM = intramuscular, Q8W = every 8 weeks

For LATTE, higher proportions of virologic suppression were observed for all three doses of CAB compared to the control arm. There was no differentiated dose-response relationship observed. For LATTE-2, both CAB Q4W and Q8W regimens had higher rate of virologic suppression at week 32 compared to the CAB oral regimen. Together with PK and safety evaluations, those efficacy results from both LATTE and LATTE-2 lead to the decision of oral and IM dosing for the subsequent phase 3 trials.

16.2. Additional Analyses for FLAIR and ATLAS

Week 48 Virologic Categories Using FDA Snapshot Algorithm

A few subjects did not have virologic data at week 48 window. Based on FDA snapshot algorithm, they were further categorized as 'discontinued due to AE or death', 'discontinued for other reasons,' and 'missing data during window but on study' (Table 161). Compared to the control arm, CAB+RPV arm had a slightly higher percentage of discontinuation due to AE.

Table 161. Week 48 Virologic Categories by FDA Snapshot Algorithm, FLAIR and ATLAS

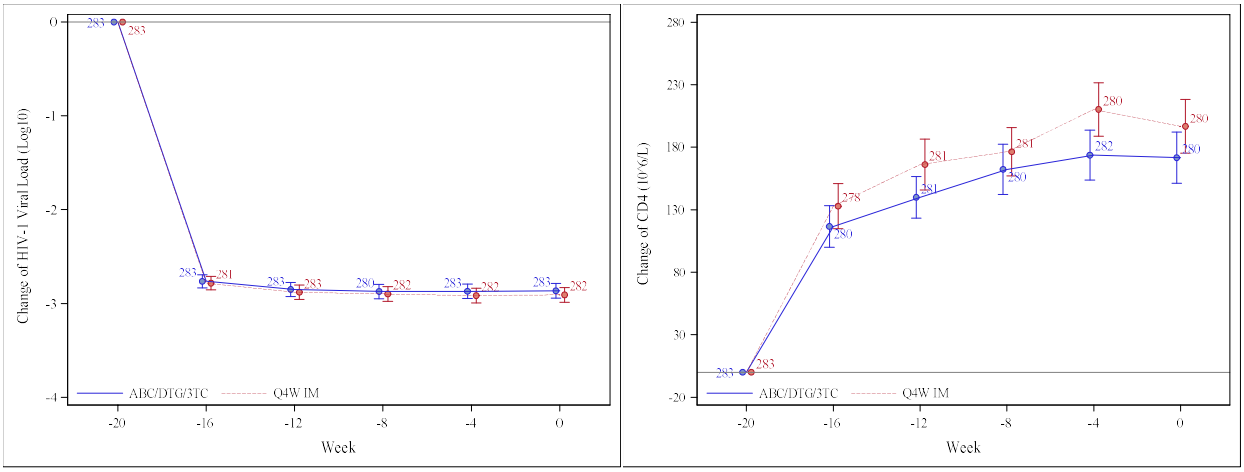
Category	Subcategory	FLAIR		ATLAS	
		CAB+RPV	CAR	CAB+RPV	CAR
HIV-1 RNA ≥50 copies/mL		6/283 (2.1%)	7/283 (2.5%)	5/308 (1.6%)	3/308 (1%)
HIV-1 RNA <50 copies/mL		265/283 (93.6%)	264/283 (93.3%)	285/308 (92.5%)	294/308 (95.5%)
No virologic data at week 48 window	Discontinued due to AE or death	8/283 (2.8%)	2/283 (0.7%)	11/308 (3.6%)	5/308 (1.6%)
	Discontinued for other reasons	4/283 (1.4%)	10/283 (3.5%)	7/308 (2.3%)	6/308 (1.9%)
	Missing data during window but on study	0	0	0	0

Source: Reviewer's analysis using ADEFFOUT.xpt
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

Change in HIV-1 RNA (Log_{10}) and CD4+ Cell Counts During Induction Phase

Subjects enrolled in FLAIR were treatment-naïve population, and ART was administered to all of them so that virologic suppression could be achieved prior to randomization. The changes in HIV-1 RNA (log_{10}) and CD4+ cell counts from the induction baseline to the end of the 20-week induction phase were plotted (Figure 48). As expected, HIV-1 RNA reduction and CD4+ cell count increase happened right after ART was used.

Figure 48. Change From Induction Baseline and 95% CI, HIV-1 RNA (Log_{10}), and CD4+ Cell Counts, Trial FLAIR, Induction Phase

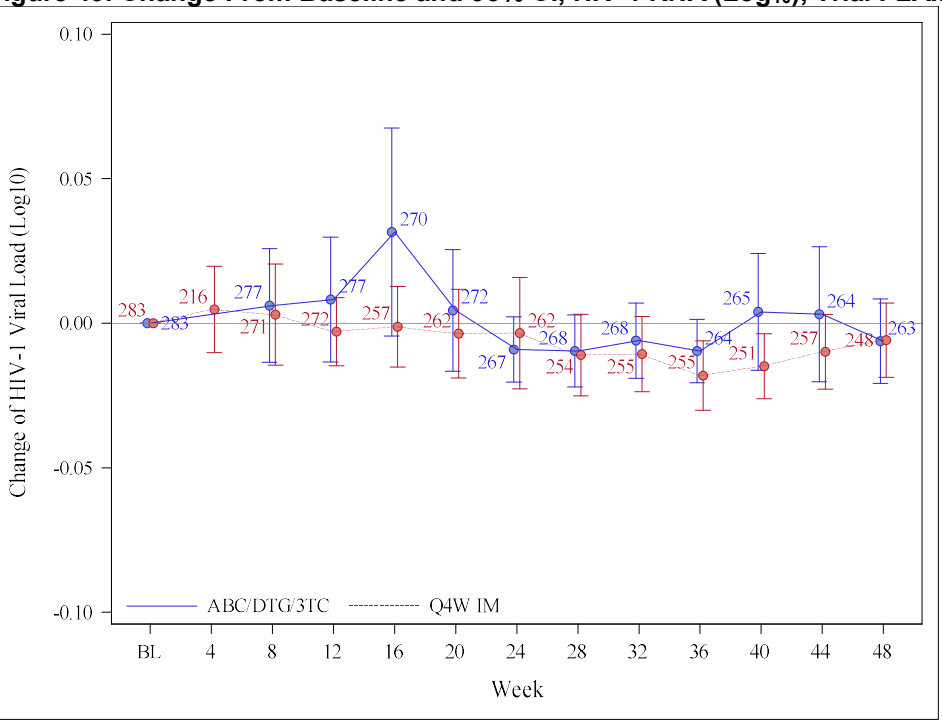


Source: Reviewer's analysis using ADLB.xpt
Note: Numbers on the graph represent the sample size at each visit. In case more than one measurements were reported at a certain visit, the measurement value with the later date was used for calculation
Abbreviations: 3TC = lamivudine, ABC = abacavir, CI = confidence interval, DTG = Dolutegravir, IM = intramuscular, Q4W = every 4 weeks

Change in HIV-1 RNA (Log_{10}) Through Week 48

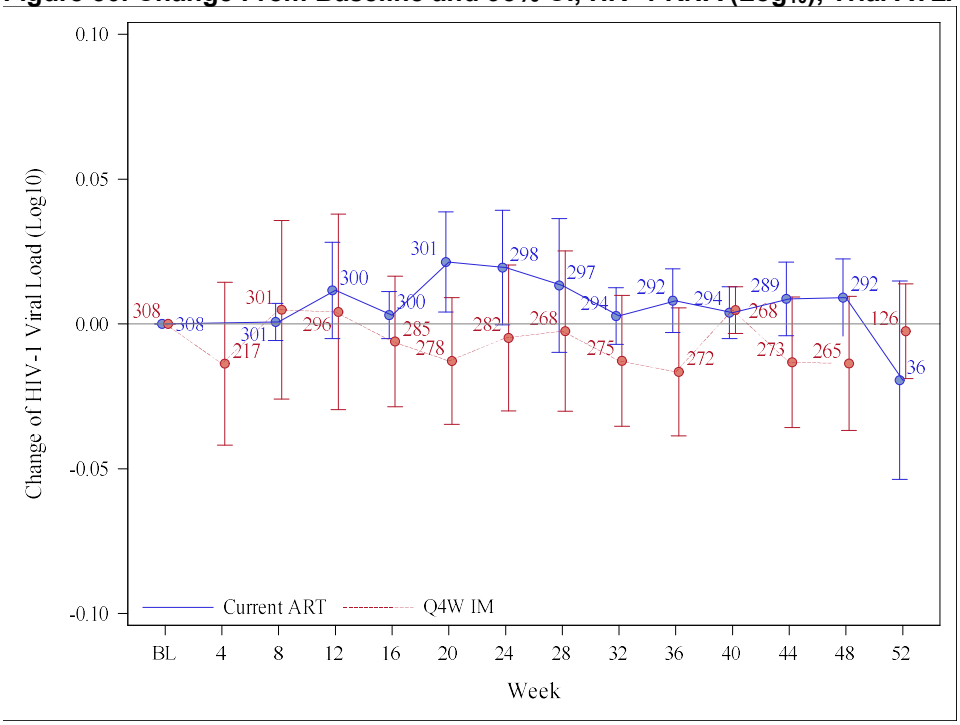
For both trials, subjects were virologically suppressed prior to randomization. Therefore, the changes in HIV-1 RNA (log_{10}) from baseline through week 48 were not expected to be clinically meaningful over time or between the two treatment arms (Figure 49 and Figure 50).

Figure 49. Change From Baseline and 95% CI, HIV-1 RNA (Log_{10}), Trial FLAIR, Maintenance Phase



Source: Reviewer's analysis using ADLB.xpt
Note: Numbers on the graph represent the sample size at each visit. In case more than one measurements were reported at a certain visit, the measurement value with the later date was used for calculation
Abbreviations: 3TC = lamivudine, ABC = abacavir, BL = baseline, CI = confidence interval, DTG = Dolutegravir, IM = intramuscular

Figure 50. Change From Baseline and 95% CI, HIV-1 RNA (Log_{10}), Trial ATLAS, Maintenance Phase

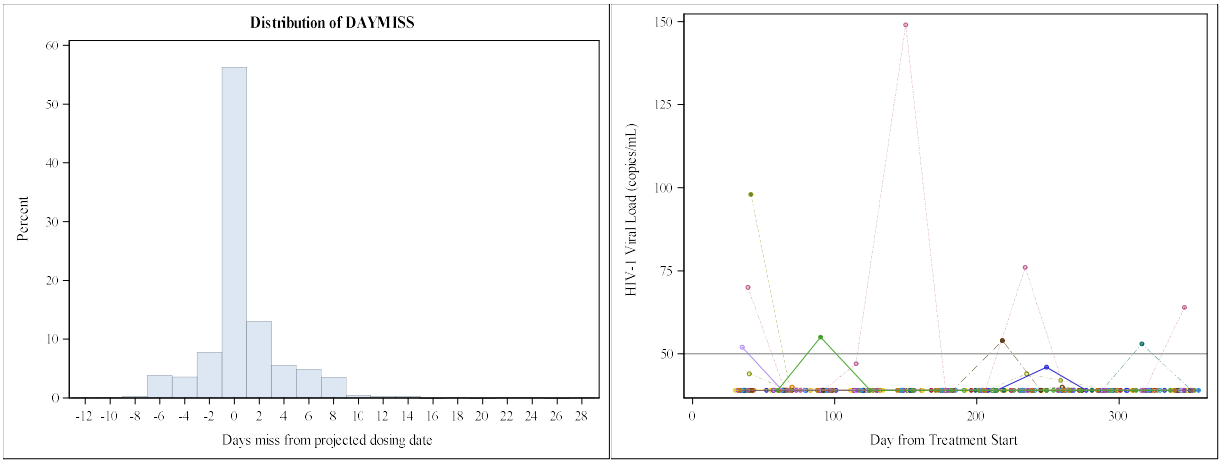


Source: Reviewer's analysis using ADLB.xpt
Note: Numbers on the graph represent the sample size at each visit. In case more than one measurements were reported at a certain visit, the measurement value with the later date was used for calculation
Abbreviations: ART = antiretroviral therapy, CI = confidence interval, IM = intramuscular, Q4W = every 4 weeks

Adherence to Injection Schedule

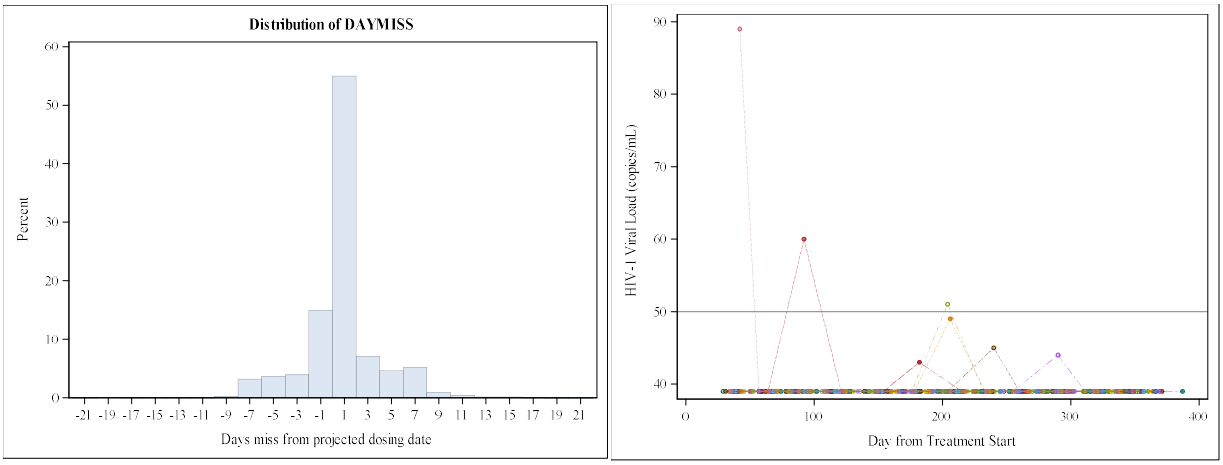
Subjects enrolled in both FLAIR and ATLAS adhered to the injection schedules well. Over 97% of the injections happened within the ±7-day window of the projected injection date. The number of subjects who had injections outside of 7-day window for FLAIR and ATLAS trials were 34 and 45, respectively. Among them, no one had virologic failure at week 48. HIV-1 RNA loads over time for these patients are plotted (Figure 51 and Figure 52). There was no apparent pattern observed between HIV-1 RNA change and the number of days missed from projected injection date.

Figure 51. Distribution of Days Missed From Projected Injection Date and HIV-1 RNA Viral Load Over Time for Subjects Who and Injection Outside of 7-Day Window, FLAIR



Source: Reviewer's analysis using ADEX.xpt and ADLB.xpt
Note: 34 patients had any injections outside of ±7-day window.

Figure 52. Distribution of Days Missed From Projected Injection Date and HIV-1 RNA Viral Load Over Time for Subjects Who and Injection Outside of 7-Day Window, ATLAS



Source: Reviewer's analysis using ADEX.xpt and ADLB.xpt
Note: 45 patients had any injections outside of ±7-day window.

CAB+RPV Oral Lead-In

The 4-week CAB+RPV OLI before the initiation of injections was designed to minimize the risk of severe ADRs during LA dosing. Because subjects randomized to the trials were virologically suppressed patients, analyses were conducted to see whether the OLI regimen effectively suppressed the viral load at the end of week 4. Results show that the CAB+RPV group had a numerically higher proportion of subjects with HIV-1 RNA ≥50 copies/mL and more missing values at week 4 visit compared to the other visits. The CAR group did not have a scheduled W4 measurement on HIV-1 RNA (Table 162 and Table 163).

Table 162. Percentage of Patient HIV-1 RNA ≥50 Copies/mL by Visit, FLAIR

Visit	CAR	CAB+RPV
BL	11/283 (3.9%)	11/283 (3.9%)
W4	0/5 (0%)	12/216 (5.6%)
W8	12/279 (4.3%)	13/271 (4.8%)
W12	10/277 (3.6%)	9/272 (3.3%)
W16	11/271 (4.1%)	13/257 (5.1%)
W20	8/273 (2.9%)	5/263 (1.9%)
W24	5/268 (1.9%)	7/262 (2.7%)
W28	5/268 (1.9%)	6/254 (2.4%)
W32	6/268 (2.2%)	6/257 (2.3%)
W36	3/265 (1.1%)	1/256 (0.4%)
W40	6/266 (2.3%)	2/251 (0.8%)
W44	7/264 (2.7%)	6/258 (2.3%)
W48	5/263 (1.9%)	6/249 (2.4%)

Source: Reviewer's analysis using ADLB.xpt
Abbreviations: BL = baseline, CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

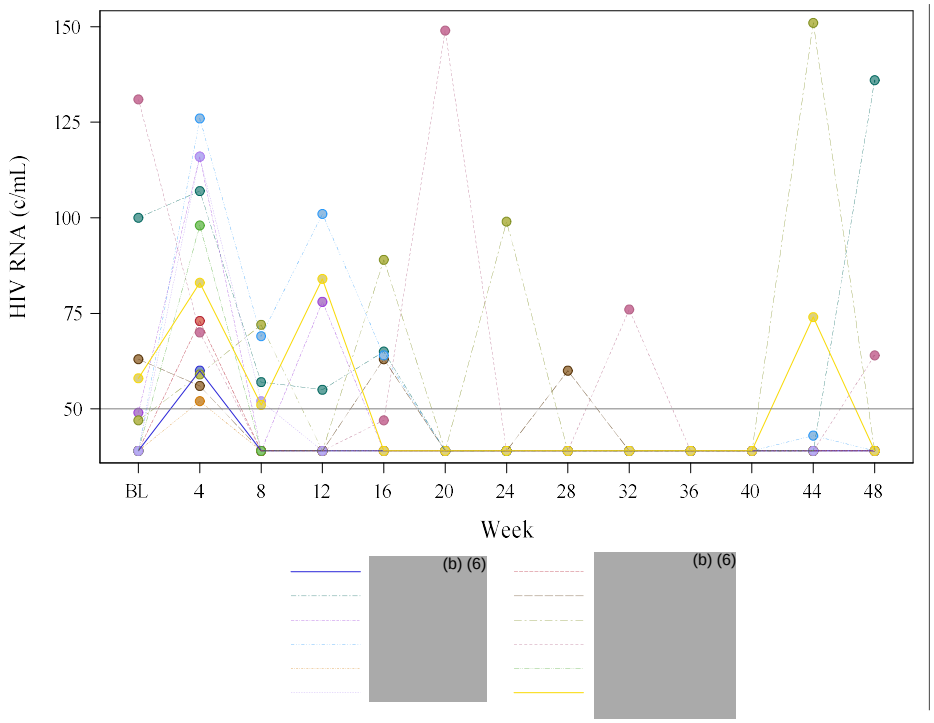
Table 163. Percentage of Patient HIV-1 RNA ≥50 Copies/mL by Visit, ATLAS

Visit	CAR	CAB+RPV
BL	3/308 (1%)	3/308 (1%)
W4	0/3 (0%)	3/217 (1.4%)
W8	4/301 (1.3%)	6/301 (2%)
W12	6/300 (2%)	4/296 (1.4%)
W16	6/300 (2%)	3/285 (1.1%)
W20	12/301 (4%)	2/278 (0.7%)
W24	9/298 (3%)	3/282 (1.1%)
W28	6/297 (2%)	4/268 (1.5%)
W32	3/294 (1%)	2/275 (0.7%)
W36	7/292 (2.4%)	0/272 (0%)
W40	5/294 (1.7%)	4/268 (1.5%)
W44	6/289 (2.1%)	1/273 (0.4%)
W48	5/292 (1.7%)	2/265 (0.8%)

Source: Reviewer's analysis using ADLB.xpt
Abbreviations: BL = baseline, CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

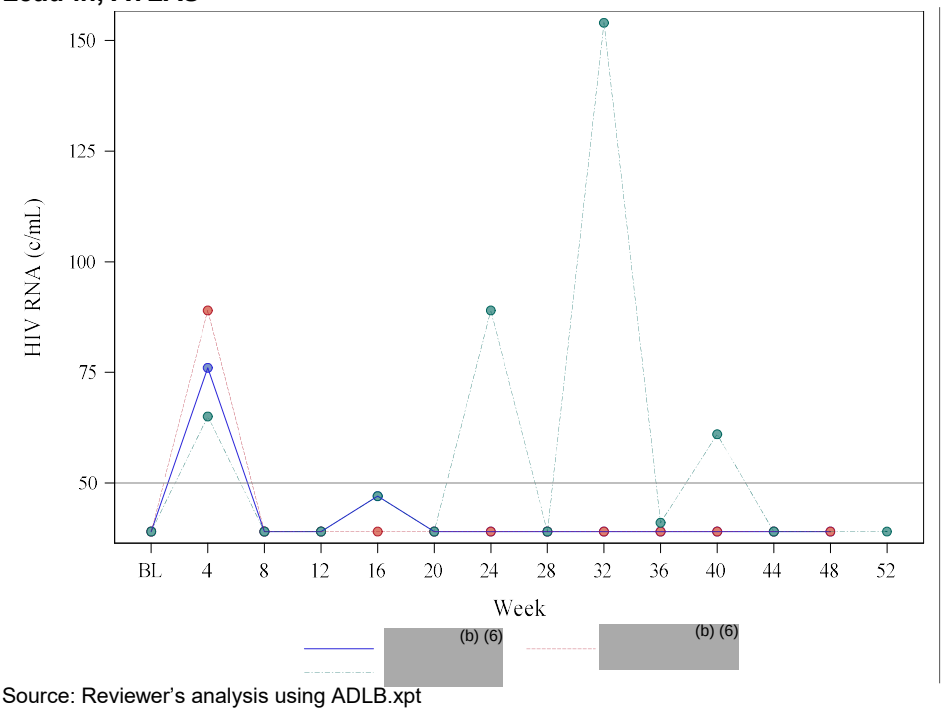
HIV viral load over time was plotted for those who had week 4 HIV-1 RNA ≥50 copies/mL (Figure 53 and Figure 54). For all of the 15 subjects (12 from FLAIR and 3 from ATLAS), HIV-1 RNA values went up and down at each visit and were all below 200 copies/mL. There was no apparent association between week 4 viral load and the week 48 virologic failure.

Figure 53. HIV-1 RNA Overtime for Patients with HIV-1 RNA ≥50 Copies/mL at the End of W4 Oral Lead-in, FLAIR



Source: Reviewer's analysis using ADLB.xpt
Abbreviations: BL = baseline

Figure 54. HIV-1 RNA Overtime for Patients with HIV-1 RNA ≥50 Copies/mL at the End of W4 Oral Lead-in, ATLAS



Source: Reviewer's analysis using ADLB.xpt
Abbreviations: BL = baseline

For the 12 subjects who had week 4 HIV-1 RNA ≥50 copies/mL in FLAIR, 7 had induction baseline HIV-1 RNA ≥100,000 copies/mL, 10 had induction baseline CD4+ cell count of <500 cells/mm^3, and 6 had induction baseline CD4+ cell count of <350 cells/mm^3. Table 164 shows the change in the HIV-1 RNA category between baseline and week 4 for FLAIR. Agreement on the baseline and week 4 HIV-1 RNA categories was tested using McNemar's test. The result shows that the baseline and week 4 HIV-1 RNA categories are not statistically different (p=0.25). For this test, we assume that the missing values at week 4 were missing at random, which means that there was no relationship between the missing data and HIV-1 RNA. However, this assumption may not be true. The Applicant did not provide reasons for the missing values.

Table 164. Change in HIV-1 RNA Category Between Baseline and Week 4, FLAIR

Baseline HIV-1 RNA	Week 4 HIV-1 RNA	
	<50	≥50
<50	201	8
≥50	3	4

Source: Reviewer's analysis using ADLB.xpt
Note: Sample size for the CAB+RPV arm was 283. Sixty-seven subjects had missing values at week 4. Among them, 63 subjects had baseline value <50 copies/mL and 4 subjects had baseline values ≥50 copies/mL.

Based on the available data, there were no alarming signals for the 4-week OLI regarding maintaining viral load suppression in the trial population. However, whether the 4-week OLI of CAB+RPV adequately maintained the viral suppression cannot be answered definitively from the statistical point of view, because the study was not designed to answer this question and a large number of missing values at week 4 was observed in both trials.

CAB+RPV Oral Bridging

For the preplanned missed CAB+RPV injection, daily oral CAB 30 mg and RPV 25 mg as short-term bridging were provided to the subjects. A total of 16 subjects had oral bridging experience (nine subjects were from FLAIR and 7 from ATLAS) (Table 165). The duration of oral bridging ranged from 4 days to 2 months.

Table 165. Patients Who Had Oral Bridging Experience

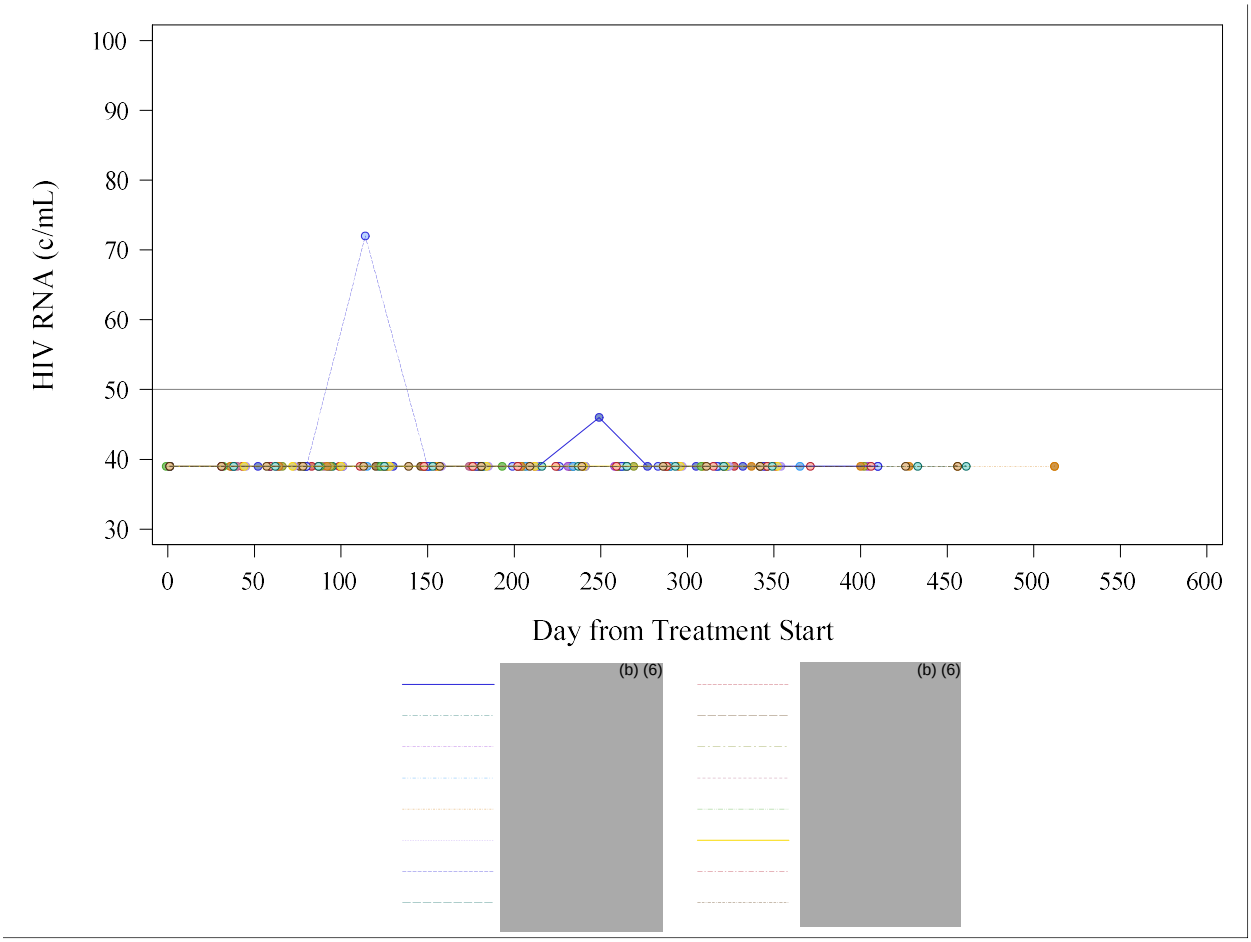
Unique Subject Identifier	Phase	Oral Start Date	Oral Start Study Day	Oral End Date	Oral End Study Day	Oral Duration
(b) (6)	Maintenance	(b) (6)	360	(b) (6)	388	29
	Maintenance		80		83	4
	Maintenance		75		79	5
	Maintenance		73		76	4
	Maintenance		121		181	61
	Maintenance		430		.	.
	Maintenance		346		365	20
	Maintenance		206		262	57
	Maintenance		458		511	54
	Maintenance		88		91	4
	Maintenance		269		296	28
	Maintenance		268		295	28

Unique Subject Identifier	Phase	Oral Start Date	Oral Start Study Day	Oral End Date	Oral End Study Day	Oral Duration
(b) (6)	Maintenance	(b) (6)	178	(b) (6)	198	21
	Maintenance		59		62	4
	Maintenance		125		153	29
	Maintenance		265		286	22

Source: Reviewer's analysis using ADEX.xpt

HIV-1 RNA values overtime were plotted for all subjects who had oral bridging experience (Figure 55). There were no signs of association between the oral bridging and HIV-1 RNA increase. However, the study was not designed to test the statistical hypothesis of whether oral bridging can adequately maintain the viral suppression, and also, the sample size was too small to conduct a meaningful statistical test.

Figure 55. HIV-1 RNA Level Overtime for Subjects Who Had Oral Bridging Experience, FLAIR and ATLAS



Source: Reviewer's analysis using ADLB.xpt
Note: A total of 16 patients had planned oral bridging experience.

Statistical Method for Needle Length and Gauge Analyses

To evaluate the association between HIV-1 RNA change from baseline and needle size, a mixed model approach was used to account for the repeated injections (the needle length and gauge used for each injection were not always the same for the subject throughout the trial) and HIV-1 RNA measurements within subject. The analysis population includes subjects who received CAB+RPV injection in both FLAIR and ATLAS. The outcome of the model was change in HIV-1 RNA (log_{10}) from baseline. Covariates of the model included age, stratification factors (10 strata for the pooled studies), baseline disease stage, baseline HIV-1 RNA, baseline BMI, needle length, needle gauge, and visit number. Compound symmetry was assumed for the correlation structure. Two mixed models were constructed to independently explore the association between needle size and HIV-1 RNA change for the CAB injections and the RPV injections. Note that there are several limitations in these analyses findings including potential model misspecifications which cannot be tested empirically.

Additional Subgroup Analyses for Sex and BMI

Table 166. Week 48 Efficacy Results by Subgroup, FDA Snapshot Algorism, FLAIR and ATLAS

		FLAIR		ATLAS	
Category	**Subcategory**	**CAB+RPV**	**CAR**	**CAB+RPV**	**CAR**
Female BMI <30					
HIV-1 RNA ≥50 copies/mL		1/50 (2%)	1/47 (2.1%)	1/68 (1.5%)	0
HIV-1 RNA <50 copies/mL		47/50 (94%)	45/47 (95.7%)	64/68 (94.1%)	69/73 (94.5%)
No virologic data at week 48 window	Discontinued due to adverse event or death	1/50 (2%)	1/47 (2.1%)	1/68 (1.5%)	2/73 (2.7%)
	Discontinued for other reasons	1/50 (2%)	0	2/68 (2.9%)	2/73 (2.7%)
	Missing data during window but on study	0	0	0	0
Male BMI ≥30					
HIV-1 RNA ≥50 copies/mL		1/27 (3.7%)	0	1/29 (3.4%)	2/35 (5.7%)
HIV-1 RNA <50 copies/mL		26/27 (96.3%)	20/20 (100%)	28/29 (96.6%)	33/35 (94.3%)
No virologic data at week 48 window	Discontinued due to adverse event or death	0	0	0	0
	Discontinued for other reasons	0	0	0	0
	Missing data during window but on study	0	0	0	0
Male BMI <30					
HIV-1 RNA ≥50 copies/mL		2/193 (1%)	6/199 (3%)	2/180 (1.1%)	1/169 (0.6%)
HIV-1 RNA <50 copies/mL		181/193 (93.8%)	183/199 (92%)	165/180 (91.7%)	163/169 (96.4%)
No virologic data at week 48 window	Discontinued due to adverse event or death	7/193 (3.6%)	1/199 (0.5%)	10/180 (5.6%)	2/169 (1.2%)
	Discontinued for other reasons	3/193 (1.6%)	9/199 (4.5%)	3/180 (1.7%)	3/169 (1.8%)

		FLAIR		ATLAS	
Category	**Subcategory**	**CAB+RPV**	**CAR**	**CAB+RPV**	**CAR**
	Missing data during window but on study	0	0	0	0
Female					
HIV-1 RNA ≥50 copies/mL		3/63 (4.8%)	1/64 (1.6%)	2/99 (2%)	0
HIV-1 RNA <50 copies/mL		58/63 (92.1%)	61/64 (95.3%)	92/99 (92.9%)	98/104 (94.2%)
No virologic data at week 48 window	Discontinued due to adverse event or death	1/63 (1.6%)	1/64 (1.6%)	1/99 (1%)	3/104 (2.9%)
	Discontinued for other reasons	1/63 (1.6%)	1/64 (1.6%)	4/99 (4%)	3/104 (2.9%)
	Missing data during window but on study	0	0	0	0
BMI ≥30					
HIV-1 RNA ≥50 copies/mL		3/40 (7.5%)	0	2/60 (3.3%)	2/66 (3%)
HIV-1 RNA <50 copies/mL		37/40 (92.5%)	36/37 (97.3%)	56/60 (93.3%)	62/66 (93.9%)
No virologic data at week 48 window	Discontinued due to adverse event or death	0	0	0	1/66 (1.5%)
	Discontinued for other reasons	0	1/37 (2.7%)	2/60 (3.3%)	1/66 (1.5%)
	Missing data during window but on study	0	0	0	0

Source: Reviewer's analysis using ADEFFOUT.xpt
Abbreviations: BMI = body mass index, CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

17. Clinical Safety Assessment

This review section contains supplemental safety analyses not included in the integrated review section (II), and additional analyses supporting the safety conclusions included in Section II.

17.1. Deaths

Summary

Refer to Section II.7.6.2 for summary assessment and conclusion.

Additional Narratives for Deaths

The following table summarizes the AEs leading to death in the CAB+RPV exposed subjects, not discussed in Section II.7.6.2.

Table 167. Summary of Other Death Narratives for Subjects in the Cabotegravir+Rilpivirine (CAB+RPV) Treatment Group During Maintenance Period, FLAIR, ATLAS

SID Age/Sex Trial	Assessment of Causality* (Y/N) Investigator	Applicant	Reviewer	Summary of Event
43/M Phase 2 (200056; LATTE-2)	Not related	Not related	Not related	Myocadiac infarction The subject was found deceased at home due to a suspected myocardial infarction (MI). Risk factors for MI include HTN, BMI 40 kg/m^2 but subject had no previous history of heart disease or received cardiovascular medications. The event occurred 1117 days after the first dose of study drug. No autopsy information was available.
54/M Phase 2 (LAI116482; LATTE)	Not related	Not related	Not related	GI hemorrhage The subject, a 54 year-old male, was treated with oral CAB in combination with other ARV for at least 168 weeks. His medical history include peptic ulcer disease, gastroesophageal reflux disease (GERD), H. Pylori, Hep C Ab positive, hepatobiliary disorder, depression, anxiety, insomnia, hypertension and smoked. He discontinued from the study for initiate treatment for Hep C. The subject had reported anorexia and weight loss in recent years. An abdominal CT scan revealed noncancerous liver lesion. Approximately 2 months after exiting the study, the subject was found deceased in his home. As the participant did not receive medical care, there are no additional medical records, surrounding this event. A coroner reported gastrointestinal bleed as the cause of death, with no antecedent cause. Per the report, significant conditions contributing to death are listed as peptic ulcer disease and prior tobacco use. Both the investigator and Applicant did not believe the event was related to study drug
Phase 2 (LAI116482; LATTE)	Possibly related	Not related	Not related	Cardiac arrest This subject received induction treatment with oral CAB 30 mg + ABC/3TC once daily for 20 weeks, with the addition of oral RPV 25 mg once daily for the last week. The subject was randomized to CAB+RPV IM Q4W and completed week 96 visit entered the extension period. The subject was last dosed on (b) (6) at week 136. Approximately 3 years after starting treatment with CAB, the subject had a fatal SAE of myocardial infarction and was found dead at his home. It was reported that the subject died after a myocardial infarction and had signs of chronic heart failure at autopsy,

SID Age/Sex Trial	Assessment of Causality* (Y/N) Investigator	Applicant	Reviewer	Summary of Event
				but no formal autopsy was provided to the study team. The subject had a BMI of 33.8 kg /m^2 (height was 186 cm and weight was 117.1 kg) at study baseline. At week 128 the subject had a BMI of 38.6 kg /m^2; weight was 135 kg. The subject was nonsmoker with no history of drug use. He was a moderate alcohol drinker. During the study visits he had some elevated blood pressure (BP) readings but the subject reported normal blood pressure readings at home. BP at baseline was 155/104 mm Hg and BP at week 128 was 161/59 mm Hg. The site did not have any reports of echocardiography or other medical records and the subject did not take any medication for heart disease. The investigator found establishing causality challenging. In the investigator's opinion the event was related to the underlying condition, but could not exclude the possibility of a relationship to study drugs.

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral therapy, BMI = body mass index, CAB = cabotegravir, CT = computerized tomography, GI = gastrointestinal, HTN = hypertension, Q4W = every 4 weeks, SAE = serious adverse event

17.2. Serious Adverse Events (CAB+RPV Exposed Subjects)

Summary

Refer to Section II.7.6.3 for summary assessment and conclusion.

Additional Analyses

The following SAEs were selected based on considerations to causality, class-effect, significance or the nonclinical signal. The description is limited to CAB+RPV-exposed subjects.

Table 168. Description of Selected SAEs During Maintenance Period, FLAIR, ATLAS

Trial.SID Age/Sex	Study Day Start of AE	Study Day End of AE	Dictionary Derived Term	Comment
(b) (6) 36/M	101	182	Hepatocellular injury	Hepatocellular injury was considered as potential safety issue related to CAB and/or RPV exposure. The cases of 'hepatocellular injury', 'hyperbilirubinemia' and 'liver function test abnormal' 'occurred in the setting of acute HAV infection. Both subjects discontinued study drug.
(b) (6) 36/M			Hyperbilirubinaemia	
(b) (6) 36/M	260	332	Liver function abnormal	

Trial.SID Age/Sex	Study Day Start of AE	Study Day End of AE	Dictionary Derived Term	Comment
(b) (6) 23/M	642	647	Colitis	Colitis and enterocolitis were considered as possible signals for GI intolerance or HSRs, both potential safety issues related to CAB and/or RPV exposure. Neither events appear to be related to HSR. Arthritis was also considered a potential HSR signal. The event was considered treatment related but resolved without discontinuation.
(b) (6) 28/M	135	137	Enterocolitis	
(b) (6) 58/M	290	392	Arthritis*	
ATLAS-2M 45/M			Pancreatitis acute	Because this fatality was secondary to acute pancreatitis, pancreatitis became a flagged safety issue. See “Deaths” discussion in Section II.7.6.2
(b) (6) 50/M	136	142	Vomiting	
(b) (6) 50/M	158	162	Pyrexia	Pyrexia was identified as a safety issue requiring additional analyses due to the disproportionate number of subjects experiencing pyrexia in the CAB+RPV treatment group compared to control groups. However, this particular event occurred in the setting of acute HCV infection.
(b) (6) 43/M	266	372	Back pain*	Musculoskeletal events were considered a potential safety issued related to monthly injections of CAB and RPV. This subject experienced ‘back pain’ immediately post-ISR (“pain”).
(b) (6) 31/F	47	47	Abortion missed	Due to the effect of DTG (another INSTI) on the fetus during first trimester, and due to CAB preclinical signal indicating fetal weight loss and stillbirths, pregnancy outcomes were considered a safety issue requiring closer evaluation to assess for potential class effect.

Source: Clinical Reviewer’s analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
*see below for additional detail
Abbreviations: AE = adverse event, CAB = cabotegravir, DTG = Dolutegravir, HAV = hepatitis A virus, HCV = hepatitis C virus, HSR = hypersensitivity reactions, INSTI = integrase strand transfer inhibitor, ISR = injection site reaction, RPV = rilpivirine

Back Pain

This 43-year-old male subject was enrolled in ATLAS trial. He completed CAB+RPV oral regimen and initiated CAB+RPV injections. Approximately 4 months after initial exposure to CAB+RPV, he developed moderate grade 2 lumbago. Serious criteria included hospitalization. Evaluations included x-ray. The subject was treated with zopiclone, pantoprazole, ibuprofen and Novalgin. CAB+RPV regimen was continued with no change. He recovered from back pain after 1 day of hospitalization. The investigator considered that there was no reasonable possibility that the lumbago may have been drug related. Given the subject continued on CAB+RPV and the AE resolved, the clinical team agrees the event is unrelated to CAB+RPV.

Arthritis

This 59-year-old male subject was enrolled in FLAIR. The subject received ABC/DTG/3TC, completed OLI with CAB+RPV, then began treatment with CAB+RPV extended-release injections. Approximately 289 days after the first dose of ABC/DTG/3TC, 149 days after the first oral dose of CAB+RPV, and 115 days after the first dose of IM CAB+RPV, he developed severe grade 3 monoarthritis and was hospitalized. He was afebrile and had no past medical history of arthritis. Work-up included evaluation for septic arthritis, autoimmune arthritis, and gout. Note, the subject had history of wound prior to the event. His WBC was within normal limits; knee aspirate had WBC >100,000 leucocytes/mm^3, with neutrophils predominance (96%); culture was negative. Cytopathology showed absence of microcrystals. The subject was treated with betamethasone and colchicine and CAB+RPV were continued as the monoarthritis was resolved. The investigator considered that there was a reasonable possibility that the monoarthritis may have been caused by CAB+RPV. He was discharged after a 4-day hospital stay. The review team agrees with the investigator that causality to CAB+RPV cannot be excluded confidently. However, because no additional arthritis events occurred despite continuing on CAB+RPV, association with study drugs seems less likely.

17.3. Adverse Events Leading to Treatment Discontinuation

Summary

Please refer to Section II.7.6.4 for summary assessment and conclusion.

Additional Analyses

Table 169 summarizes selected AEs leading to discontinuation observed during the maintenance phase. Factors such as frequency of an event and type of AE (e.g., falls within the prespecified AESI category) were taken into consideration when the following AEs were selected.

Table 169. Selected Adverse Events Leading to Discontinuation, During Maintenance Period, ATLAS, FLAIR

Preferred Terms (PT)	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Any subject who discontinued treatment due to an AE	22 (4%)	4 (1%)	5 (2%)
Injection site pain	6 (1%)	0 (0%)	0 (0%)
Diarrhoea	2 (0.3%)	0 (0%)	0 (0%)
Headache	2 (0.3%)	0 (0%)	0 (0%)
Nausea	1 (0.2%)	1 (0.4%)	0 (0%)
Vomiting	1 (0.2%)	0 (0%)	0 (0%)
Hepatocellular injury*	1 (0.2%)	0 (0%)	0 (0%)
Hyperbilirubinaemia*	1 (0.2%)	0 (0%)	0 (0%)
Liver function test abnormal#	1 (0.2%)	0 (0%)	0 (0%)
Transaminases increased^	1 (0.2%)	0 (0%)	0 (0%)
Injection site swelling	1 (0.2%)	0 (0%)	0 (0%)
Injection site nodule	1 (0.2%)	0 (0%)	0 (0%)

Preferred Terms (PT)	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Memory impairment	1 (0.2%)	0 (0%)	0 (0%)
Anxiety	1 (0.2%)	0 (0%)	0 (0%)
Asthenia	1 (0.2%)	0 (0%)	0 (0%)
Depression suicidal	1 (0.2%)	0 (0%)	0 (0%)
Discomfort	1 (0.2%)	0 (0%)	0 (0%)
Myalgia	1 (0.2%)	0 (0%)	0 (0%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
[1] Coded as MedDRA preferred terms
*SID (b) (6) referenced in SAE section;
#SID referenced in SAE section
^SID (b) (6) subject's only recorded AE is 'transaminase increased'. Subject is a 28 years-old female from Russia who experienced grade 3 elevation in transaminase at the week 4 visit. Event was not considered serious or related to study drug by the investigator.
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

17.4. Treatment-Related Adverse Events

Summary

Refer to Section II.7.6.5 for summary assessment and conclusion.

Additional Analysis

The table below summarizes ADRs, regardless of severity with at least 1% incidence in the CAB+RPV treatment group.

Table 170. ADR* Regardless of Severity and Reported in at Least 1% of Subjects in the Cabotegravir+Rilpivirine (CAB+RPV) Treatment Group During Maintenance Period, FLAIR, ATLAS

ADR Regardless of Severity	CAB/RPV N=591	ABC/DTG/3TC N=283	CAR N=308
ISRs^	477 (81%)	0 (0.0%)	0 (0.0%)
Pyrexia&	46 (7.7%)	0 (0.0%)	7 (2.3%)
Fatigue%	38 (6.4%)	7 (2.5%)	0 (0.0%)
Headache	25 (4.2%)	4 (1.4%)	0 (0.0%)
Musculoskeletal pain$	19(3.2%)	1 (0.4%)	0 (0.0%)
Rash and hypersensitivity@	18(3%)	3(1%)	0 (0.0%)
Nausea	15 (2.5%)	6 (2.1%)	0 (0.0%)
Sleep disorders#	11(1.9%)	1 (0.4%)	1(0.3%)
Dizziness	9 (1.5%)	1 (0.4%)	0 (0.0%)
Diarrhea	8 (1.4%)	1 (0.4%)	0 (0.0%)
Anxiety	8 (1.4%)	2(0.7%)	1(0.3%)
Depressive disorders	8 (1.4%)	0 (0.0%)	1(0.3%)
Abnormal dreams	7(1.2%)	1 (0.4%)	2 (0.6%)

Source: Clinical reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
*ADR defined as "treatment-related" as assessed by the investigator.
^ Injection site reactions
& Pyrexia: includes pyrexia, feeling hot, chills, influenza-like illness, body temperature increased.
% Fatigue: includes fatigue, malaise, asthenia.
$ Musculoskeletal pain: includes musculoskeletal pain, musculoskeletal discomfort, back pain, myalgia, pain in extremity.
@ Rash and Hypersensitivity: includes erythema, pruritis, pruritis generalized, rash, rash erythematous, rash generalized, rash macular, rash vesicular, conjunctivitis, lip swelling, eosinophilia
# Sleep disorders: includes insomnia, poor quality sleep, somnolence

Abbreviations: 3TC = lamivudine, ABC = abacavir, ADR = adverse drug reaction, CAB = cabotegravir, CAR = current antiretroviral, DTG = dolutegravir, ISR = injection site reaction, RPV = rilpivirine

17.5. Treatment-Emergent Adverse Events

Summary and Analysis

Overall, 561 (95%) subjects in the CAB+RPV treatment group, 225 (80%) subjects in the ABC/DTG/3TC treatment group, and 220 (71%) subjects in the current ART treatment group experienced at least one TEAE. TEAEs with at least 3% incidence in the CAB+RPV treatment group (regardless of causality, severity) are summarized in Table 171.

As discussed in Section II.7.4, the higher frequency of AEs observed in the CAB+RPV treatment group is not unusual for switch studies.

Table 171. Treatment Emergent Adverse Events[1] With At Least 3% Incidence in the Cabotegravir+Rilpivirine (CAB+RPV) Treatment Group During Maintenance Period, FLAIR, ATLAS

Dictionary Derived Term	CAB+RPV[2] N=591	ABC/DTG/3TC N=283	Current ART N=308
Injection site pain	458 (7.5%)	0 (0.0%)	0 (0.0%)
Nasopharyngitis	108 (8.3%)	48 (17.0%)	42 (13.6%)
Injection site nodule	81 (3.7%)	0 (0.0%)	0 (0.0%)
Headache	73 (2.4%)	21 (7.4%)	17 (5.5%)
Upper respiratory tract infection	70 (1.8%)	28 (9.9%)	25 (8.1%)
Injection site induration	68 (1.5%)	0 (0.0%)	0 (0.0%)
Diarrhoea	54 (9.1%)	25 (8.8%)	15 (4.9%)
Injection site swelling	46 (7.8%)	0 (0.0%)	0 (0.0%)
Pyrexia	43 (7.3%)	4 (1.4%)	9 (2.9%)
Back pain	43 (7.3%)	13 (4.6%)	10 (3.2%)
Influenza	42 (7.1%)	20 (7.1%)	14 (4.5%)
Vitamin D deficiency	31 (5.2%)	13 (4.6%)	12 (3.9%)
Nausea	30 (5.1%)	11 (3.9%)	5 (1.6%)
Fatigue	29 (4.9%)	8 (2.8%)	6 (1.9%)
Injection site erythema	26 (4.4%)	0 (0.0%)	0 (0.0%)
Cough	26 (4.4%)	12 (4.2%)	14 (4.5%)
Bronchitis	25 (4.2%)	10 (3.5%)	12 (3.9%)
Dizziness	24 (4.1%)	3 (1.1%)	5 (1.6%)
Myalgia	24 (4.1%)	5 (1.8%)	3 (1.0%)
Respiratory tract infection viral	24 (4.1%)	12 (4.2%)	17 (5.5%)
Injection site pruritus	23 (3.9%)	0 (0.0%)	0 (0.0%)
Pharyngitis	23 (3.9%)	9 (3.2%)	12 (3.9%)
Insomnia	22 (3.7%)	4 (1.4%)	4 (1.3%)
Oropharyngeal pain	21 (3.6%)	4 (1.4%)	11 (3.6%)
Anxiety	21 (3.6%)	6 (2.1%)	7 (2.3%)
Haemorrhoids	20 (3.4%)	3 (1.1%)	2 (0.6%)
Gastroenteritis	20 (3.4%)	11 (3.9%)	10 (3.2%)
Influenza like illness	19 (3.2%)	7 (2.5%)	3 (1.0%)
Asthenia	18 (3.0%)	1 (0.4%)	0 (0.0%)
Injection site bruising	17 (2.9%)	0 (0.0%)	0 (0.0%)
Rash	17 (2.9%)	8 (2.8%)	4 (1.3%)
Abdominal pain	17 (2.9%)	8 (2.8%)	1 (0.3%)
Oral herpes	16 (2.7%)	4 (1.4%)	5 (1.6%)

Dictionary Derived Term	CAB+RPV[2] N=591	ABC/DTG/3TC N=283	Current ART N=308
Tonsillitis	16 (2.7%)	6 (2.1%)	4 (1.3%)
Anogenital warts	16 (2.7%)	6 (2.1%)	3 (1.0%)
Syphilis	16 (2.7%)	6 (2.1%)	9 (2.9%)
Blood creatine phosphokinase increased	15 (2.5%)	6 (2.1%)	4 (1.3%)
Arthralgia	15 (2.5%)	7 (2.5%)	8 (2.6%)
Respiratory tract infection	15 (2.5%)	8 (2.8%)	12 (3.9%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
[1] Treatment-emergent adverse event defined as any AE occurring during the maintenance period of the trial
[2] Pooled phase 3 population or ISS
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

17.6. Submission Specific Primary Safety Concerns

Summary

Refer to Section II.7.6.6 for discussion on AESI, which include:

- Injection reactions
- Pyrexia
- Hypersensitivity reactions and rash
- Hepatobiliary events
- Psychiatric AEs of interest (including depressive disorders)
- Neurologic AEs of interest (including seizure)
- GI AEs of interest (including pancreatitis)
- Musculoskeletal events related to injection or rhabdomyolysis
- Weight increase
- Embryo-fetal toxicity

This section summarizes the additional analyses conducted for AESI − hepatobiliary, psychiatric, neurologic, and injection reactions. Additionally, AEs in the cardiovascular and renal SOC are summarized below.

17.6.1. Hepatobiliary Adverse Events

Additional Analysis

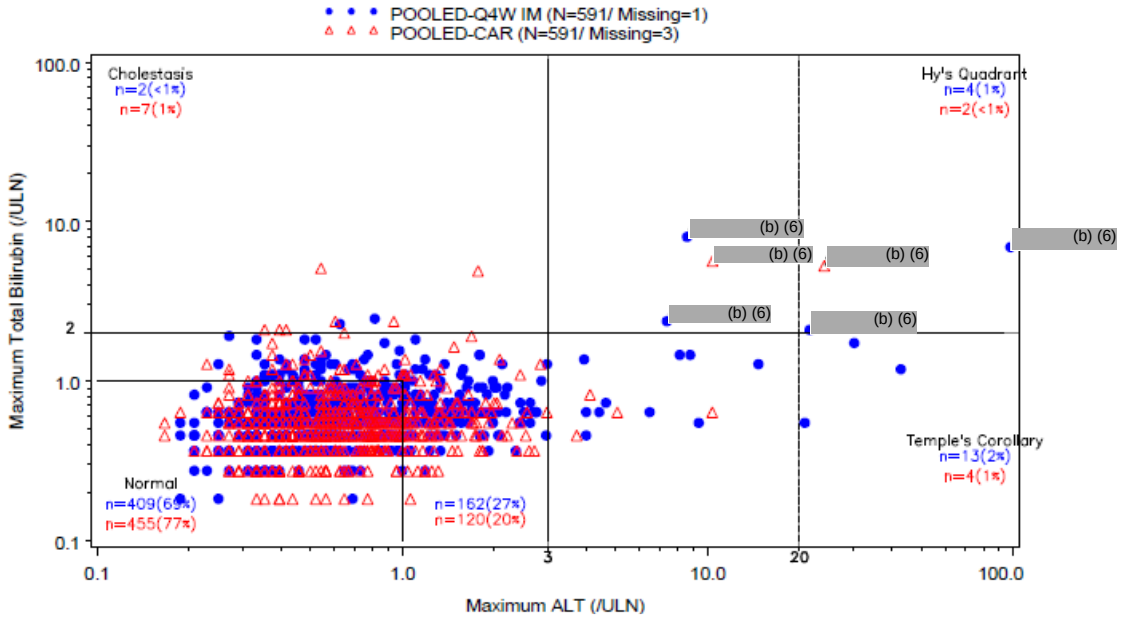
Table 172. Hepatobiliary Events, by Preferred Terms During Maintenance Period, FLAIR, ATLAS

Preferred Term	CAB+RPV (N=591)	ABC/DTG/3TC (N=283)	CAR (N=308)
Hepatobiliary disorders	9 (1.5)	1 (0.4)	0 (0.0)
Hyperbilirubinaemia	3 (0.5)	0 (0.0)	0 (0.0)
Bile duct stone	1 (0.2)	0 (0.0)	0 (0.0)
Biliary tract disorder	1 (0.2)	0 (0.0)	0 (0.0)
Cholecystitis	1 (0.2)	0 (0.0)	0 (0.0)
Cholecystitis acute	1 (0.2)	0 (0.0)	0 (0.0)
Cholelithiasis	1 (0.2)	0 (0.0)	0 (0.0)
Hepatic steatosis	1 (0.2)	0 (0.0)	0 (0.0)
Hepatitis toxic	1 (0.2)	0 (0.0)	0 (0.0)

Preferred Term	CAB+RPV (N=591)	ABC/DTG/3TC (N=283)	CAR (N=308)
Hepatocellular injury	1 (0.2)	0 (0.0)	0 (0.0)
Hydrocholecystis	1 (0.2)	0 (0.0)	0 (0.0)
Nonalcoholic steatohepatitis	1 (0.2)	0 (0.0)	0 (0.0)
Hepatic cirrhosis	0 (0.0)	1 (0.4)	0 (0.0)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

Figure 56. Applicant's Analysis: eDish Plot of Maximum Postbaseline Total Bilirubin vs. Maximum Postbaseline ALT (ULN)



Source: Applicant's analysis, CSR ISS page 347
Abbreviations: ALT = alanine aminotransferase, CAR = current antiretroviral, IM = intramuscular, Q4W = every 4 weeks, ULN = upper limit of normal

17.6.2. Psychiatric Adverse Events

Additional Analysis

Table 173. Summary of Psychiatric AEs During Maintenance Period, FLAIR, ATLAS

Outcome	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Any psychiatric AE	70 (11.8%)	27 (9.5%)	24 (7.8%)
SAE	0	2 (0.7%)	1 (0.3%)
Treatment discontinuation	2 (0.3%)	1 (0.4%)	1 (0.3%)
Treatment interruption	0	0	0
Treatment related	27 (4.6%)	3 (1.1%)	4 (1.3%)
Hospitalization	0	2 (0.7%)	1 (0.3%)
Severity			
Grade 1	55 (9.3%)	17 (6%)	16 (5.2%)
Grade 2	23 (3.9%)	9 (3.2%)	8 (2.6%)
Grade 3	0	1 (0.4%)	2 (0.6%)

Outcome	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Grade 4	0	0	0

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Table 174. Summary of Selected Psychiatric AE During Maintenance Period, FLAIR, ATLAS

Selected Grouped Terms	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Mood disorders	23	8	9
Anxiety disorder	27	8	12
Adjustment disorders	4	2	0
Sleep disorders	31	10	7
Abnormal dreams	8	1	2

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Grouped terms for mood disorder: Affect lability, Affective disorder, Depressed mood, Depression, Depression suicidal, Intentional self-injury, Major depression, Mood altered, Mood swings, Suicidal behaviour, Suicidal ideation, Suicide attempt, Irritability
Grouped terms for Anxiety disorder: Acute stress disorder, Anxiety, Anxiety disorder, Nervousness, panic attack, Panic disorder, Stress, Tension
Grouped terms for Adjustment disorders: adjustment disorder, adjustment disorder with depressed mood
Grouped terms for sleep disorder: Insomnia, Nightmare, Sleep disorder, Poor quality sleep, Somnolence
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

17.6.3. Neurologic Adverse Events

Additional Analyses

Table 175. Summary of Neurologic Adverse Events During the Maintenance Period, FLAIR, ATLAS

Outcome	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Any subject with neurologic AE	128 (21.7%)	33 (11.7%)	35 (11.4%)
SAE	1 (0.2%)	0 (0%)	0
Hospitalization	0	0 (0%)	1 (0.3%)
Treatment related	34 (5.8%)	8 (2.8%)	0 (0%)
Discontinuation	3 (0.5%)	2 (0.7%)	0 (0%)
Treatment interruption	1 (0.2%)	0 (0%)	0 (0%)
Severity			
Grade 1	103 (17.4%)	25 (8.8%)	27 (8.8%)
Grade 2	31 (5.2%)	9 (3.2%)	10 (3.2%)
Grade 3 or higher	3 (0.5%)	0	1 (0.3%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Table 176. Description of Selected Neurologic Adverse Events During Maintenance Period, FLAIR, ATLAS

AEs by Grouped Terms	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Headache-related AEs			
Total	81 (14%)	23 (8%)	18 (6%)
Headache	71 (%)	21 (4%)	17 (2%)
Migraine	6 (%)	2 (0.7%)	1 (0.3%)
Tension headache	2 (%)	0 (0%)	0 (0%)

AEs by Grouped Terms	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Seizure or loss of consciousness			
Total (excluding seizure)	31 (5%)	5 (2%)	6 (1%)
Dizziness	23 (5%)	3 (0.7%)	5 (1%)
Syncope	5 (1%)	0 (0%)	1 (0.3%)
Presyncope	2 (0%)	2 (0.7%)	0 (0%)
Loss of consciousness	1 (0.2%)	0 (0%)	0 (0%)
Seizure	0 (0%)	0 (0%)	1 (0.3%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

17.6.4. Injection Reactions

Estimating the incidence of AE among subjects with CAB or RPV exposure (C_{max}) >10 or 400 µg/mL, respectively, (n=28).

Figure 57. A and B: Cabotegravir (CAB) and Rilpivirine (RPV) Concentration (C_{max}) >10 or 400 µg/mL for CAB and RPV, Respectively

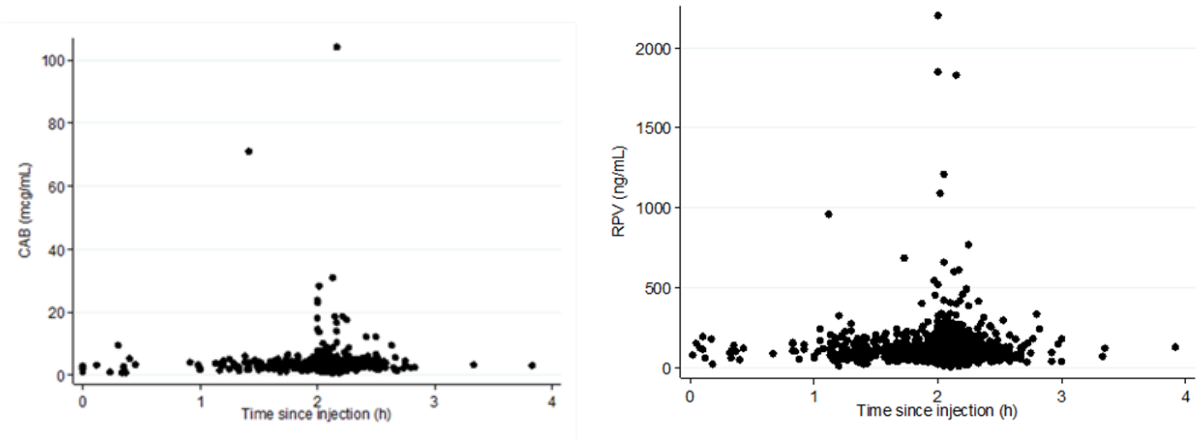


Table 177. TEAE Incidence for Subjects With Cabotegravir Concentration (C_{max}) >10 ng/mL (n=18) or Rilpivirine Concentration (C_{max}) >400 ng/mL (n=10) During Maintenance Period, FLAIR and ATLAS

Preferred Term	CAB+RPV N=26 n (%)
Injection-site reactions	
Injection site pain	21 (81)
Injection site induration	5 (19)
Injection site nodule	3 (12)
Injection site nodule	3 (12)
Injection site swelling	2 (8)
Injection related reaction	1 (4)
Injection site bruising	1 (4)
Injection site erythema	1 (4)
Injection site haematoma	1 (4)
Injection site warmth	1 (4)

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Preferred Term	CAB+RPV N=26 n (%)
Pyrexia	
Body temperature increased, pyrexia, influenza-like illness, chills, hot flush	8 (31)
Vascular	
Orthostatic hypotension	1 (4)
Neurologic	
Headache	7 (27)
Migraine	2 (8)
Dizziness	1 (4)
Tinnitus	1 (4)
Psychiatric	
Anxiety	2 (8)
Insomnia	2 (8)
Depression	1 (4)
Memory impairment	1 (4)
Abnormal dreams	1 (4)
Affect lability	1 (4)
Skin	
Pruritus	1 (4)
Rash maculo-papular	1 (4)
Skin lesion	1 (4)
Xeroderma	1 (4)
GI	
Diarrhoea	3 (12)
Gastroenteritis	2 (8)
Nausea	2 (8)
Abdominal discomfort	2 (8)
Abdominal pain	1 (4)
Chronic gastritis	1 (4)
Musculoskeletal	
Myalgia	1 (4)
Ankle fracture	1 (4)
Back pain	1 (4)
Injury	1 (4)
Pain in extremity	1 (4)
Paraesthesia	1 (4)
Infections	
Nasopharyngitis	5 (19)
Upper respiratory tract infection	5 (19)
Pharyngitis	2 (8)
Respiratory tract infection	2 (8)
Anogenital warts	2 (8)
Body tinea	1 (4)
Herpes zoster	1 (4)
Influenza	1 (4)
Oropharyngeal gonococcal infection	1 (4)
Cystitis	1 (4)
Exposure to communicable disease	1 (4)
Laryngitis	1 (4)
Proctitis gonococcal	1 (4)
Respiratory tract infection viral	1 (4)

Preferred Term	CAB+RPV N=26 n (%)
Sexually transmitted disease	1 (4)
Syphilis	1 (4)
Tinea versicolour	1 (4)
Tonsillitis	1 (4)
Tonsillitis bacterial	1 (4)
Urinary tract infection	1 (4)
Varicella	1 (4)
Viral upper respiratory tract infection	1 (4)
Vulvovaginitis	1 (4)
Other	
Asthenia	4 (15)
Fatigue	1 (4)
Procedural pain	1 (4)
Anal neoplasm	1 (4)
Anal pruritus	1 (4)
Breast mass	1 (4)
Cough	1 (4)
Cerumen impaction	1 (4)
Food allergy	1 (4)
Food poisoning	1 (4)
Nasal obstruction	1 (4)
Reflux laryngitis	1 (4)
Thrombophlebitis superficial	1 (4)
Vitamin D decreased	1 (4)

Source: adae.xpt; Software: Python
Abbreviations: CAB = cabotegravir, GI = gastrointestinal, RPV = rilpivirine, TEAE = treatment-emergent adverse event

17.6.5. Renal

Table 178. Summary of Treatment-Emergent Renal Events During Maintenance Period, FLAIR, ATLAS

Outcome	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Any subj with renal AE			
Grade 1	19 (3.2%)	7 (2.5%)	3 (1%)
Grade 2	4 (0.7%)	2 (0.7%)	3 (1%)
Grade 3	1 (0.2%)	0	0
Grade 4	0	0	0
Serious	0	0	0
Hospitalization	0	0	0
Led to treatment discontinuation	0	1 (0.4%)	1 (0.3%)
Led to treatment interruption	0	0	0
Treatment related	0	2 (0.7%)	1 (0.3%)
Unresolved/ongoing AE[#]	4 (0.7%)	1 (0.4%)	0
Selected terms of AEs			
Renal failure/impairment or nephropathy	4 (0.7%)	2 (0.7%)	1 (0.3%)
Renal colic	4 (0.4%)	2 (0.7%)	2 (0.6%)
Hematuria	2 (0.3%)	1 (0.4%)	1 (0.3%)
Proteinuria	3 (0.5%)	1 (0.4%)	1 (0.3%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
#Unresolved AEs in CAB+RPV treatment group: chronic kidney disease; dysuria; urgency; proteinuria
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

Table 179. Serum Creatinine, Worse-Grade Toxicity During Maintenance Period, FLAIR, ATLAS

Toxicity Grade	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Grade 1	9 (1.5%)	9 (3.1%)	6 (1.9%)
Grade 2	1 (0.2%)	2 (0.7%)	1 (0.3%)
Grade 3	1 (0.2%)	0	0
Grade 4	0	1 (0.4%)	0

Toxicity grade based on NIH DAIDS Toxicity Table
Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADLB datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

Table 180. Proteinuria, Worse-Grade Toxicity During Maintenance Period, ATLAS, FLAIR

Toxicity Grade	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Grade 1	0	0	0
Grade 2	120 (20%)	61 (22.5%)	82 (26.6%)
Grade 3	9 (1.5%)	12 (4.2%)	8 (2.6%)
Grade 4	1 (0.2%)	1 (0.4%)	0

Toxicity grade based on NIH DAIDS Toxicity Table
Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADLB datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

17.6.6. Cardiovascular

Table 181. Summary of Treatment-Emergent Cardiovascular Events

Outcome	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Any subj with cardiac AE			
Grade 1	7 (1.2%)	0	1 (0.1%)
Grade 2	1 (0.2%)	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Serious	0	0	0
Hospitalization	0	0	0
Led to treatment discontinuation	0	0	0
Led to treatment interruption	0	0	0
Treatment-related*	1 (0.2%)	0	0
Unresolved/ongoing AE^	2 (0.3%)	0	0
Selected terms of AEs			
Sinus arrhythmias	1 (0.2%)	0	1 (0.1%)
Conduction disorders	2 (0.3%)	0	0
Palpitation	1 (0.2%)	0	0
Cardiovascular disorder	3 (0.5%)	0	0

*av block 1st degree
^av block; ventricular extrasystoles
Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

17.7. Laboratory Finding

17.7.1. Hematology

Table 182. Hematology, Worse Grade Toxicity During Maintenance Period, ATLAS, FLAIR

Toxicity Grade	CAB+RPV N=591	ABC/DTG/3TC N=283	Current ART N=308
Hemoglobin (low)			
Grade 1	15 (3%)	5 (2%)	10 (3%)
Grade 2	4 (<1%)	0	4 (1%)
Grade 3	3 (<1%)	2 (<1%)	1 (<1%)
Grade 4	0	0	0
Neutrophils (low)			
Grade 1	10 (2%)	5 (2%)	5 (2%)
Grade 2	10 (2%)	6 (2%)	4 (1%)
Grade 3	1 (<1%)	0	1 (<1%)
Grade 4	1 (<1%)	1 (<1%)	0
Platelets (low)			
Grade 1	7 (1%)	3 (1%)	4 (1%)
Grade 2	3 (<1%)	1 (<1%)	2 (<1%)
Grade 3	1 (<1%)	1 (<1%)	0
Grade 4	1 (<1%)	1 (<1%)	0

Toxicity grade based on NIH DAIDS Toxicity Table
Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADLB datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine

Table 183. Hemoglobin Change From Baseline, FLAIR

		CAB+RPV N=283 n (%)			CAR N=283 n (%)		
Laboratory Parameter	Visit	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)
Hemoglobin (g/L)	Week 4	279	1.7 (6.6)	2 (-17, 21)	273	0.1 (6.5)	0 (-17, 21)
Hemoglobin (g/L)	Week 24	259	2.5 (7.2)	2 (-13, 39)	264	2 (7.1)	2 (-21, 20)
Hemoglobin (g/L)	Week 48	243	1.4 (8.2)	2 (-21, 31)	260	2.1 (8.3)	3 (-25, 25)

Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine, SD = standard deviation

Table 184. Hemoglobin Change From Baseline, ATLAS

		CAB+RPV N=308 n (%)			CAR N=308 n (%)		
Laboratory Parameter	Visit	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)
Hemoglobin (g/L)	Week 4	300	-0.4 (6.9)	0 (-33, 17)	300	-1.1 (6.8)	-1 (-17, 23)
Hemoglobin (g/L)	Week 24	279	1.4 (8.8)	1 (-35, 26)	294	0 (8.4)	0 (-23, 40)
Hemoglobin (g/L)	Week 48	255	0.3 (9.2)	0 (-31, 40)	284	0.8 (9)	0 (-27, 40)

Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine, SD = standard deviation

17.7.2. Chemistry

Table 185. Total Cholesterol, HDL, and LDL Change From Baseline at Week 48, FLAIR

		CAB+RPV N=268 n (%)			CAR N=275 n (%)		
Laboratory Parameter*	Visit	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)
Cholesterol (mg/dL)	Week 48	250	6.6 (26.8)	5.8 (-135.3, 77.3)	254	1.1 (26.1)	3.9 (-175.9, 94.7)
HDL cholesterol, direct (mg/dL)	Week 48	250	4.1 (10)	3.9 (-30.9, 44.5)	254	2.7 (9.8)	1.9 (-32.9, 34.8)
LDL cholesterol calculation (mg/dL)	Week 48	248	4.4 (22.6)	3.5 (-56.8, 86.2)	252	-2.7 (22.2)	-1.6 (-119.9, 68.5)
LDL cholesterol direct (mg/dL)	Week 48	4	-1.9 (12.6)	-1.9 (-10.8, 7)	2	NA**	NA

Source: ad b.xpt; Software: Python
*Serum or plasma; data excluding subjects on lipid lowering drugs
**Baseline missing
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RPV = rilpivirine, SD = standard deviation

Table 186. Total Cholesterol, HDL, and LDL Change From Baseline at Week 48, ATLAS

		CAB+RPV N=275 n (%)			CAR N=286 n (%)		
Laboratory Parameter*	Visit	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)
Cholesterol (mg/dL)	Week 48	249	2.4 (26.9)	1.9 (-69.6, 133.4)	273	-2.2 (27.2)	0 (-125.7, 73.5)
HDL cholesterol, direct (mg/dL)	Week 48	249	1.4 (10.4)	1.9 (-40.6, 32.9)	273	0.2 (10.3)	0 (-58, 30.9)
LDL cholesterol calculation (mg/dL)	Week 48	247	3.1 (23.8)	2.1 (-54.1, 156.2)	268	-0.8 (21.2)	-1.2 (-80.4, 60.3)
LDL cholesterol direct (mg/dL)	Week 48	2	13.1 (NA)	13.1 (13.1, 13.1)	5	1.4 (13.2)	1.9 (-12, 14.3)

*Serum or plasma; data excluding subjects on lipid lowering drugs
Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RPV = rilpivirine, SD = standard deviation

Table 187. Total Cholesterol, HDL, and LDL Change From Baseline at Week 48 Among Subjects With Weight Change >1 kg at Week 48, FLAIR

		CAB+RPV N=138 n (%)			CAR N=145 n (%)		
Laboratory Parameter*	Visit	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)
Cholesterol (mg/dL)	Week 48	137	8.8 (24.6)	7.7 (-46.4, 77.3)	144	5.1 (22.9)	5.8 (-71.5, 54.1)
HDL cholesterol, direct (mg/dL)	Week 48	137	3.8 (10.9)	3.9 (-30.9, 44.5)	144	1.5 (9.7)	1.9 (-32.9, 30.9)
LDL cholesterol calculation (mg/dL)	Week 48	135	5.7 (22.6)	4.2 (-56.8, 76.6)	142	0.2 (20.9)	1.2 (-76.6, 58.4)
LDL cholesterol direct (mg/dL)	Week 48	3	-1.9 (12.6)	-1.9 (-10.8, 7)	2	NA**	NA

*Serum or plasma; data excluding subjects on lipid lowering drugs
**Baseline missing
Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RPV = rilpivirine, SD = standard deviation

Table 188. Total Cholesterol, HDL, and LDL Change From Baseline at Week 48 Among Subjects With Weight Change >1 kg at Week 48, ATLAS

		CAB+RPV N=109 n (%)			CAR N=117 n (%)		
Laboratory Parameter*	Visit	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)
Cholesterol (mg/dL)	Week 48	109	-0.7 (27.4)	0 (-71.5, 59.9)	117	-0.3 (23.8)	0 (-63.8, 67.7)
HDL cholesterol, direct (mg/dL)	Week 48	109	0.2 (10.6)	0 (-40.6, 21.3)	117	-2.6 (10.8)	-1.9 (-58, 21.3)
LDL cholesterol calculation (mg/dL)	Week 48	108	1.6 (22.9)	3.9 (-63.8, 59.9)	115	0.8 (19.3)	0 (-54.5, 52.6)
LDL cholesterol direct (mg/dL)	Week 48	0	NA**	NA	2	14.3 (NA)	14.3 (14.3, 14.3)

*Excluding subjects on lipid lowering drugs
**Baseline missing
Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RPV = rilpivirine, SD = standard deviation

Table 189. Incidence of Elevated Serum Glucose and Positive Urine Glucose During Maintenance Period, FLAIR, ATLAS

	FLAIR				ATLAS			
	CAB+RPV N=283 n (%)		CAR N=283 n (%)		CAB+RPV N=308 n (%)		CAR N=308 n (%)	
Laboratory Parameter	**N**	**n (%)**	**N**	**n** (%)	**N**	**n (%)**	**N**	**n (%)**
Hyperglycemia	283	75 (26.5)	283	76 (26.9)	300	68 (22.7)	304	83 (27.3)
Positive urine glucose (dipstick)	281	3 (1.1)	283	1 (0.4)	298	2 (0.7)	299	5 (1.7)

Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

Table 190. Incidence of Elevated Serum Glucose and Positive Urine Glucose During Maintenance Period Among Subjects With Weight Change >1 kg at Week 48, FLAIR, ATLAS

	Trial 201584				Trial 201585			
	CAB+RPV N=138 n (%)		CAR N=145 n (%)		CAB+RPV N=109 n (%)		CAR N=117 n (%)	
Laboratory Parameter	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Hyperglycemia	138	37 (26.8)	145	44 (30.3)	109	27 (24.8)	117	30 (25.6)
Positive urine glucose (dipstick)	138	2 (1.4)	145	0	108	0	115	1 (0.9)

Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine

Table 191. Serum Glucose Change (Increase) From Baseline at Week 48, FLAIR

	CAB+RPV N=283 n (%)			CAR N=283 n (%)		
Laboratory Parameter	**N**	**Mean Change From Baseline (SD)**	**Median Change From Baseline (Min, Max)**	**N**	**Mean Change From Baseline (SD)**	**Median Change From Baseline (Min, Max)**
Serum glucose (mg/DL)	283	20.3 (15.2)	16.21 (1.8 - 111.69)	283	20.2 (14)	16.22 (1.8 - 79.27)

Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine, SD = standard deviation

Table 192. Serum Glucose Change (Increase) From Baseline Among Subjects With Weight Change >1 kg at Week 48, FLAIR

	CAB+RPV N=138 n (%)			CAR N=145 n (%)		
Laboratory Parameter	**N**	**Mean Change From Baseline (SD)**	**Median Change From Baseline (Min, Max)**	**N**	**Mean Change From Baseline (SD)**	**Median Change From Baseline (Min, Max)**
Serum glucose (mg/DL)	138	22.5 (18.2)	16.21 (1.8 - 111.7)	145	22.2 (15.7)	18.01 (1.8 - 79.3)

Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine, SD = standard deviation

Table 193. Serum Glucose Change (Increase) From Baseline at Week 48, ATLAS

	CAB+RPV N=308 n (%)			CAR N=308 n (%)		
Laboratory Parameter	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)
Serum glucose (mg/DL)	300	34.5 (22)	28.82 (1.8 - 165.73)	304	30.7 (31.8)	19.81 (1.8 - 226.99)

Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine, SD = standard deviation

Table 194. Serum Glucose Change (Increase) From Baseline Among Subjects With Weight Change >1 kg at Week 48, Trial ATLAS

	CAB+RPV N=109 n (%)			CAR N=117 n (%)		
Laboratory Parameter	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)	N	Mean Change From Baseline (SD)	Median Change From Baseline (Min, Max)
Serum glucose (mg/DL)	109	33.7 (18.2)	32.42 (5.4 - 88.27)	117	24.9 (15.1)	19.82 (1.8 - 72.05)

Source: ad b.xpt; Software: Python
Abbreviations: CAB = cabotegravir, CAR = current antiretroviral, RPV = rilpivirine, SD = standard deviation

17.8. Safety Analyses by Special Subgroups

Similar to the analyses for the primary ITT population, the safety analyses for the subgroup population is also descriptive. The protocol prespecified stratification by gender at randomization, allowing enrollment of a reasonable sample size of female subjects in the trials. Interpretation of results from other subgroup analyses are limited because there was no stratification at randomization, leading to small sample sizes across the subgroups. Interpretation of outcomes should be with caution as apparent differences could be driven by the small sample sizes or higher variabilities within groups.

Gender

Twenty-eight percent of the enrolled population was female, with each treatment group enrolling similar proportions. Exposure-related differences in AEs were not anticipated as steady-state CAB and RPV exposures are similar between males and females. The exposures to CAB and RPV are similar during OLI dosing, and after the first injection.

Summary of AEs for male and female subjects are displayed in Table 195 and Table 196, respectively. In general, the incidence of AEs was similar between the two genders, although the incidence of treatment-related and severe AEs (grade 3, 4) were higher in males compared to females.

Table 195. Summary of Adverse Events (AEs) Among Male Subjects in FLAIR and ATLAS Trials, Maintenance Period

Adverse Event(s)	CAB+RPV N=220	ABC/DTG/ 3TC N=219	CAB+RPV N=209	Current ART N=204	CAB+RPV N=429	Current ART N=423
Any AE	210(95%)	175 (80%)	203(97%)	148(73%)	413(96%)	323(76%)
Grade 3/4 AE	28(13%)	9(4%)	28(13%)	17(8%)	56(13%)	26(6%)
Treatment-related AE	188(85%)	24(11%)	177(85%)	6(3%)	365(85%)	30(7%)
Grade 3 or 4 drug-related AE	14(6%)	0	12(6%)	1(<1)	26(6%)	1(<1%)
AEs leading to discontinuation	8(4%)	3(1%)	10(5%)	2(<1%)	18(4%)	5(1%)
SAE	17(8%)	9(4%)	8(4%)	8(4%)	25(6%)	17(4%)
Treatment-related SAE	1(<1%)	0	0	1(<1%)	1(<1%)	1(<1%)
SAEs leading to death	0	0	0	0	0	0

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Among the female subjects, similar to the overall population, the incidences of AEs and treatment-related AEs were higher in the CAB+RPV-treated female subjects compared to female subjects in the pooled control group (Table 196). No significant differences were observed for serious or severe AEs; incidence of treatment discontinuation was also similar between the treatment groups.

Table 196. Summary of Adverse Events (AEs) Among Female Subjects in FLAIR and ATLAS Trials, Maintenance Period

Adverse Event(s)	CAB+RPV N=63	ABC/DTG/ 3TC N=64	CAB+RPV N=99	Current ART N=104	CAB+RPV N=162	Current ART N=168
Any AE	57(90%)	50 (78%)	91(92%)	72(69%)	148(91%)	122(73%)
Grade 3/4 AE	3(5%)	2(3%)	7(7%)	7(7%)	10(6%)	9(5%)
Treatment-related AE	48(76%)	4 (6%)	78(79%)	2(2%)	126 (78%)	6(4%)
Grade 3 or 4 drug-related AE	0	0	2(2%)	0	2 (1%)	0
AEs leading to discontinuation	1(2%)	1(2%)	3(3%)	3(3%)	4 (2%)	4(2%)
SAE	1(2%)	3(5%)	5(5%)	6(6%)	6 (4%)	9(5%)
Treatment-related SAE	0	0	0	0	0	0
SAEs leading to death	0	0	0	1(<1%)	0	1(<1%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Race

The phase 3 trials primarily enrolled white/Caucasian/European-descent population (68%). The largest minority group enrolled was black/African-American (23%). Therefore, the subgroup analysis for race was focused on the black/African-American population and white/Caucasians. More black/African-American subjects were enrolled in the control group compared to the CAB+RPV treatment group – 23% versus 18%, respectively. This imbalance is acceptable because the trial design did not prespecify stratification by race.

Table 197 and Table 198 summarize the AEs reported for white/Caucasian and blacks/African-American populations, respectively. In general, the characteristics of AEs were similar between the two population. Because race was not a stratification factor, the comparison between the groups is limited.

Table 197. Summary of Adverse Events (AEs) Among White/Caucasian Subjects in FLAIR and ATLAS Trials, Maintenance Period

Adverse Event(s)	CAB+RPV N=216	ABC/DTG/3TC N=201	CAB+RPV N=214	Current ART N=207	CAB+RPV N=430	Current ART N=408
Any AE	205(95%)	155 (77%)	209(98%)	150(72%)	414 (96%)	305(75%)
Grade 3/4 AE	27(13%)	9(4%)	25(12%)	11(5%)	52(12%)	20(5%)
Treatment-related AE	185(86%)	19(9%)	188(88%)	6(3%)	373(87%)	25(6%)
Grade 3 or 4 treatment-related AE	12(6%)	0	11(5%)	1(<1%)	23 (5%)	1(<1%)
AEs leading to discontinuation	8(4%)	2(<1%)	11(5%)	3(1%)	19(4%)	5(1%)
SAE	14(6%)	10(5%)	9(4%)	3(1%)	23 (5%)	13(3%)
Treatment-related SAE	1(<1%)	0	0	1(<1%)	1(<1%)	1(<1%)
SAEs leading to death	0	0	0	0	0	0

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Among black/African American subjects, as summarized in Table 198, the incidences of AEs and severe AEs were similar between the treatment groups. Treatment-related severe AEs were reported more frequently in the CAB+RPV treatment group, while discontinuation and SAEs were more common in the pooled control group. The overall characteristics of the AEs were generally similar to the ITT population.

Table 198. Summary of Adverse Events (AEs) Among Black/African-American Subjects in FLAIR and ATLAS Trials, Maintenance Period

Adverse Event(s)	CAB+RPV N=47	ABC/DTG/3TC N=57	CAB+RPV N=62	Current ART N=77	CAB+RPV N=109	Current ART N=133
Any AE	42(89%)	45 (80%)	54(87%)	51(66%)	96 (88%)	96(72%)
Grade 3/4 AE	3(6%)	1(2%)	6(10%)	9(12%)	9(8%)	10(8%)
Treatment-related AE	32(66%)	2 (4%)	43(69%)	0	74(68%)	2(2%)
Grade 3 or 4 treatment-related AE	2(4%)	0	1(2%)	0	3 (3%)	0
AEs leading to discontinuation	0	1(2%)	0	2(3%)	0	3(2%)
SAE	2(4%)	2(4%)	2(3%)	10(13%)	4 (4%)	12(9%)
Treatment-related SAE	0	0	0	0	0	0
SAEs leading to death	0	0	0	1(<1%)	0	1(<1%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Age

As few 'geriatric' (>65 years of age) subjects were enrolled, the Applicant defined older subjects as those ≥50 years of age. The clinical team agrees with this approach to increase the sample size for age-based safety analysis. Overall, 21% of the subjects (224) were 50 years of age or older. The percentage of older subjects in the control group (21%) was slightly higher than that in the CAB+RPV treatment group (17%). This slight imbalance is acceptable because no age stratification was prespecified.

The safety finding between subjects < versus ≥50 years of age was generally comparable during the maintenance period, as summarized in Table 199 and Table 200, respectively. Rigorous comparison between the groups was not conducted because age was not a stratification factor.

Table 199. Summary of AEs Among <50 Years Old Subjects in FLAIR and ATLAS Trials, Maintenance Period

Adverse Event(s)	CAB+RPV N=250	ABC/DTG/ 3TC N=254	CAB+RPV N=242	Current ART N=212	CAB+RPV N=492	Current ART N=466
Any AE	234(94%)	201(79%)	231(95%)	147(69%)	465(95%)	348(75%)
Grade 3/4 AE	27(11%)	9(4%)	30(12%)	18(8%)	57(12%)	27(6%)
Treatment-related AE	207(83%)	25(10%)	200(83%)	6(3%)	407(83%)	31(7%)
Grade 3 or 4 treatment-related AE	12(5%)	0	12(5%)	1(1%)	24(5%)	1(<1%)
AEs leading to discontinuation	8(3%)	4(2%)	10(4%)	2(<1%)	18(4%)	6(1%)
SAE	14(6%)	10(4%)	11(5%)	12(6%)	25(5%)	22(5%)
Treatment-related SAE	0	0	0	1(<1%)	0	1(<1%)
SAEs leading to death	0	0	0	1(<1%)	0	1(<1%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Table 200 summarizes the general characteristics of the AEs reported among older subjects (≥50 years old). Except for treatment-related SAE or fatal SAE, the incidence for all other AEs were higher in the CAB+RPV treatment group compared with the pooled control group. The smaller number of older subjects relative to the other subgroups could drive this observation. Compared with the overall ITT population, however, the incidences observed among older subject are similar.

Table 200. Summary of AEs Among Older (≥50 Years Old) Subjects in FLAIR and ATLAS Trials, Maintenance Period

Adverse Event(s)	CAB+RPV N=33	ABC/DTG/ 3TC N=29	CAB+RPV N=66	Current ART N=96	CAB+RPV N=99	Current ART N=125
Any AE	33 (100%)	24 (83%)	63(95%)	73(76%)	96 (97%)	97(78%)
Grade 3/4 AE	4 (12%)	2 (7%)	5(8%)	6(6%)	9(9%)	8(6%)
Treatment-related AE	29 (88%)	3 (4%)	55(83%)	2(2%)	84(85%)	5(4%)
Grade 3 or 4 treatment-related AE	2 (6%)	0	2(3%)	0	4 (4%)	0
AEs leading to discontinuation	1 (3%)	0	3(5%)	3(3%)	4(4%)	3(2%)
SAE	4 (12%)	2 (7%)	2(3%)	2(2%)	6 (6%)	4(3%)
Treatment-related SAE	1 (3%)	0	0	0	1(1%)	0
SAEs leading to death	0	0	0	0	0	0

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, RPV = rilpivirine, SAE = serious adverse event

Hepatitis B and/or C Virus Coinfection

Hepatitis B coinfection was an exclusion criterion for study enrollment. No conclusions can be made about the safety of CAB+RPV in hepatitis B coinfected subjects. During the phase 3 maintenance period, three subjects in the CAB+RPV treatment group had acute hepatitis B infection. PP's LSC, all discontinued treatment, with ALT ranging from 8× UNL to 42× ULN at the time of discontinuation.

As discussed below in Section 17.9.3, one HCV coinfected subject enrolled in the phase 2 trial (LATTE-2) met protocol-defined LSC and developed suspected moderate DILI while on oral CAB. The subject had evidence of liver damage (grade 3 or 4 fibrosis) accompanied by ongoing HCV replication (chronic active hepatitis) when treatment was initiated. Careful enrollment criteria were then implemented: asymptomatic, with stable HCV without advanced liver disease, and lacking necessity for HCV treatment during the first 48 weeks of study.

As summarized by Applicant, in FLAIR and ATLAS, subjects with HCV coinfection were enrolled in each pooled treatment groups (7%). All had stable HCV without advanced chronic HCV infection, advanced liver disease, liver fibrosis, or liver decompensation. Their outcomes were generally similar to the mono-infected HIV subjects. The subjects in the CAB+RPV treatment group did not develop signs or symptoms of DILI during their study participation, suggesting that the risk of DILI is not higher in HIV/HCV coinfected subjects, although limited conclusions can be drawn about this small subpopulation. Among subjects who had acute hepatitis C during the phase 3 trials (i.e., HCV negative at baseline), none who met the LSC resumed study drug treatment.

17.9. Other Safety Explorations

17.9.1. Safety Summary of Oral Lead-in Period

Summary

During the development program, the Applicant elected to include an OLI as part of the regimen for CAB+RPV to allow for assessment of tolerability and safety events among subjects prior to switching to the extended-release injectable CAB+RPV. Specifically, concerns for HSR and hepatoxicity informed the dosing design for the phase 2 and 3 clinical trials.

The purpose of the safety review for the OLI period is to identify if OLI has advantage in identifying subjects who may not tolerate the CAB+RPV regimen. The result of this analysis will also be informative for the ongoing clinical trials where the Applicant is assessing the regimen without the OLI.

Overall, 187 (32%) subjects experienced at least one AE. Nasopharyngitis, headache, and vitamin D deficiency were among the most commonly reported AEs. SAEs were reported in four subjects and included enterocolitis, pyrexia, abortion missed, and hepatitis A. None were considered treatment-related. A total of six subjects discontinued treatment prior to switching to the extended-release formulation. The events were not related to HSR or nonviral hepatotoxicity.

In summary, few subjects discontinued the OLI for AEs and no subjects discontinued due to HSR or drug-related hepatotoxicity. Future dosing regimens may be considered without OLI after review of the ATLAS-2 trial which is evaluating a treatment arm without an OLI.

Additional Analyses

Table 201. Summary of Adverse Events (AEs) Occurring During the OLI Period

Adverse Event(s)	FLAIR N=283	ATLAS N=308	Total N=591
Any subject with OLI AE	95 (34%)	92(30%)	187 (32%)
SAE*	3(1%)	1(0.3%)	4 (0.7%)
Severity of SAEs			
Grade 3[&]	5(1.8%)	3(1%)	8 (1.4%)
Grade 4[%]	0	1(0.3%)	1(0.2%)
AE leading to discontinuation**	3(1%)	3(1%)	6 (1%)
Treatment-related AE[$]	22(7%)	17(6%)	39 (6.6%)
Hepatic events	3(1%)	1(0.3%)	4 (0.7%)
Rash grouped terms	3(1%)	3(1%)	6(1%)

*Abortion missed, enterocolitis, hep A, pyrexia
** asthenia/myalgia; depression suicide, H/A; hep C, Hep A, inc transaminase
& H/A; dec phosp, inc lipase; inc TG; inc lipase, sleep D/P, skin cancer, inc transam
% Increased bili (not same subj as phos or the hepatic ae subject)
$ Treatment related events clustered around depression D/O, anxiety, GI (pain, dyspepsia, nausea, vomiting, diarrhea), fatigue, H/A, sleep related events, 1 lipase. NO HEPATIC OR RASH.
Grouped rash terms: rash, rash generalized, rash pruritic, rash vesicular, pruritis generalized, erythema
Hepatic events: biliary tract D/O, non-alc steatohepatitis, hepatic steatosis, increased bili
Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: AE = adverse event, OLI = oral lead-in, SAE = serious adverse event

Table 202. Summary of AEs Occurring During OLI Period, by SOC

Primary System Organ Class	Dictionary Derived Term	CAB+RPV N=591	ABC/DTG/ 3TC N=283	Current ART N=308
	Subjects(filtered)	87 (14.7%)	15 (5.3%)	25 (8.1%)
General disorders and administration site conditions	Chills	9 (1.5%)	0 (0.0%)	2 (0.6%)
	Feeling hot	4 (0.7%)	0 (0.0%)	0 (0.0%)
	Feeling of body temperature change	1 (0.2%)	0 (0.0%)	0 (0.0%)
	Influenza like illness	21 (3.6%)	7 (2.5%)	4 (1.3%)
	Pyrexia	46 (7.8%)	9 (3.2%)	15 (4.9%)
Investigations	Body temperature increased	14 (2.4%)	0 (0.0%)	4 (1.3%)

Source: Clinical Reviewer's analysis of integrated summary of safety (ISS) ADAE datasets (212887, JReview)
Abbreviations: 3TC = lamivudine, ABC = abacavir, AE = adverse event, ART = antiretroviral therapy, CAB = cabotegravir, DTG = dolutegravir, OLI = oral lead-in, RPV = rilpivirine

17.9.2. Neurology – Review of Seizure Events

17.9.2.1. DNP Memo for Division of Antivirals

NDA:	212887, 212888
Drug:	Cabotegravir/rilpivirine combination product
Proposed Indication:	HIV-1 infection, treatment (b) (4)
Consultation Requestor:	Yodit Belew, MD Division of Antivirals
Desired Completion:	09/20/2019
Date Review Completed:	09/16/2019
Reviewer:	Emily R. Freilich, MD
Team Leader:	Philip Sheridan, MD Division of Neurology Products (DNP)

Background

The Division of Antivirals (DAV) has requested a consultation for the drug CAB under NDAs 212887 and 212888. These NDAs are currently under review by DAV for the treatment of HIV-1 infection, in both oral tablet (NDA 212887) and long-acting parenteral injection (212888) dosage forms. The LA form is a combination product with RPV, an NNRTI that has previously been approved as oral tablet. There have been a number of patients in development who had a seizure, and therefore, DAV has asked DNP to evaluate the association of CAB and seizures.

Alternative HIV treatments are often being developed to help improve patient adherence to treatment, and to prevent the emergence of resistance and transmission of the virus. It is felt that LA ARV agents may improve patient compliance and may also allow for reaching underserved patient populations. It may also serve to improve the QoL for patients with HIV. The parenteral route of administration would also hopefully reduce the GI AEs and eliminate dosing restrictions with regard to food and reduce drug-drug interactions.

The current submissions are for both the oral CAB tablets (proposed tradename VOCABRIA), which will be doses with RPV oral for oral bridging and OLI regimens, and the CAB+RPV LA injection (proposed tradename CABENUVA), to be dosed once a month for maintenance therapy. The development program includes a total of 1,590 patients dosed with CAB. This includes the two pivotal phase 3 studies, two phase 2 studies, and 509 patients dosed in phase

1/clinical pharmacology studies. There are also approximately 500 patients enrolled in an ongoing phase 3b study (ATLAS-2M).

Of note, CAB LA is also under development for prevention of HIV infection in at-risk individuals (pre-exposure prophylaxis, PrEP studies), which includes approximately 2,600 patients included in the completed phase 2 studies and the two ongoing phase 3 studies.

Cabotegravir

CAB is a new molecular entity belonging to the INSTI class, an INSTI. The oral tablet and the long-acting injectable (LAI, in combination with RPV) are currently under review for the treatment of HIV infection in this submission. As noted above, CAB alone is also under development for prevention of HIV under IND 122744, with two ongoing phase 3 trials, sponsored by NIH/NIAID/DAIDS.

Of note, the oral CAB has a terminal half-life of approximately 41 hours. The CAB LA has a longer half-life due to absorption rate-limited PK. It is noted that, from popPK analysis, 47% of patients were predicted to have quantifiable plasma CAB concentrations 1 year after the last IM injection, and 17% were predicted to have quantifiable plasma CAB concentrations 96 weeks after the last injection. In the phase 2b study outlined below, 4 out of 12 (33%) had quantifiable CAB concentrations at the 12-month follow-up visit.

RPV

RPV is an NNRTI that has been approved in oral form since 2011 for the treatment of HIV infection. The LAI formulation is an investigational drug currently under review as a combination with CAB for the treatment of HIV infection.

Of note, due to drug-drug interactions that may significantly reduce the exposure of RPV and limit its effectiveness or lead to increased viral resistance, RPV is not to be taken with antiseizure medications carbamazepine, oxcarbazepine, phenobarbital, and phenytoin, as well as other medications.

There is no mention of seizures as a listed ADR in the current prescribing information and seizures were not previously identified as a safety signal in the previous development program of RPV.

Potential for Neurotoxicity and Class Effects

Both RPV and CAB are both known to penetrate the CSF. The NNRTI class of drugs, including RPV, and the INSTI class (CAB), are known to cause neuropsychiatric AEs, including depressive disorders, anxiety, insomnia/sleep disorders, and headache. Neither RPV or CAB has a nonclinical signal for seizures.

There was no evidence of a safety signal for seizures in the prior RPV clinical development program. However, older NNRTIs in the same class, such as EFV and etravirine (ETR) have been associated with convulsions in adult and pediatric patients, generally in the presence of a known medical history of seizures. Risk of convulsions is listed as a warning in the prescribing information for EFV and as an uncommon ADR in the prescribing information for ETV.

Reviewer's comment: Of note, the pivotal studies that led to the approval for RPV used EFV as the active comparator, so it may be important to note if there were any cases of convulsion in the RPV treatment arm that were missed because there was no difference between investigational drug and the active comparator.

In the INSTI class, DTG was recently found to be associated with NTDs, based on an observational epidemiologic study. In vitro data suggests that DTG may be a partial antagonist of the α folate 1 receptor, which may be the cause of the NTDs. Similar in vitro data suggests that CAB may also be a partial antagonist on the α folate 1 receptor.

Seizure is not a known or labeled ADR for any other drugs in the INSTI class; (b) (4) .

Given the nature of the treatment of HIV and need for multiple concomitant retroviral treatments, there are many other treatments used in the CAB development program, either as concomitant treatments or active comparators. There are also many similar drugs with similar mechanisms of action. The prescribing information for the active comparator treatments and other INSTI and NNRTI treatments were reviewed for this consult, including RPV, DTG, ABC, 3TC, EFV, FTC, TDF, and etravirine (ETR).

Seizures or convulsions are described in the prescribing information as noted above for ETV and EFV, which are both NNRTIs. Seizures are also included in the prescribing information for the fixed dose combination of DTG with ABC and 3TC, which lists seizures as an adverse reaction noted in postmarketing experience. Convulsions are also noted in the prescribing information for 3TC itself, which notes that convulsions were noted in a few neonates treated with 3TC. There are no described seizures in the labels of FTC, TDF, or the fixed dose combination of the two drugs, which is used as the active comparator in the ongoing and still blinded PrEP trials.

(b) (4). There were no seizures in the development program for the initial approval of oral DTG. Subsequently, there were reports of seizures in the postmarketing experience for Triumeq, which is a fixed-dose combination of DTG/3TC/ABC. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Materials Reviewed

For the completion of this consult, I reviewed the consult request form and the table of cases provided by the Applicant. For background material, I also reviewed the submitted clinical summary, clinical overview, and summary of clinical safety, as well as the protocols for the phase 3 studies for NDA 212887/212888.

I reviewed the submitted case narratives for the events of seizures, as well as the FAERs database for any additional cases of seizures. I also reviewed the submitted safety reports for IND 122744 for the prevention of HIV-infection (PrEP).

The prescribing information for all the comparator treatments and similar drugs in the INSTI and NNRTI class were also reviewed as noted above.

Review of Clinical Data

Clinical Studies Referenced in Review

- LAI116815 (phase 1, bioavailability study) – open-label, single-dose parallel study to evaluate the relative bioavailability of two new formulations of (b) (4) Given to healthy volunteers, with a 14-day lead in, followed by a single IM dose of 400 mg IM CAB of various particle size
- LAI116482 (LATTE, phase 2b) – randomized, partially-blind, dose-ranging study with active control comparing oral CAB 10, 30, or 60 mg in combination with RPV and other NRTIs in HIV-infected patients
- 200056 (LATTE-2, phase 2b) –randomized, parallel-group, open-label study with a 20-week induction period of oral CAB followed by IM CAB/RPV maintenance every 4 or 8 weeks or oral CAB plus alternative NRTI medications
- 201584 (FLAIR, phase 3)- multicenter, randomized, parallel-group, open-label, noninferiority study with a 20-week induction phase of standard treatment (ABC/DTG/3TC) fixed-dose combination followed by switch to oral CAB 30 mg/RPV 25 mg×4 weeks then IM CAB LA/RPV LA 600/900×1 and 400/600 mg q4 weeks vs. continued oral ARV regimen
- 201585 (ATLAS, phase 3) – multicenter, randomized, parallel-group, open-label, noninferiority study with comparison of continued ARV treatment to oral CAB 30 mg and RPV 25 mg×4 weeks followed by IM CAB/RPV LQ every 4 weeks

- 207966 (ATLAS-2M, phase 3b) – randomized, multicenter, parallel-group, noninferiority, open-label study in HIV patients who are virologically suppressed with CAB/RPV LA 400/600 mg IM every 4 weeks compared to CAB/RPV LA 600/900 mg IM every 8 weeks
- 201103 (HPTN 077, phase 2a) – multicenter, double-blind, two-arm, randomized, placebo-controlled trial of the safety, tolerability and acceptability of CAB LA in HIV uninfected men and women at low to minimal risk for acquiring HIV infection, using daily oral CAB 30 mg or placebo×4 weeks followed by 1 week wash out, and then CAB LA 800 mg IM injection every 12 weeks
- 201738 (HPTN 083, phase 2b/3) – randomized, multicenter, double-blind, double-dummy, noninferiority study in men at high risk for HIV acquisition with daily lead-in of oral CAB or oral TDF/FTC (300/200 mg fixed-dose combination)×5 weeks, then CAB LA 600 mg IM q4 weeks×1, then q8 weeks vs. continued daily oral TDF/FTC
- 201739 (HPTN 084, phase 2b/3)- randomized, multicenter, double-blind, superiority study in African women at risk of HIV acquisition with an OLI phase of oral CAB×4 weeks vs. daily TDF/FTC followed by CAB LA 600 mg IM q4 weeks×1 then q8 weeks vs. continued daily oral TDF/FTC

Seizure and Seizure-Like Events

In the development program of CAB/RPV for treatment of HIV, there were reports of six patients who had seizures in the treatment arm and two seizures reported in the comparator treatment arm. The reported seizures with treatment are described in detail below in Table 203. Also, in the phase 3 program, there was one seizure reported in a patient in the comparator arm for Study 201585 that was not serious and did not lead to study drug discontinuation.

Table 203. Reported Events of Seizures in Cabotegravir (CAB) Development Program

Study/ Subject ID	Dose/Exposure	Age	Time to Onset	Event Details	Risk Factors
201584 (FLAIR, phase 3) Subj ID (b) (6)	ABC/3TC/DTG daily x6 months (induction) CAB oral 30 mg and RPV oral 25 mg daily x5 weeks Then CAB/RPV 600/900 injection x1, then monthly 400/600 mg injections. Withdrew from study (b) (6) due to injection site reaction (last dose (b) (6)	59-year-old male	26 weeks and 2 days from first oral dose (2 months after last dose of CAB/RPV)	• GTC at home and in ambulance, with subsequent confusion, nystagmus. • Viral prodrome, found to have + flu A, treated with multiple antivirals/antibiotics, given Pabrinex (thiamine, riboflavin, pyridoxine nicotinamide, ascorbic acid) for h/o ETOH consumption = diagnosis of influenza meningoencephalitis. 3 months later also diagnosed with b/l chronic subdural hematomas requiring evacuation.	• Influenza meningoencephalitis • Multiple concomitant medications that lower seizure threshold (oseltamivir, teicoplanin, acyclovir • Chronic ETOH use • Bilateral subdural hematomas
LAI116482 (LATTE, phase 2b)	30 mg CAB oral plus ABC/3TC for 24 weeks, then CAB 30 mg oral + RPV 25 mg oral	38-year-old male	191 weeks and 1 day	Virologically suppressed on CAB for 3.7 years. Partner witnessed possible seizure-like event of flailing in sleep with saliva from mouth/nose and difficult to arouse, no recollection the following day. + history of GHB and crystal meth use, and had used “morphine” on the day of the event.	Long latency period • Illicit drug use (? morphine) on day of event
LAI116815 (phase 1, BA single dose IM study)	30 mg CAB oral for 4 weeks followed by single dose 400 mg IM CAB	20-30 - year-old male	42 weeks and 5 days	42.5 weeks after initial dose, had myoclonus followed by full GTC in the morning, after drinking large amounts of ETOH night. EEG c/w history of JME, had history of seizure activity at age 13.	h/o seizure (likely JME diagnosis) • Alcohol night before *Note: Patient had no detectable CAB levels in blood 6 months prior to event
207966 (ATLAS-2M)	30 mg CAB and 25 mg RPV oral×4 weeks followed by loading dose CAB/RPV LA 600/900 mg×1,	60-70-year old	23 weeks and 5 days	4 days prior to presentation reported headaches and visual symptoms, then collapsed at home with witnessed GTC. Given Dexamethasone and oral	• New diagnosis brain tumor No prior neurologic symptoms

Study/ Subject ID	Dose/Exposure	Age	Time to Onset	Event Details	Risk Factors
	then monthly CAB/RPV LA 400/600 mg injections			levetiracetam (LEV) in ER. MRI showed large R frontotemporal tumor, with mass effect, suggestive of glial tumor or metastatic lesion. Had surgery 3 days later.	
207966 (ATLAS-2M) SID: (b) (6)	30 mg oral CAB and 25 mg RPV oral×4 weeks, then CAB/RPV LA 600/900 mg×1, then monthly 400/600 CAB/RPV LA, then q8 weeks CAB/RPV 600/900 mg	45-year-old male	74 weeks and 3 days (last dose (b) (6) pancreatitis (b) (6) seizure (b) (6))	Patient presented with severe abdominal pain and was diagnosed with acute severe pancreatitis. Was admitted to ICU on (b) (6) and experienced cardiopulmonary arrest on (b) (6) requiring CPR with continued impairment in consciousness. Imaging showed b/l cerebral infarcts and PRES. EEG showed slow waves and low brain activity, CSF was normal. Developed multiple complications, then 2 months later, on (b) (6) had focal seizure for several minutes treated with levetiracetam (LEV) and diazepam. Another episode a few days later, continued LEV. At the time of seizure was on multiple medications. Patient died.	S/p cardiac arrest with bilateral strokes and PRES Concomitant medication at time of seizure included meropenem which lowers seizure threshold
200056 (LATTE-2, phase 2b) SID (b) (6)	30 mg CAB plus ABC/3TC oral×20 weeks 25 mg RPV oral added×4 weeks, then IM CAB/RPV LA 800/600 mg×1, then monthly CAB/RPV LA 400/600 mg	37-year-old male	49 weeks and 6 days	Developed acute-onset status epilepticus for presumed 6 hours w/o medical attention which resulted in anoxic brain injury and death. Found unresponsive and unconscious and seizing, MRI with diffuse cerebral edema, + papaverine on urine/serum spect and social history + for recreational drug use. +	• Papaverine in urine although initial tox screen negative (indicates heroin use) • Long latency from initiation of investigational product • Recreational drug use on social history

Study/ Subject ID	Dose/Exposure	Age	Time to Onset	Event Details	Risk Factors
				DNR and family withdrew care, but denied autopsy	

Abbreviations: 3TC = lamivudine, ABC = abacavir, CAB = cabotegravir, CPR = cardiopulmonary resuscitation, CSF = cerebrospinal fluid, DNR = do not resuscitate, DTG = dolutegravir, EEG = electroencephalogram, ER = emergency room, ETOH = ethanol, GTC = generalized tonic clonic, ICU = intensive care unit, JME = juvenile myoclonic epilepsy, LA = long-acting, MRI = magnetic resonance imaging, RPV = rilpivirine

Reviewer's comment: The above six cases occurred during the clinical development of CAB and RPV for treatment of HIV. Most of the cases had confounding variables which are more likely to be the etiology of the seizures. However, there are at least two cases that occurred after a long time on CAB which had a simultaneous exposure to illicit drugs, but no other clear cause for the seizure activity. The possibility that exposure to CAB contributed to lowering the seizure threshold in otherwise high-risk patients cannot be excluded.

Furthermore, it should also be noted that patients who were at risk for seizures or had a known history of seizures were excluded from the phase 3 studies. It is possible that there may have been more events had those patients not been excluded. These cases warrant a minimum of further surveillance, and potentially a mention in the labeling as a rare but possible AE.

In the ongoing studies of CAB LA for prevention of HIV (PrEP), there have also been six seizures reported (Table 204). However, five of these patients are still blinded and it is unknown which treatment they are receiving, except for the initial patient who was in an earlier phase 2a study.

Table 204. Reports of Seizure in the Cabotegravir (CAB) PrEP Development Program*

(b) (4)

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Study/Subj ID	Dose/Exposure	Age	Time to Onset	Details	Other Risk Factors
(b) (4)					

* All cases remain blinded except case 1
Abbreviations: CAB = cabotegravir, CT = computed tomography, EEG = electroencephalogram, ER = emergency room, ETOH = ethanol, FTC = emtricitabine, GTC = generalized tonic clonic, IM = intramuscular, LOC = loss-of-control, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, TDF = tenofovir

Reviewer's comment: The above six cases were reported to the IND for the use of CAB for the prevention of HIV in high-risk patients (PrEP). These cases have fewer confounding variables than those in the current NDA submission. However, many of these patients are still blinded. It would be helpful to know which treatment they were receiving, or if there is an uneven distribution between the treatment arms. If all of these patients, or the majority of them, were indeed receiving CAB, it would appear that the exposure to CAB may be a contributing factor in the cause of the seizure or to lowering the seizure threshold in patients already at risk for seizures. See conclusions below.

Other Reported Neurologic Adverse Events

Neuropsychiatric AEs were considered an AE of special interest because they are common in this population, INSTI inhibitors have previously been associated with reports of mood disorders, suicidal ideation, and sleep disorders, and RPV is associated with depression as an ADR.

Overall, neuropsychiatric events occurred with low frequency, and were similar between the treatment groups in the phase 3 clinical studies. There were no serious neuropsychiatric events reported, and two neuropsychiatric AEs led to withdrawal (one patient with suicidal ideation, and one with anxiety). The incidence of sleep disorders, especially insomnia, were higher in the CAB/RPV treatment group compared to the comparator arm, and there was a higher incidence for mood disorders. The events of mood disorders did not include any SAEs or any AEs that led to study withdrawal. The incidence of anxiety and suicidal ideation were higher only in those patients with prior history of psychiatric illness.

Summary and Reviewer Conclusions

The crude incidence of acute symptomatic seizures or single, unprovoked seizures is estimated to be between 0.02 to 0.06% per year. The incidence of seizures in patients with HIV is estimated to be significantly higher, approximately 6% per year. However, this number comes from early studies of HIV prior to the development of ART, when many patients had advanced disease or AIDs, and may have been having seizures because of invasion of the CNS by the virus, primary CNS opportunistic infections, or other seizure risk factors (i.e., polysubstance abuse, etc.). The incidence of seizures in the CAB development program would not be expected to have been quite so high, as the patients were all virologically suppressed on ART at the time of enrollment, and those patients in the ongoing PrEP studies are HIV negative. Furthermore, because seizures were noted early in CAB development, patients who were considered high risk for seizures or had a history of seizures were excluded from the phase 3 studies, which may have led to an underestimating of the incidence of such events.

The calculated crude incidence of seizures in the development program for this submission is six patients out of 2,090 patients enrolled in studies for the treatment of HIV, which is approximately (b) (4)%. If all five of the patients in the ongoing blinded PrEP studies did receive CAB, the incidence would be (b) (4)%. While not a high number, it is higher than the overall estimated annual incidence of single, unprovoked seizures, although potentially not higher than the incidence in patients with HIV.

I also reviewed the labels for other medications that have been shown to lower the seizure threshold, bupropion, and meropenem. The prescribing information for bupropion describes an increased relative risk for seizures of 0.4% in the clinical studies, which clearly increased with higher dose. Meropenem had a 0.7% incidence of seizures in the overall clinical development program.

While many of the cases in the current clinical development program are not convincing for a causal relationship to the drug, there are a few cases that do not have an identifiable etiology for the seizures, and it cannot be ruled out that the exposure to CAB may have lowered the seizure threshold in these patients. Furthermore, if the patients outlined above in Table 204 are indeed in the CAB treatment arm, then that would confirm a safety signal for seizures. Without the blinded treatment arm information, it is difficult to draw a formal conclusion or make a determination regarding labeling.

As noted above, patients who were high risk for seizures were excluded from the phase 3 studies, which may have led to a decreased incidence of such events. There may also be a potential class effect of neurotoxicity with potential for both seizures and NTDs, as they were also recently

reported with a similar drug DTG. Taken together, it appears that there is a probable safety signal, pending more information about CAB exposure in the ongoing studies.

Consult Questions

DAV has asked for DNP's assessment of the case reports related to seizures.

1) Do you believe CAB use may be associated with seizure events?

Reviewer's comment: As noted above, it is hard to make a formal determination given the unknown exposure in the patients listed in Table 204. However, even if only a few of those patients were receiving CAB, it appears that here is likely an association with CAB and the lowering of the seizure threshold, particularly in patients that are already high-risk for seizures.

2) If so, please provide labeling recommendations.
3) If the cases do not support the above conclusion, do you have any additional recommendations beyond routine postmarket pharmacovigilance?

Labeling Recommendations

At a minimum, I believe seizures should be listed as a rare but uncommon side effect occurring in (b) (4)% of patients in clinical development. If the majority of the PrEP cases are found to be in the CAB treatment arm, or there is a very uneven distribution of cases, then a warning similar to that in EFV would be warranted. Potential language would be:

(b) (4)

Emily R. Freilich, MD
Clinical Reviewer

17.9.2.2. DNP Consultation Memo ADDENDUM

NDA:	212887, 212888
Drug:	Cabotegravir/rilpivirine combination product
Proposed Indication:	HIV-1 infection, treatment (b) (4)
Consultation Requestor:	Yodit Belew, MD Division of Antivirals
Desired Completion:	09/20/2019
Date Review Completed:	09/16/2019
Date of Addendum:	10/21/2019
Reviewer:	Emily R. Freilich, MD
Team Leader:	Philip Sheridan, MD Division of Neurology Products (DNP)

Addendum

After finalizing our initial review, the Division of Antivirals requested unblinding of the cases of seizure in the ongoing PrEP trials, which was able to be done without unblinding of the trial sponsors. Furthermore, the Applicant also updated the total number of patients who have been exposed to CAB through the ongoing studies, prompting this addendum.

As previously noted, there were a total of six patients with seizures in the CAB studies that are currently under review (phases 1 to 3b studies for treatment of HIV). An additional six patients had seizures in the still ongoing PrEP development program for prevention of HIV. However, five of these six patients remained blinded at the time of my original review.

Of the original six patients I noted who had received CAB in the PrEP development program, one patient received CAB in the phase 2 completed study and five patients were part of the ongoing blinded studies. One of these patients in study HPTN084 remains blinded.

Of the remaining four patients from Study HPTN083, one of the four patients received CAB, and the other three patients received the active comparator.

The results of the unblinding are reassuring given that three of the six seizures in the ongoing program were in active comparator arm, which is not known to be associated with seizures. There was also an additional patient with a seizure in the blinded study HTPN084. This results in a total of 6+2+2 (blinded) potential cases of seizures in development. With the prior estimate of exposed patients, this resulted in a possible incidence rate of (b) (4)%. Also noted is that many of the cases had possible alternate etiologies and confounding factors. At that time, it was discussed that while the incidence was quite low, there was enough concern for possible association with the treatment, and it was felt that seizure should be added to the label as a rare AE.

The Applicant then submitted an updated denominator with the current total patient exposure from the CAB development program to include 5,694 total patients, an additional 974 patients from the ongoing HPTN083 and HPTN084 studies. This would leave a crude incidence (worst-case scenario) of (b) (4)%, and an even lower incidence rate if only treatment-related cases were considered.

The higher number of total patient exposure, combined with the unblinding of the four patients in Study HTPN083, result in a lower incidence rate at less than (b) (4)%, and weakening the possible

association between the treatment and the seizures. However, as previously noted, the studies did exclude patients who were deemed high risk for seizures, so the incidence in such studies may be underestimated, and close pharmacovigilance should be recommended in the postmarketing space if the drug is approved. We agree with continuing to keep seizure as an adverse event of special interest, and recommend close pharmacovigilance for any seizure-related events.

_____

Emily R. Freilich, MD

Clinical Reviewer

17.9.3. Phase 2b Trials, LATTE and LATTE-2

Selected Treatment-Emergent AEs

LATTE

Table 205. Summary of Select Adverse Events During LATTE Trial

Grouped Terms Preferred Terms	CAB 10 mg (N=60) n (%)	CAB 30 mg (N=60) n (%)	CAB 60 mg (N=61) n (%)	Efavirenz (N=62) n (%)
Rash or hypersensitivity reactions (grouped terms)	6 (10.0)	4 (6.7)	9 (14.8)	17 (27.4)
Rash	3 (5.0)	2 (3.3)	3 (4.9)	8 (12.9)
Eye swelling	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis	2 (3.3)	1 (1.7)	1 (1.6)	1 (1.6)
Skin lesion	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Pruritus generalized	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Pruritus	0 (0.0)	0 (0.0)	1 (1.6)	2 (3.2)
Joint swelling	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)
Rash generalized	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)
Rash macular	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.8)
Rash maculo-papular	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Conjunctivitis	0 (0.0)	1 (1.7)	0 (0.0)	2 (3.2)
Anxiety disorder (grouped terms)	3 (5.0)	4 (6.7)	2 (3.3)	5 (8.1)
Anxiety disorder	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Panic attack	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.6)
Anxiety	2 (3.3)	3 (5.0)	2 (3.3)	4 (6.5)
Depressive disorders (grouped terms)	3 (5.0)	5 (8.3)	2 (3.3)	4 (6.5)
Depressed mood	1 (1.7)	0 (0.0)	1 (1.6)	0 (0.0)
Irritability	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Mood swings	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Mood altered	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Affective disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Depression	2 (3.3)	5 (8.3)	1 (1.6)	1 (1.6)
Pyrexia (grouped terms)	1 (1.7)	5 (8.3)	3 (4.9)	5 (8.1)
Feeling hot	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.2)
Influenza like illness	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)
Chills	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)
Pyrexia	1 (1.7)	3 (5.0)	3 (4.9)	3 (4.8)
Sleep disorders (grouped terms)	2 (3.3)	6 (10.0)	7 (11.5)	17 (27.4)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.5)
Poor quality sleep	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Nightmare	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)
Insomnia	2 (3.3)	6 (10.0)	7 (11.5)	14 (22.6)
Hepatobiliary disorders (SOC)	0 (0.0)	2 (3.3)	2 (3.3)	0 (0.0)
Hepatic steatosis	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Hepatitis	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)
Cholelithiasis	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)
Hepatic lesion	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0)

Source: adae.xpt; Software: Python
Abbreviations: CAB = cabotegravir, SOC = system organ class

LATTE-2

Table 206. Summary of Select AEs During LATTE-2 Trial (Cabotegravir-Treated Arm)

Grouped Terms Preferred Terms	CAB 30 mg (N=286) n (%)
Anxiety Disorder (grouped terms)	9 (3.1)
Anxiety	5 (1.7)
Anxiety disorder	2 (0.7)
Nervousness	1 (0.3)
Panic attack	1 (0.3)
Depressive disorders (grouped terms)	13 (4.5)
Depression	8 (2.8)
Affect lability	1 (0.3)
Affective disorder	1 (0.3)
Depressed mood	1 (0.3)
Irritability	1 (0.3)
Mood altered	1 (0.3)
Mood swings	1 (0.3)
Pyrexia (grouped terms)	7 (2.4)
Pyrexia	6 (2.1)
Feeling hot	1 (0.3)
Rash or hypersensitivity reactions (grouped terms)	18 (6.3)
Rash	5 (1.7)
Conjunctivitis	4 (1.4)
Pruritus	2 (0.7)
Skin lesion	2 (0.7)
Dermatitis	1 (0.3)
Hypersensitivity	1 (0.3)
Joint swelling	1 (0.3)
Photosensitivity reaction	1 (0.3)
Rash papular	1 (0.3)
Rash vesicular	1 (0.3)
Sleep disorders (grouped terms)	9 (3.1)
Insomnia	6 (2.1)
Nightmare	2 (0.7)
Poor quality sleep	1 (0.3)
Hepatobiliary disorders (SOC)	1 (0.3)
Hepatic steatosis	1 (0.3)

Source: adae.xpt; Software: Python
Abbreviations: AE = adverse event, CAB = cabotegravir, SOC = system organ class

Hepatotoxicity

The sentinel case leading to close liver monitoring occurred in a subject enrolled in the phase 2 trial. The case led to a request by the Division for quarterly summary of all liver-related events in subjects enrolled in any CAB trial.

The sentinel event occurred in a 54-year-old male with history of hepatitis C enrolled in LATTE 2 and received CAB 30 mg PO +ABC/3TC. He developed grade 4 possible DILI on day 35 of the induction phase, requiring hospitalization. The event was reported in July 2014 under IND 109678 (SN 087).

The rationale for quarterly update request was to assess for the risks and benefits of extended-release CAB, in both HIV-infected subjects and in adults at risk of HIV acquisition who were enroll in phase 2 or 3 HIV prevention trials (PrEP trials). The risk considerations included the challenges in rapidly eliminating CAB exposure in the event of DILI or HSRs during extended-release CAB treatment. The Division believed that close monitoring may facilitate early identification of hepatotoxicity trends and help assess the overall risks/benefits of CAB early in the drug development.

Additionally, in accordance with the FDA premarketing clinical liver safety guidance, liver chemistry threshold stopping criteria were included in the protocols to assure subject safety and to evaluate liver event etiologies. The following criteria were included in the phase 2b/3 trials:

- ALT ≥3× ULN **and** bilirubin ≥2× ULN (>35% direct bilirubin; bilirubin fractionation required)
- ALT ≥8× ULN;
- ALT ≥3× ULN (if baseline ALT is <ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, **or**;
- ALT ≥3× baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥5× ULN and <8× ULN that persists >2 weeks (with bilirubin <2× ULN and no signs or symptoms of acute hepatitis or hypersensitivity);
- ALT ≥5× ULN but <8× ULN and cannot be monitored weekly for >2 weeks;

As requested, GSK/ViiV submitted quarterly liver safety reviews. In sum, 14 reports were submitted. Early in 2018, the Division concluded no further quarterly reports were needed after reviewing the cumulative summary reports.

Summarized below are characteristics of subjects meeting the LSC during the quarterly reporting period.

Table 207. Subjects Meeting Liver Stopping Criteria Prior to NDA Submission

		Subjects Who Met Liver Stopping Criteria	
Study	No. of Subjects Exposed	Total No.	No. of Possible DILI
205712	15	2	0
201120 (ÉCLAIR, phase 2a)	105	1	0
LAI116482 (LATTE, phase 2b)	181	4	2
200056 (LATTE-2, phase 2b)	309	14	2
201584 (FLAIR phase 3)	284	5	0
201585 (ATLAS phase 3)	319	7	0
201738 (HPTN083)	464	5	0
Total	2376	39	4

Source: Clinical Reviewer's Analysis
Abbreviations: DILI = drug-induced liver injury

Majority of subjects with severe (grade 3 or 4) elevation in ALT/AST leading to treatment discontinuation experienced acute viral hepatitis (A, B or C), or other infection such as syphilis. Additional details are provided below for subjects considered to have experienced possible or probable DILI (n=4). Although the cases were identified as possible DILI, only one subject had elevated bilirubin (the sentinel case). Even in the sentinel case, the coinfection with hepatitis C is a confounding factor as an etiology of DILI.

Table 208. Additional Information for Cases Considered Possible or Probable DILI

SID	Dose	ALT ULN	AST ULN	Bili ULN	Comment	Study Withdrawal? Reason
(b) (6)	CAB 60 mg	12× ULN	7× ULN	WNL	Possible DILI Week 4 onset, pre-existing steatohepatitis	Y, Liver Stopping Criteria
	CAB 60 mg	10× ULN	5× ULN	WNL	Possible DILI Week 8 onset, steatohepatitis	Y, Liver Stopping Criteria
SID (b) (6)	PO CAB 30 mg	7× ULN	11× ULN	2× ULN	Probable DILI Week 4 onset, patient with chronic active hepatitis C and Grade 3 or 4 fibrosis	Y, Liver Stopping Criteria
SID (b) (6)	PO CAB 30 mg	9× ULN	6.4× ULN	WNL	Probable DILI Underlying hepatic steatosis as a confounding factor	Y, not possible to exclude CAB as a possible contributing factor

Source: Clinical Reviewer's Analysis
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CAB = cabotegravir, DILI = drug-induced liver injury, PO = by mouth, ULN = upper limit of normal, WNL = within normal limits

18. Mechanism of Action/Drug Resistance Additional Information and Assessment

18.1. Mechanism of Action

CAB inhibits HIV IN by binding to the IN active site and blocking the strand transfer step of retroviral DNA integration.

Integration of linear HIV DNA into the host cell genome is essential for viral replication, and is mediated by the viral IN enzyme through two consecutive reactions: 3' processing and strand transfer. For 3' processing, two GT dinucleotides are trimmed off CAGT sequences in the long terminal repeats (LTRs) of the viral DNA; the trimmed viral DNA bound to IN and cellular cofactors forms the pre-integration complex. Following translocation of the pre-integration

complex to the nucleus, the strand transfer reaction integrates the viral DNA via the CA-3'OH ends with the host genome resulting in the formation of the provirus.

Using full-length recombinant HIV IN isolated from *E. coli* complexed with biotinylated donor DNA and tritiated target DNA substrate, CAB inhibited HIV-1 IN catalyzed strand transfer with a mean IC_{50} value of 3.0nM (study report RH2007/00068/00). Strand transfer inhibition by CAB was also evaluated independently by the Applicant's collaborator, (b) (4) and had a mean IC_{50} value of 13.0nM in a similar assay, except using digoxigenin-labelled target DNA and a colorimetric readout (study report RH2007/00218/00).

To broadly evaluate how CAB was inhibiting HIV-1 in cell culture, the Applicant determined viral DNA levels from different stages of replication by quantitative polymerase chain reaction (qPCR), measuring total PCR for late reverse transcription products, Alu PCR for proviral DNA and 2'LTR PCR for 2'LTR circles. HIV-1 replication (in MT-4) cells was confined to a single cycle by performing the cell culture in the presence of ritonavir. CAB and control IN inhibitor RAL inhibited the amount of proviral DNA in a dose-dependent manner, and increased the level of 2'LTR circles, but did not affect the levels of late RT products (study report RH2010/00019/00), indicating that CAB acts on the integration step of the replication cycle.

Binding of tritiated CAB to IN:DNA duplexes was assessed using wild-type IN or IN harboring Q148 RAS.[44] The half-life of dissociation was reduced from 51 hours against wild-type IN to 6.3, 2.0 or 2.2 hours against IN harboring Q148H, Q148K or Q148R substitutions, respectively, supporting the evidence for the mechanism of action of CAB.

Further evidence of the mechanism of action of CAB was provided by cell culture resistance studies, in which amino acid substitutions emerged in IN following serial passage in the presence of drug (Section 18.3).

RPV is a NNRTI of HIV-1. It noncompetitively inhibits the virus-encoded RT and thereby disrupts viral replication. Using a primer extension-based scintillation proximity assay, the median inhibitory activity (IC_{50}) of HIV-1 RT by RPV was 42nM (NDA202022 SDN000).

Please refer to NDA202022 SDN000 (Lisa Naeger, Ph.D.) for complete virology review of RPV.

18.2. Antiviral Activity in Cell Culture

The antiviral activity of CAB in cell culture was evaluated against laboratory strains of HIV grown in MT4 cells (5-day assay, cell viability readout) and peripheral blood mononucleocytes (PBMCs; stimulated with phytohemagglutinin and IL-2; 7-day assay, RT activity readout), and in a pseudo-HIV (PHIV) assay. For the PHIV assay, CIP4 cells were infected with VSV-G-pseudotyped luciferase expressing lentiviral vector pGJ3-Luci for 2 days. Efavirenz was included as a positive control for all three assays, and cytotoxicity (CC_{50} value) determined in parallel. Table 209 summarizes the CAB antiviral activity data (study report RH2007/00068/00).

In the MT-4 assay, CAB had a mean EC_{50} value of 0.57nM against CXCR4-tropic HIV-1 strain IIIB. In the PBMC assay, CAB inhibited CCR5-tropic HIV-1 strain Ba-L with a mean EC_{50} value of 0.22nM. The control compound, EFV, had EC_{50} values in MT-4 cells and PBMCs of 2.8nM (95% CI: 2.0nM to 3.9nM, n=27) and 2.3nM (95% CI: 1.5 to 3.4nM, n=12), respectively.

In the PHIV assay, CAB had an EC_{50} value of 0.74nM (95% CI: 0.54nM to 1.0nM, n=15), and the control compound, EFV, had an EC_{50} value of 1.5nM (95% CI: 1.2nM to 1.9nM, n=32). The mean CC_{50} values of CAB in the MT-4 and PHIV assays were 3.6μM and >5.0μM, respectively, giving selectivity indices (SI) of 6,300 and >6,800, respectively.

Similar, independent experiments were described in Study Report RH2007/00218/00, with CAB inhibiting HIV-1_{IIIB} in MT-4 cells with a mean EC_{50} value of 1.3nM (SD=0.4, n=3), and HIV-1_{BaL} in PBMCs with a mean EC_{50} value of 0.34nM (SD=0.07, n=5). The mean CC_{50} value in these experiments was 11μM (SD=2.5nM, n=3; SI=8,900).

Table 209. Antiviral Activity of Cabotegravir (CAB) Against Laboratory Strains of HIV-1 (Study Report RH2007/00068/00)

Assay	HIV Strain	Mean EC_{50} Value (nM)	95% CI (n)	CC_{50} Value (μM)	95% CI (n)	Selectivity Index
MT-4	IIIB	0.57	0.39-0.83 (21)	3.6	1.8-7.0 (11)	6,300
PBMC	Ba-L	0.22	0.14-0.34 (11)	ND	ND	ND
PHIV	NA	0.74	0.54-1.0 (15)	>5.0	NA (10)	>6,800

Abbreviations: CAB = cabotegravir, CI = confidence interval, CC_{50} = cytotoxicity, EC_{50} = half maximal effective concentration, NA = not applicable; ND = not determined

Additional antiviral testing in cell culture was performed against recombinant viruses containing IN and RNase H derived from clinical isolates of HIV clade B (study report RH2007/00092/01). A modified PhenoSense™ vector (Monogram Biosciences) was used for cloning, and antiviral activity determined using a single cycle replication assay in peripheral blood lymphocytes (PBLs) with a luciferase readout.[45] The median EC_{50} value for recombinant virus with IN from clinical isolates was 1.3nM (range 1.0nM to 1.6nM, n=13), and for virus with IN from laboratory strains the median EC_{50} value was 1.4nM (range 1.1nM to 1.6nM, n=3) (Table 210).

Table 210. Susceptibility of Recombinant Clade B Clinical Isolates of HIV-1 in PBLs (Study Report RH2007/00092/01)

Virus	EC_{50} Value (nM)
Clinical isolates	
ASJM 108	1.6
ASM 34	1.4
ASM 42	1.3
NIH 57	1.5
NIH 660	1.0
NIH 657	1.4
NIH 714	1.4
NIH 727	1.3
CV 110	1.1
CV 154	1.2
CV 163	1.2
CV 243	1.1
CV 281	1.1
Laboratory isolates	
HIV-1_{IIIB}	1.1
HIV-1_{HXB2}	1.6
HIV-1_{NL4-3}	1.4

Abbreviations: EC_{50} = half maximal effective concentration, PBL = peripheral blood lymphocytes

CAB was further evaluated in PBMCs against a panel of 24 HIV-1 isolates, which included 3 isolates of each HIV-1 group M subtype (A, B, C, D, E, F and G) and 3 isolates from HIV-1 group O, and against 3 HIV-2 isolates (study report RH2008/00133/00). In addition, CAB was evaluated against three HIV-1 subtype B viruses in monocyte-derived macrophages. HIV-1_{Ba-L} was used as a reference strain in these experiments. PBMCs were incubated in the presence of drug and virus for 7 days, then antiviral activity determined by measurement of RT activity. For assays in monocytes/macrophages (also 7 days total), antiviral activity was determined by measurement of HIV p24 antigen by ELISA. Compound cytotoxicity was measured in these experiments in parallel with antiviral activity using MTS staining. Table 211 summarizes the results.

The median EC_{50} value of CAB against clinical HIV-1 isolates (excluding HIV-1_{Ba-L}), was 0.19nM (range 0.02nM to 1.06nM, n=24). Against the HIV-2 isolates, the median EC_{50} values of CAB was 0.12nM (range 0.10nM to 0.14nM, n=4). In the macrophage assay, the median EC_{50} value of CAB against subtype B isolates, excluding HIV-1_{Ba-L}, was 0.38nM (range 0.29nM to 1.36nM, n=3). The mean EC_{50} value for individual HIV-1 subtypes A to G ranged from 0.10nM to 0.38nM, and for group O isolates it was 0.64nM.

Table 211. Antiviral Activity of Cabotegravir (CAB) Against HIV-1 and HIV-2 Isolates in PBLs and Macrophages (Study Report RH2008/00133/00)

HIV Isolate	Envelope Subtype	EC_{50} Value (nM) [b]	Mean EC_{50} Value for Each Subtype/Group (nM) [b]	EC_{90} Value (nM)
		HIV-1		
92RW009	A1	0.13		0.85
92UG037	A1	0.09	0.31	0.67
92UG029	A1	0.71		2.48
92BR014	B	0.50		0.95
JR-CSF	B	0.05		0.16
92TH026	B	0.02	0.19	0.26
Ba-L [a]	B	<0.10		0.66
Ba-L [a]	B	0.17		0.30
92BR025	C	0.12		0.29
93IN101	C	<0.10	0.17	0.81
93IN101	C	0.22		1.40
93MW959	C	0.13		0.30
92UG001	D	0.34		1.04
92UG024	D	0.55	0.38	3.09
92UG046	D	0.24		1.27
93TH073	E	0.16		>100
CMU08	E	0.36	0.30	0.85
CMU06	E	0.37		0.84
93BR019	F	0.16		0.52
93BR020	F	0.07	0.10	0.44
93BR029	F	<0.10		0.25
93BR029	F	0.06		0.29
JV1083	G	0.43		1.48
RU132	G	0.16	0.22	0.53
G3	G	0.06		0.13

HIV Isolate	Envelope Subtype	EC_{50} Value (nM) [b]	Mean EC_{50} Value for Each Subtype/Group (nM) [b]	EC_{90} Value (nM)
BCF01	O	0.30		2.57
BCF02	O	0.55	0.64	2.50
BCF03	O	1.06		3.05
HIV-2				
CDC310319	NA	0.11		1.17
CDC310342	NA	0.14	0.12	0.59
CDC310342	NA	0.12		0.56
CBL-20	NA	0.10		0.89
HIV-1 subtype B in macrophages				
Ada	B	0.29		1.84
Ba-L [a]	B	1.64	0.68	6.96
92BR014	B	1.36		8.42
92TH026	B	0.38		4.88

[a] Laboratory isolates
[b] Shaded values (laboratory isolates or EC_{50} value <0.10nM) excluded from determination of medians and means
Abbreviations: CAB = cabotegravir, EC_{50} = half maximal effective concentration, EC_{90}=90% maximal effective concentration, NA = not applicable, PBL = peripheral blood lymphocytes

RPV had antiviral activity against wild-type laboratory strain HIV-1_{IIIB} in the MT4 T-cell line with a median EC_{50} value of 0.73nM and a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07nM to 1.01nM (NDA202022 SDN000). RPV was less active against group O primary isolates with EC_{50} values ranging from 2.9 to 8.5nM and demonstrated limited activity in cell culture against HIV-2 with a median EC_{50} value of 5,220nM (range 2,510nM to 10,830nM).

18.2.1. Antiviral Activity Against Non-HIV Viruses

The antiviral activity of CAB was evaluated against a panel of 11 viruses other than HIV (study report 2019N395410). The panel included: coxsackie A strain A7 and coxsackie B strain B3 Nancy (LLC-MK2 cells), HBV strain Ayw1 (HepG2 cells), herpes simplex 2 strain MS (Vero cells), influenza A/California/07/2009 (H1N1) virus (Madin-Darby Canine Kidney cells), measles virus strain Edmonston (Medical Research Council cell strain 5 cells), parainfluenza virus type 3 strain C243 (LLC-MK2 cells), poliovirus CHAT type 1 (LLC-MK2 cells), rhinovirus type 14 (HeLa cells), vaccinia virus strain WR-56 (Vero E6 cells) and Venezuelan equine encephalopathy virus strain TC-83 (Vero cells). No antiviral activity was observed up to 100µM for any virus except rhinovirus, against which CAB had an EC_{50} value of 12.6µM. No cytotoxicity up to 100µM was observed in any of the cell lines tested, although slight cytotoxicity was noted at 100µM in Vero E6 and Medical Research Council cell strain 5 cells.

18.2.2. Antiviral Activity of CAB in the Presence of Human Serum Proteins

The impact of human serum albumin (HSA; 40 mg/mL) and α_1 acid glycoprotein (AAG; 2 mg/mL) on the cell culture antiviral activity of CAB was determined in MT-4 and PHIV assays (study report RH2007/00068/00). The MT-4 assay was also performed in the presence of up to

30% human serum, and the EC_{50} values extrapolated by linear regression to determine the value in 100% serum.

The mean EC_{50} values of CAB against HIV-1_{IIIB} in MT-4 cells and in the PHIV assay in the presence of 40 mg/mL HSA were 220nM (95% CI: 180nM to 270nM, n=14) and 46nM (95% CI: 35nM to 61nM, n=30), respectively, representing fold-shifts compared to the EC_{50} value determined in the absence of HSA (Table 209) of 390 and 63, respectively. In the presence of 2 mg/mL AAG, the EC_{50} values in the MT-4 and PHIV assays were 0.33nM (95% CI: 0.20 to 0.54, n=6) and 1.2nM (95% CI: 0.55nM to 2.5nM, n=7), respectively, representing fold-shifts in activity of 0.57 and 1.6, respectively. The shift in EC_{50} value of CAB in the MT-4 assay extrapolated to 100% human serum was 660 (95% CI: 460 to 940, n=5), giving a protein-adjusted (pa)EC_{50} value against HIV-1_{IIIB} of 376nM, and a paEC_{50} value against HIV-1 clinical isolates in PBMCs of 125nM (660×0.19nM).

18.2.3. Cytotoxicity

The cytotoxicity of CAB was evaluated in parallel with antiviral activity in MT4 and CIP4-Luci cells (Table 209), and against several cell lines used to determine the antiviral activity against a panel of viruses other than HIV (Section 18.2.1). Cytotoxicity assessments were also made in proliferating leukemia and lymphoma cell lines, and in PHA-stimulated and unstimulated PBLs by measuring ATP levels (Table 212); study report RH2007/00034/00). The CC_{50} values against these cell lines ranged from 5.0µM to 120µM, giving a minimum therapeutic index (based on the lowest CC_{50} value of 5.0µM and highest EC_{50} value of 1.6nM [Table 209]) of 3,100.

Table 212. Cytotoxicity of Cabotegravir (CAB) in Proliferating B and T Cells, and Stimulated and Unstimulated PBLs (Study Report RH2007/00034/00)

Cell Type	n	CC_{50} Value (µM)	95% Confidence Interval (µM)
IM-9	4	6.4	4 - 10
U-937	4	5.0	3.4 – 7.3
MT-4	4	9.2	4.5 - 19
Molt-4	4	13	11 - 17
Stimulated PBL	8	42	29 - 61
Unstimulated PBL	8	120	53 - 280

Abbreviations: CAB = cabotegravir, CC_{50} = cytotoxicity, PBL = peripheral blood lymphocytes

18.2.4. Antiviral Activity of CAB in Combination With Other Antiretroviral Drugs

The antiviral activity of CAB in combination with other ARV drugs was determined against HIV-1_{IIIB} in an MT-4 cell protection assay, using MTT staining to determine cell viability. No antagonism was observed at concentrations spanning the EC_{50} values of the respective compounds when CAB was tested in combination with the NNRTI RPV, or the nucleos(t)ide RT inhibitors FTC, 3TC, or TDF. As a control, combination of ribavirin and stavudine (d4T) showed antagonism as expected. No cytotoxicity was observed in any of the combination experiments. The activity of CAB in combination with other INSTIs or with PIs was not assessed.

18.3. Resistance Studies in Cell Culture

18.3.1. Resistance Selection in Cell Culture

The development of resistance to CAB was assessed in cell culture by serial passage of HIV-1_{IIIB} in MT-2 cells up to 112 days in the presence of increasing concentrations of CAB (study report RH2007/00210/00). The IN region of HIV-1 proviral DNA from infected cells was analyzed genotypically by sequencing PCR-amplified products. Viruses harboring amino acid substitutions were tested for susceptibility to CAB in HeLa-CD4+ cells harboring a β-galactosidase reporter gene driven by HIV-1 LTR. Table 213 shows the amino acid substitutions identified and their impact on susceptibility of virus to CAB. During the course of the experiment, substitutions IN T124A, Q146L, S153Y and T124A/S153Y emerged, each with generally decreased but variable susceptibility to CAB, and the highest decrease in susceptibility of 8.4-fold by T124A/S153Y at day 84. Notably, amino acid position 124 of HIV-1 IN is polymorphic (A or T).

Table 213. Amino Acid Substitutions Identified on Serial Passage of HIV-1 in the Presence of Cabotegravir (CAB), and Respective Fold Increases in EC_{50} Values of Variant Viruses

Days of Culture	IN Substitution	Fold Increase
14	T124A	1.2-1.9
28	T124A	1.4-5.5
42	T124A	<0.88-4.0
56	T124A	1.1-4.6
	Q146L	3.3
	S153Y	4.7
	T124A/S153Y	6.4
70	T124A	1.1-3.8
	Q146L	1.3
	S153Y	2.8-3.0
	T124A/S153Y	3.6
84	T124A	1.3-5.7
	Q146L	2.9
	S153Y	4.3-5.1
	T124A/S153Y	8.4
	T124A/I162M	2.8
98	T124A	1.3-5.2
	Q146L	3.9
	S153Y	4.7-6.0
	T124A/S153	6.3
112	T124A	1.1-7.4
	Q146L	4.6
	S153Y	5.1-5.6
	T124A/S153Y	6.6

Abbreviations: CAB = cabotegravir, EC_{50} = half maximal effective concentration,
Source; Study Report RH2007/00210/00

Amino acid substitutions identified in cell culture passage of CAB were evaluated further by generating recombinant virus using the HIV-1 infectious clone pNL432 (study report 2013N166667_00). Antiviral activity against recombinant virus was determined in HeLa-CD4+ cells harboring an LTR-driven β-galactosidase gene, and measuring β-galactosidase expression

after 3 days of incubation. CAB retained activity against both Q146L and T124A/S153Y (increase in EC_{50} value approximately 2-fold). Of the control compounds EVG, RAL and EFV, only EVG showed a reduction in activity against recombinant virus, and only against virus with Q146L.

An additional resistance selection experiment was performed in which wild-type and recombinant HIV-1_{NL432} were passaged in MT-2 cells in the presence of three starting concentrations of CAB, 6.4nM, 32nM, and 160nM, equivalent to 3.8×, 18.8×, and 37.6× the EC_{50} value in MT-2 cells (study report 2013N166665_00). The recombinant viruses included those harboring Q148K and Q148R substitutions, to which CAB had shown reduced activity, and E92Q, Q148H, and N155H, to which CAB had not shown reduced activity (Table 215). No virus with reduced susceptibility to CAB was selected on passage of wild-type, E92Q- or N155H-expressing virus in the presence of 6.4nM CAB for 56 days (Table 214). Passage of virus harboring Q148H, Q148K, or Q148R substitutions in the presence of 6.4nM CAB, and in the presence of 32nM CAB in the case of Q148H and Q148K, resulted in the selection of additional substitutions. These additional substitutions had varying impact on the susceptibility of virus to CAB, but susceptibility was clearly decreased for viruses derived from passage of Q148H and Q148K viruses.

Table 214. Amino Acid Substitutions and Fold-Resistance Values of Viruses During Passage With Cabotegravir (CAB)

Virus Used for Passage	Initial/Final Drug Conc. (nM)	Days of Culture				Fold Increase in EC_{50} Value
		14	28	42	56	
NL432	6.4/160	None	None	None	None	0.85–1.3
	32	No replication				
	160	No replication				
E92Q	6.4/6.4	E92Q	E92Q	E92Q	E92Q	0.52–0.77
	32	No replication				
	160	No replication				
Q148H	6.4/160	G140S/Q148H	G140S/Q148H	G140S/Q148H E138K/G140S/Q148H L74M/V75A/G140S/Q148H	G140S/Q148H E138K/G140S/Q148H L74M/V75A/G140S/Q148H	2.0 17 21–160
	32/160	No replication	G140S/Q148H	G140S/Q148H G140S/Q148H/G149A C56S/G140S/Q148H/G149A	T122N/G140S/Q148H G140S/Q148H/M154I C56S/G140S/Q148H/G149A	16 2.2 55–130
	160	No replication				

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

Virus Used for Passage	Initial/Final Drug Conc. (nM)	Days of Culture				Fold Increase in EC_{50} Value
		14	28	42	56	
Q148K	6.4/160	Q148K	E138K/Q148K	E138K/Q148K	E138K/Q148K	89–260
	32/160	E138K/Q148K	E138K/Q148K	E138K/Q148K	E138K/Q148K V72I/E138K/Q148K	53–190 410
	160	No replication				
Q148R	6.4/160	Q148R	Q148R E138K/Q148R	74M/Q148R E138K/Q148R	L74M/Q148R E138K/Q148R	ND 3.0–11
	32	No replication				
	160	No replication				
N155H	6.4/6.4	N155H	N155H	N155H	N155H	1.1–2.0
	32	No replication				
	160	No replication				

Abbreviations: CAB = cabotegravir, EC_{50} = half maximal effective concentration, ND=not determined
Source: Study Report 2013N166665_00

RPV-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes, as well as NNRTI-resistant HIV-1 (NDA202022 SDN000). The frequently observed amino acid substitutions that emerged in cell culture selection experiments and conferred decreased susceptibility to RPV included: L100I; K101E and P; V106I and A; V108I; E138K and G, Q, R; V179F and I; Y181C and I; V189I; G190E; H221Y; F227C; and M230I and L. Combinations of two or three NNRTI RAS had decreased susceptibility to RPV ranging from 3.7- to 554-fold.

18.3.2. Cross-Resistance

Cross-resistance has been observed among approved INSTI drugs. The antiviral activity of CAB was assessed in cell culture against HIV-1 strains resistant to the other INSTIs and other classes of HIV-1 inhibitors (Table 215). For evaluation against other INSTI-resistant strains, substitutions associated with resistance to RAL, S-1360 and L-870810, were introduced into the HIV-1 infectious clone, NL432, by site-directed mutagenesis. Antiviral activity of CAB against the NL432-derived viruses was determined in HeLa-CD4+ cells harboring an LTR-driven β-galactosidase reporter gene; the other INSTIs were tested in parallel as controls (study report RH2007/00213/00; data for DTG from study reports RH2007/00115/00 and RH2008/00143/00 submitted to NDA 204790). For EC_{50} value determination, β-galactosidase expression was measured using a luminescent reagent.

Three single amino acid substitutions reduced the susceptibility of HIV-1_{NL432} to CAB (fold-change compared to wild-type ≥5.0): G118R, Q148K, and Q148R; all three of these also reduced virus susceptibility to RAL, S-1360 and L-870810. A total of 11 viruses with more than one substitution showed decreased susceptibility to CAB, of which all except one (G140S/Q148K; fold-change=3.7) also had reduced susceptibility to RAL. Dolutegravir only had reduced susceptibility (≥5-fold) to virus harboring the single substitution G118R, or double substitutions, G140S/Q148R, and Q148R/N155H.

Table 215. Antiviral Activity of Cabotegravir, Dolutegravir, and Raltegravir Against IN-Resistant Viruses by HeLa-CD4+ Cells Assay (Study Reports RH2007/00213/00 and 2013N166662_00) [a]

IN Amino Acid Substitution	Cabotegravir EC_{50} Value Fold Increase (SD)	Dolutegravir EC_{50} Value Fold Increase (SD)	Raltegravir EC_{50} Value Fold Increase (SD)
Wild type	1.0	1.0	1.0
T66A	0.31 (0.03)	0.26 (0.01)	0.61 (0.09)
T66I	0.33 (0.08)	0.26 (0.09)	0.51 (0.10)
T66K	2.7 (0.44)	2.3 (0.35)	9.6 (1.3)
E92I	1.8 (0.21)	1.5 (0.19)	2.1 (0.62)
E92Q	1.5 (0.11)	1.6 (0.12)	3.5 (1.4)
E92V	1.5 (0.15)	1.3 (0.20)	1.4 (0.18)
G118R	8.9 (0.86)	10 (4.7)	7.2 (1.5)
G118S	1.1 (0.35)	1.1 (0.21)	1.2 (0.30)
F121Y	1.0 (0.28)	0.81 (0.12)	6.1 (1.3)
T124A	0.97 (0.15)	0.95 (0.19)	0.82 (0.08)
G140S *	0.81 (0.11)	0.86 (0.30)	1.5 (0.47)
Y143C *	1.1 (0.29)	0.95 (0.26	3.9 (0.48)
Y143H *	1.1 (0.21)	0.89 (0.11)	2.3 (0.46)
Y143R *	1.4 (0.22)	1.4 (0.29)	20 (1.9)
P145S	0.43 (0.03)	0.49 (0.08)	0.87 (0.20)
Q146R	1.7 (0.25)	1.6 (0.17)	1.2 (0.26)
Q148H *	0.86 (0.12)	0.97 (0.67)	23 (1.6)
Q148K	5.6 (0.61)	1.1 (0.19)	83 (6.6)
Q148R	5.1 (1.8)	1.2 (0.21)	47 (9.3)
I151L	2.5 (0.48)	3.6 (3.6)	8.4 (4.7)
S153Y	2.0 (0.63)	2.5 (1.1)	1.3 (0.19)
M154I	0.87 (0.10)	0.93 (0.27)	0.82 (0.18)
N155H	1.7 (0.18)	1.2 (0.12)	11 (5.1)
N155H *	2.1 (0.48)	0.99 (0.094)	13 (1.1)
N155S	1.5 (0.29)	1.4 (0.36)	6.2 (1.9)
N155T	1.5 (0.26)	1.9 (0.32)	5.2 (2.0)
T66I/E92Q	1.0 (0.38)	1.2 (0.19)	18 (3.6)
T66I/L74M	0.38 (0.11)	0.35 (0.08)	2.0 (0.81)
T66I/N155S	ND	ND	ND
T66K/L74M	6.3 (1.8)	3.5 (0.94)	40 (13)
L74M/N155H *	2.5 (0.041)	0.91 (0.17)	32 (6.0)
E92Q/N155H *	5.3 (2.8)	2.5 (1.2)	>190 b
T97A/N155H *	2.9 (0.27)	1.1 (0.46)	46 (3.1)
F121Y/T125K	1.4 (0.55)	0.98 (0.35)	11 (0.49)
E138A/Q148R *	13 (0.86)	ND	150 (16)
E138K/Q148H *	0.92 (0.080)	0.89 (0.24)	31 (7.3)
E138K/Q148K	81 (24)	19 (8.0)	330 (75)
E138K/Q148R	12 (3.4)	4.0 (1.1)	110 (37)
G140C/Q148K	ND	ND	ND
G140C/Q148R	22 (4.9)	4.9 (1.8)	200 (42)
G140S/Q148H *	6.1 (0.75)	2.6 (1.4)	>220 b
G140S/Q148K	5.6 (2.5)	1.5 (0.10)	3.7 (1.3)
G140S/Q148R	12 (3.5)	8.4 (4.0)	200 (5.3)
Y143H/N155H *	5.1 (1.9)	1.7 (0.27)	59 (23)
Q148R/N155H *	61 (28)	10 (1.4)	>210 b
N155H/G163K *	1.6 (0.26)	1.4 (0.40)	22 (3.1)

VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

IN Amino Acid Substitution	Cabotegravir EC_{50} Value Fold Increase (SD)	Dolutegravir EC_{50} Value Fold Increase (SD)	Raltegravir EC_{50} Value Fold Increase (SD)
N155H/G163R *	1.9 (0.28)	1.1 (0.18)	27 (7.2)
N155H/D232N *	2.5 (0.39)	1.4 (0.25)	26 (4.5)
T66I/S153Y/N155S	ND	ND	ND
V72I/F121Y/T125K	2.0 (0.61)	1.3 (0.54)	13 (7.1)
E138A/S147G/Q148R *	3.7 (0.98)	1.9 (0.89)	36 (4.5)
V72I/F121Y/T125K/I151V	1.6 (0.66)	1.2 (0.32)	7.0 (2.8)

Shaded cells: fold increase in EC_{50} value ≥5.0
* CAB and raltegravir data from study report 2013N166662_00; viruses were not evaluated against S-1360, L-870,810 or dolutegravir in this study
[a] In study report RH2007/00213/00, the mean EC_{50} value of CAB and raltegravir against wild-type HIV-1_{NL432} was 1.6nM and 6.1nM, respectively; in study report 2013N166662_00, the mean EC_{50} value of CAB and raltegravir against wild-type HIV-1_{NL432} was 1.8nM and 5.4nM, respectively. Each value represents the mean and SD for 3-5 independent experiments, and each experiment was performed in duplicate.
Because the EC_{50} value exceeded the determination range in all 3 experiments, the highest fold-change is shown.
Abbreviations: CAB = cabotegravir, EC_{50} = half maximal effective concentration, ND = not determined, SD = standard deviation

To summarize the resistance data, the following INSTI resistance substitutions were associated with reduced susceptibility (>5-fold) to CAB: G118R; Q148K; Q148R; T66K+L74M; E92Q+N155H; E138A+Q148R; E138K+Q148K/R; G140C+Q148R; G140S+Q148H/K/R; Y143H+N155H; and Q148R+N155H. Passage of virus harboring IN Q148H/K/R in the presence of CAB resulted in the acquisition of one or more additional substitutions which led to reduced susceptibility (2.2- to 410-fold) to CAB, including C56S, V72I, L74M, V75A, T122N, E138K, G140S, G149A, and M154I. The individual contribution of most of these substitutions to reduced susceptibility to CAB was not determined; G140S or M154I alone did not confer reduced susceptibility, but G140S did in the context of Q148H/K/R, as did E138K in the context of Q148K/R, and L74M reduced susceptibility in the context of T66K, but not T66I or N155H (Table 215).

18.3.3. Cell Culture Antiviral Activity of CAB Against NNRTI, NRTI, and PI Resistant Virus

The cell culture antiviral activity of CAB was determined against HIV-1 harboring amino acid substitutions conferring resistance to RT and PIs which had been engineered into the HIV-1 infectious clone, NL432. Antiviral activity was determined in HeLa-CD4+ cells harboring an LTR-driven β-galactosidase reporter gene.

Viruses harboring the NNRTI substitutions K103N or Y188L, or the NRTI substitutions M184V, D67N/K70R/T215Y or V75I/F77L/F116Y/Q151M, were susceptible to CAB, with EC_{50} values within 3-fold of that against wild-type (NL432) virus (study report 2013N166663_00). Control compounds AZT, 3TC and EFV, showed the expected susceptibilities to each variant virus (i.e., AZT and 3TC had reduced activity to virus with D67N/K70R/T215Y and V75I/F77L/F116Y/Q151M, 3TC also had reduced activity against M184V, and EFV had reduced activity to K103N and Y188L).

Viruses harboring the protease substitutions M46I/I47V/I50V and L24I/M46I/L63P/A71V/G73S/V82T did not have reduced susceptibility to CAB (study report 2013N166664_00). Control PI compounds amprenavir and ritonavir showed the expected susceptibilities to the variant viruses (i.e., amprenavir had reduced activity against

M46I/I47V/I50V, and ritonavir had reduced activity against L24I/M46I/L63P/A71V/G73S/V82T).

19. Clinical Virology Additional Information

In FLAIR, there were four CVFs (HIV-1 RNA >400 copies/mL) in the CAB arm and three virologic failures in the comparative CAR arm. Three of the virologic failures in the CAB arm (subjects (b) (6), and (b) (6)) and three virologic failures in the CAR arm (subjects (b) (6), and (b) (6)) had postbaseline resistance data. The baseline characteristics (i.e., subtype, country, sex, BMI) and resistance data are shown in Table 216.

Table 216. Baseline Characteristics and Resistance Data for Virologic Failures in FLAIR (Study 201584) (FDA Analysis)

PID	Timepoint (HIV RNA Copies/mL)	Arm	Subtype	Country	Sex	Age	BMI	INSTI RAS[1]	NNRTI RAS[2]	Phenotype[3]
(b) (6)	Baseline (22,712)	CAB+/RPV	A1	Russia	M	44	37	L74I T124S	V90I	RPV 1.0 CAB 0.95 DTG 0.89
	WK24 (493)							**G140R**	**K101E**	**RPV 2.63** **CAB 6.7** DTG 2.2
(b) (6)	Baseline (53,712)	CAB+/RPV	A1	Russia	F	29	37	L74I T124S		RPV 1.1 CAB 0.67 DTG 0.61
	WK20 (811)							E87D **Q148R**	**E138E/A/K/T**	**RPV 7.1** **CAB 5.22** DTG 0.95
(b) (6)	Baseline (20,322)	CAB+/RPV	A1	Russia	F	50	30	L74I T124S	V179I	RPV 0.43 CAB 0.69 DTG 0.89
	WK48 (488)							**Q148R**	D110D/N **E138K** P150/S K154K/E T165T/A F171F/L T200I E203D **H221H/L** G231G/E	RPV 0.97 **CAB 9.4** DTG 1.1
(b) (6)	Baseline (26,998)	CAB+/RPV	AG	Russia	F	26	19	T124S		RPV 0.76 CAB 0.78 DTG 0.95
	WK8 (1,259)							ND	ND	ND
(b) (6)	Baseline (21,551)	CAR	A1	Russia	F	26	24	L74I T124S	V179I S68G	ABC 1.1 3TC 1.2 DTG 0.7 CAB 0.79

PID	Timepoint (HIV RNA Copies/mL)	Arm	Subtype	Country	Sex	Age	BMI	INSTI RAS[1]	NNRTI RAS[2]	Phenotype[3]
[redacted]	WK12 (2,959)							E35E/K A175A/S	K104K/Q	ABC 1.1 3TC 1.2 DTG 0.75 CAB 0.74
[redacted]	Baseline (10,371)	CAR	B	Spain	M	33	23	T124N	G196E	ABC 0.89 3TC 1.2 DTG 0.79 CAB 0.93
	WK16 (3,044)									ABC 0.89 3TC 1.3 DTG 0.81 CAB 0.87
[redacted]	Baseline (2,691)	CAR	B	US	M	20	24	T124N	A98S	ABC 0.86 3TC 1.3 DTG 0.68 CAB 0.68
	WK8 (7,518)								R125R/G	ABC 0.91 3TC 1.2 DTG 0.74 CAB 0.69

*PID [redacted] no injections and off-treatment for 18 days
[1]Bolded indicates INSTI resistance-associated substitutions (RAS)
[2]Bolded indicates NNRTI resistance-associated substitutions (RAS)
[3]Bolded indicates phenotypic resistance
Abbreviations: 3TC = lamivudine, ABC = abacavir, CAB = cabotegravir, CAR = current antiretroviral, DTG = dolutegravir, ND = not determined, RPV = rilpivirine, 3TC = lamivudine

In ATLAS, there were three virologic failures in the CAB arm (subjects [redacted] and [redacted]) and four virologic failures in the comparative CAR arm (subjects [redacted] and [redacted] and all seven had postbaseline resistance data. The baseline characteristics (i.e., subtype, country, sex, BMI) and resistance data are shown in Table 217.

Table 217. Baseline Characteristics and Resistance Data for Virologic Failures in ATLAS (Trial 201585) (FDA analysis)

PID	Timepoint (HIV RNA Copies/mL)	Arm	Subtype	Country	Sex	Age	BMI	INSTI RAS[1]	NNRTI RAS[2]	Phenotype[3]
(b) (6)	Baseline	CAB+RPV	A1	Russia	F	39	23.4	L74I T124S	E138E/A	
	WK8 (79,166)							L74I T124S	**E138A**	**RPV 2.4** CAB 0.82 DTG 0.89
(b) (6)	Baseline	CAB+RPV	A	Russia	M	38	25.8	L74I T124S	V179I	
	WK24 (544)		A1					L74I T124S **N155H**	V111V/G **E138E/K**	**RPV 6.5** **CAB 2.7** DTG 1.2
(b) (6)	Baseline	CAB+RPV	AG	France	F	40	31.5	T125A	S68N V108V/I E138K	
	WK12 (695)								**V108I**	**RPV 3.7** CAB 1.2 DTG 0.99
(b) (6)	Baseline	CAR	A1	Russia	M	37	30.7	L74I T124S	M184M/I	
	WK20 (1,295)								S68S/G T139R M184V G190S	EFV: ND 3TC: ND AZT: ND CAB 0.91
(b) (6)	Baseline	CAR	B	US	M	28	24.4	G193R		
	WK32 (524)							P90P/S	M184I S251S/N	EVG 1.3 **FTC >97** TDF 0.4 CAB 1.1
(b) (6)	Baseline	CAR	B	US	M	58	23.6	T124N		
	WK20 (339)							NONE	NONE	EVG 1.1 FTC 1.1 TDF 0.9 CAB 0.8
(b) (6)	Baseline	CAR	B	US	M	30	33.7	T125V	M41I	
	WK40 (392)							V88V/I I162I/V	V35I E89E/K E135V **M230M/I** V45M	EVG 1.2 FTC 0.91 TDF 0.65 CAB 0.92

[1]Bolded indicates INSTI resistance-associated substitutions (RAS)
[2]Bolded indicates NNRTI resistance-associated substitutions (RAS)
[3]Bolded indicates phenotypic resistance
Abbreviations: 3TC = lamivudine, BMI = body mass index, CAB = cabotegravir, CAR = current antiretroviral, DTG = dolutegravir, EFV = efavirenz, EVG = elvitegravir, FTC = emtricitabine, INSTI = integrase strand transfer inhibitor, ND = not determined, NNRTI = nonnucleoside reverse transcriptase inhibitor, RAS = resistance-associated substitutions, RPV = rilpivirine, TDF = tenofovir, 3TC = lamivudine

20. Other Drug Development Considerations Additional Information

20.1. Patient-Reported Outcomes

The Division seeks Clinical Outcome Assessments (COA) Staff input on the COAs that the Applicant used in Studies ATLAS and FLAIR, and on the (b) (4)

(b) (4)

(b) (4) (b) (4) FDA encourages sponsors to engage with the Agency early in the drug development process, and frequently throughout drug development, to ensure that proposed study designs are appropriate to meet stated study objectives and to maximize the potential for studies to produce data that are meaningful and informative to support regulatory decision-making (b) (4).

20.2. Fit-for-Purpose Summary

Table 218 summarizes the fit-for-purpose assessment.

Table 218. Fit-For-Purpose Assessment (Based on Available Evidence)

COA Name(s)	Attribute Sufficiently Established[1]	Supported By:	Location of Supporting Materials
(b) (4)	☐ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☒ No	☐ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☐ Evidence of content validity ☐ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☐ COA well-defined and concept is able to be accurately communicated ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate	
	☐ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☒ No	☐ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☐ Evidence of content validity ☐ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☐ COA well-defined and concept is able to be accurately communicated ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate	

Abbreviations: COA = clinical outcome assessment

20.3. Context of Use

20.3.1. Clinical Trial Population

Refer to Section 15

20.3.2. Clinical Trial Design

Refer to Section 15.

Reviewer comment: From a COA perspective, Studies ATLAS and FLAIR were not adequately designed to support claims based on patient experience data. (b) (4)

[1] See Clinical Outcome Assessments and Scoring Algorithms sections below for more detailed information.

(b) (4)

20.3.3. Endpoint Position, Definition, and Assessment Schedule

Reviewer comments:

For clarification, it is important to note differences with regard to how the HIVTSQs and HIVTSQc were used in studies ATLAS and FLAIR.

For study ATLAS:

1. ***The HIVTSQs (status) was administered to patients in both treatment arms.*** (b) (4)
2. ***The HIVTSQc (change) was administered at week 48 only to patients in the CABENUVA injection arm. The intent was for patients in the LA injection arm to compare their experiences with CABENUVA injection to their previous oral therapy prior to entering the study.***
3. ***The Reason for Switch Questionnaire was administered to all patients prior to randomization at day 1. At week 52, the Reason for Switch Questionnaire was administered only to participants in the "Current ART" arm (i.e., at the end of the maintenance phase, after which point the patients in the "Current ART" arm would switch over from oral to CABENUVA injectable treatment).***
4. ***The Preference Questionnaire was administered at week 48 only to patients randomized to the LA injection arm. The Preference Questionnaire was additionally administered at week 96 to patients who switched over from the "Current ART" arm to the CABENUVA injection arm at the end of the maintenance phase.***

For study FLAIR:

1. ***The HIVTSQc (change) was administered at week 48 to patients in both treatment arms.*** (b) (4)
2. ***HIVTSQs (status) was administered to both treatment arms throughout the study, but the Applicant acknowledges that, in FLAIR, a ceiling effect for HIVTSQs was noted at baseline for both treatment arms. At baseline, scores for several items were near the maximum possible score, and no differences in HIVTSQs individual items were found between treatment groups. To try to account for this HIVTSQs ceiling effect, the Applicant administered the HIVTSQc at week 48.***
3. ***The PIN, Preference Questionnaire, and pain NRS questionnaires were administered only to patients in the LA injection arm. The pain NRS was collected 30 to 60 minutes postinjection, and also 1 week after the injections at week 5 and week 41.***
4. ***The Preference Questionnaire was administered at week 48 only to patients randomized to the LA injection arm. The Preference Questionnaire was not administered thereafter.***

20.3.4. Labeling or Promotional Claims Based on the COAs

The Applicant has proposed specific targeted COA-related labeling claims in section 14 of product labeling. The targeted labeling claims are:

(b) (4)

Reviewer comments:

As discussed in the reviewer's comments under the "Clinical Trial Design" section of this COA review, this study design is not adequate to support a claim of (b) (4)

(b) (4)

(b) (4)

However, as noted previously, problems with the study design preclude the acceptability of these items to support labeling claims.

20.3.5. Concepts of Interest and Conceptual Framework

The concepts of interest for the HIVTSQs and HIVTSQc are described by the Applicant as static treatment satisfaction and change in treatment satisfaction, respectively.

Reviewer comments:

Though the HIVTSQ is presented as a treatment satisfaction questionnaire, only items 1, 3, 4, 8, 10, and 12 are actually aimed at assessing treatment satisfaction. (b) (4)

Elements of the HIVTSQs and HIVTSQc may be important and relevant to patients in the target patient population on a conceptual level. Face-to-face patient interviews were conducted in 39 patients enrolled in the phase 2b study, Study LATTE-2 (i.e., Study 200056). In the interviews, patients were asked about 1. Their experience with the clinic and the injection; 2. The perceived benefits and drawbacks of their treatment; 3. Their preference between oral treatment an LA injectable treatment; 4. Whether they would recommend LA injectable treatment to others, and why; and 5. Their willingness to pay and how they would like the treatment to be delivered.

A brief summary of patient interview findings is as follows:

1) The majority of patients had minor ISRs such as soreness and minor bruising for 1 to 2 days postinjection.
2) LA injection was reported as offering greater privacy to patients and having less stigma compared to daily oral therapy (e.g., no pill bottle visible to others; no daily reminder of the disease).
3) LA injection was reported as being more convenient than daily oral therapy (e.g., not needing to remember to take a pill every day; not worrying about refills).

20.3.6. Clinical Outcome Assessments

HIV Treatment Satisfaction Questionnaire – Status Version (HIVTSQs)

The HIVTSQs is a 12-item PRO assessment. There is no explicitly defined recall period; the instrument's instructions only instruct patients to respond based on their experience "over the

past few weeks." Several items (items 2, 5, 6, and 11) additionally include the term "recently." A copy of the instrument is available in Appendix 20.4.13.

HIV Treatment Satisfaction Questionnaire – Change Version (HIVTSQc)

The HIVTSQc is a 12-item PRO assessment that contains the same items, verbatim, as the HIVTSQs. However, the instructions and response options are different (see Section II.6 of this review) to assess change rather than current status. The instrument instructs patients to respond based on how "your experience of current treatment has changed" from "before the study began." A copy of the instrument is available in Figure 59**.**

Reviewer comment: The recall period for the HIVTSQs ("over the past few weeks") is not well-defined. Patients should be instructed to consider a specific time frame (e.g., "over the past week," "over the past 4 weeks," etc.) rather than "past few weeks," which is subject to interpretation. Additionally, the inclusion of the term "recently" in certain items (items 2, 5, 6, and 11), which is a further modifier to the recall period, is inappropriate and adds even more subjectivity to interpretation.

20.3.7. Scoring Algorithms

HIV Treatment Satisfaction Questionnaire – Status Version (HIVTSQs)

HIVTSQs total score is calculated by summing the scores of items 1 through 11. Item 12 ("how satisfied are you with the amount of discomfort or pain involved with your present form of treatment?") is not included in the total score. Individual item scores range from 0 to 6, where 0="very dissatisfied" and 6="very satisfied." The HIVTSQs total score can range from 0 to 66.

HIV Treatment Satisfaction Questionnaire – Change Version (HIVTSQc)

HIVTSQc total score is calculated by summing the scores of items 1 through 11. Item 12 ("how satisfied are you with the amount of discomfort or pain involved with your present form of treatment?") is not included in the total score. Individual item scores range from -3 to 3, where -3="much less satisfied now" and 3="much more satisfied now." The HIVTSQc total score can range from -33 to 33.

Reviewer comment: Item 12 is not included in the calculation of the HIVTSQ total score, but item 12 is relevant to patient experiences with the product, given that the long-acting injection may cause discomfort or pain. Discomfort or pain associated with injection may be a significant reason why a patient may not want to receive an injectable product when an oral formulation is available.

20.3.8. Appendices

Figure 58. Appendix A: HIV Treatment Satisfaction Questionnaire – Status Version (HIVTSQs)

The following questions are concerned with your medical treatment for HIV and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?
   very satisfied 6 5 4 3 2 1 0 very dissatisfied

2. How well controlled do you feel your HIV has been recently?
   very well controlled 6 5 4 3 2 1 0 very poorly controlled

3. How satisfied are you with any side effects of your present treatment?
   very satisfied 6 5 4 3 2 1 0 very dissatisfied

4. How satisfied are you with the demands made by your current treatment?
   very satisfied 6 5 4 3 2 1 0 very dissatisfied

5. How convenient have you been finding your treatment to be recently?
   very convenient 6 5 4 3 2 1 0 very inconvenient

6. How flexible have you been finding your treatment to be recently?
   very flexible 6 5 4 3 2 1 0 very inflexible

7. How satisfied are you with your understanding of your HIV?
   very satisfied 6 5 4 3 2 1 0 very dissatisfied

8. How satisfied are you with the extent to which the treatment fits in with your life-style?
   very satisfied 6 5 4 3 2 1 0 very dissatisfied

9. Would you recommend your present treatment to someone else who is being offered this HIV treatment?

Yes, I would definitely recommend the treatment	6	5	4	3	2	1	0	No, I would definitely not recommend the treatment

10. How satisfied would you be to continue with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

11. How easy or difficult have you been finding your treatment to be recently?

very easy	6	5	4	3	2	1	0	very difficult

12. How satisfied are you with the amount of discomfort or pain involved with your present form of treatment?

very satisfied	6	5	4	3	2	1	0	very dissatisfied

Figure 59. Appendix B: HIV Treatment Satisfaction Questionnaire – Change Version (HIVTSQc)

For approximately 12 months you have been taking part in an HIV treatment study. At the start of the study you may have had a change of treatment. Today we would like to know how your experience of your current treatment has changed from your experience of treatment before the study began. Please answer each question by circling a number on each of the scales to indicate the extent to which you have experienced changes. If you have experienced no change, please circle '0'.

1. How satisfied are you with your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

2. How well controlled do you feel your HIV has been recently?

much better controlled now	3	2	1	0	-1	-2	-3	much worse controlled now

3. How satisfied are you with any side effects of your present treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

4. How satisfied are you with the demands made by your current treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

5. How convenient have you been finding your treatment to be recently?

much more convenient now	3	2	1	0	-1	-2	-3	much less convenient now

6. How flexible have you been finding your treatment to be recently?

much more flexible now	3	2	1	0	-1	-2	-3	much less flexible now

7. How satisfied are you with your understanding of your HIV?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

8. How satisfied are you with the extent to which the treatment fits in with your life-style?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

9. How likely would you be to recommend your present treatment to someone else who is being offered this HIV treatment?

much more likely to recommend the treatment now	3	2	1	0	-1	-2	-3	much less likely to recommend the treatment now

10. How satisfied would you be to continue with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

11. How easy or difficult have you been finding your treatment to be recently?

much easier now	3	2	1	0	-1	-2	-3	much less easy now

12. How satisfied are you with the amount of discomfort or pain involved with your present form of treatment?

much more satisfied now	3	2	1	0	-1	-2	-3	much less satisfied now

20.4. CDRH Assessment

Date:	10/28/2019
To:	Andrew Gentles
Requesting Center/Office	CDER/OND **Clinical Review Division:** OAP/DAVP
From:	Kathleen Fitzgerald CDRH/OPEQ/OHT3/DHT3C/THT3C3
Through (Team Lead)	Rumi Young, Combination Products Team Lead Injection Team CDRH/OPEQ/OHT3/DHT3C/THT3C1
Through (Branch Chief)	CPT Alan Stevens, Branch Chief CDRH/OPEQ/OHT3/DHT3C/THT3C1
Subject	NDA 212888, Cabotegravir LA + Rilpivirine LA injectable ICC1900382 Syringe, Safety Needle and Vial Adaptor
Recommendation	Filing Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Filing Recommendation ☒ Device Constituent Parts of the Combination Product are acceptable for Filing ☐ Device Constituents Parts of the Combination Product are acceptable for Filing with Information requests for the 74-day Letter, see Section 20.4.13 ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing, see Section 20.4.5 for Deficiencies
	Midcycle Recommendation Date: 9/20/2019 ☐ CDRH did not provide a Midcycle Recommendation ☐ CDRH has no approvability issues at this time. ☒ CDRH has additional Information Requests, See Section 20.4.13 ☐ CDRH has Major Deficiencies that may present an approvability issue, see Section 20.4.13
	Final Recommendation Date: 10/28/2019 ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Postmarket Requirements/Commitments, see Section 20.4.2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable – see Section 20.4.2.2 for Complete Response Deficiencies

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Assistant Director or Branch Chief (AD/BC)**

20.4.1. Submission Overview

Submission Information	
Submission number	NDA 212888
Applicant	ViiV HealthCare
Drug/biologic	CAB LA + RPV LA injectable
Indications for use	Treatment of HIV-1 infection
Device constituent	Syringe, Safety Needle and Vial Adaptor
Related files	ICC1600651, ICC1600684, ICC1700368, ICC1700816 and ICC1801005

Review Team	
Lead device reviewer	Kathleen Fitzgerald

The CDRH review is being managed under ICC #: ICC1900382

Below is a list of the discipline-specific CON#.

Discipline-Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
None		

Important Dates	
Discipline-specific review memos due	N/A
Final lead device review memo due	November 1, 2019

20.4.2. Executive Summary and Recommendation

CDRH recommends the combination product is:

☒ Approvable – the device constituent of the combination product is approvable for the proposed indication

☐ Approvable with PMC or PMR, see Section 20.4.2.2

☐ Not acceptable – the device constituent of the combination product is not approvable for the proposed indication for the following reasons: . We have major deficiencies to convey, see Section 20.4.2.2.

	Adequate			
Section	**Yes**	**No**	**NA**	**Reviewer Conclusions**
Device description	X			
Design controls	X			
Risk analysis	X			
Design verification	X			

Section	Adequate			Reviewer Conclusions
	Yes	No	NA	
Consultant discipline reviews			X	
Clinical validation	X			
Human factors validation			X	Reviewed by DMEPA
Labeling	X			
Quality systems/ manufacturing controls	X			

20.4.2.1. Comments to the Review Team

☒ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team.

20.4.2.2. Complete Response Deficiencies

☒ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Applicant as part of the CR letter:

20.4.2.3. Recommended Postmarket Commitments/Requirements

CDRH has postmarket commitments or requirements	☐
CDRH does not have postmarket commitments or requirements	☒

20.4.3. Purpose/Background

20.4.3.1. Scope

ViiV HealthCare is requesting approval of CAB LA+RPV LA injectable. The device constituent of the combination product is a syringe, safety needle and vial adaptor.

Choose an item. has requested the following consult for review of the device constituent of the combination product:

NDA 212888 (CABENUVA, CAB LA+RPV LA injectable copack) is to be used as a once-monthly injection in pts with HIV-1 infection. The injectable product is supplied as a combination product copack. The pack includes one single-dose vial of CAB, one single-dose vial of RPV, two vial adapters, two syringes, two injection needles and instructions for use. Please review the device constituent parts of this application.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device constituent parts of the copack kit combination product for device compatibility and functional performance.

This review will not cover the following review areas:

Drug product or the primary container closure vial.

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

20.4.3.2. Prior Interactions

Related Files

ICC1600651, ICC1600684, ICC1700368, ICC1700816 and ICC1801005.

20.4.3.3. Indications for Use

Combination Product	Indications for Use
CAB LA + RPV LA injectable	Treatment of HIV-1 infection
Syringe, safety needle and vial adaptor	Delivery of the drug product

20.4.4. Device Description

Device Description Review Summary/Conclusion		
Filing deficiencies: ☐ Yes ☒ No ☐ N/A	Midcycle deficiencies: ☒ Yes ☐ No ☐ N/A	Final deficiencies ☐ Yes ☒ No ☐ N/A

Reviewer Conclusion

Midcycle comments:

Final review comments: The Applicant has provided complete device description information. All the device constituent parts are 510(k) cleared and the LOAs were provided.

Materials reviewed	
Document title: NDA 212888	Location: 3.2.R

20.4.4.1. Device Description

Select device type:	☐	Auto-injector	☐	Nasal spray	☐	Prefilled syringe	☒ Other
	☐	Infusion pump	☐	Oral syringe	☐	Subdermal implant kits	
	☐	Metered-dose pump	☐	Pen-injector	☒	Vial adapters	

Two copack kits have been developed in order to accommodate the dosing regimen. The copacks are described as [redacted] (b) (4) in alignment with the injection volume common to both products in each copack.

Table 219. CABENUVA Constituent Parts

Co-Pack	Drug Product Constituent Parts	Device Constituent Parts		
2-mL	(1) Vial of Cabotegravir Injectable Suspension, 400 mg/2 mL (1) Vial of Rilpivirine Extended-release Suspension for Injection, 600 mg/2 mL	(2) Sterile single-use vial adapters	(2) Sterile 5-mL single-use syringes	(2) Sterile single-use 23-gauge 1.5-inch safety needles
3-mL	(1) Vial of Cabotegravir Injectable Suspension, 600 mg/3 mL (1) Vial of Rilpivirine Extended-release Suspension for Injection, 900 mg/3 mL	(2) Sterile single-use vial adapters	(2) Sterile 5-mL single-use syringes	(2) Sterile single-use 23-gauge 1.5-inch safety needles

Figure 60. CABENUVA Vial Adapter (Left) and Syringe (Right)

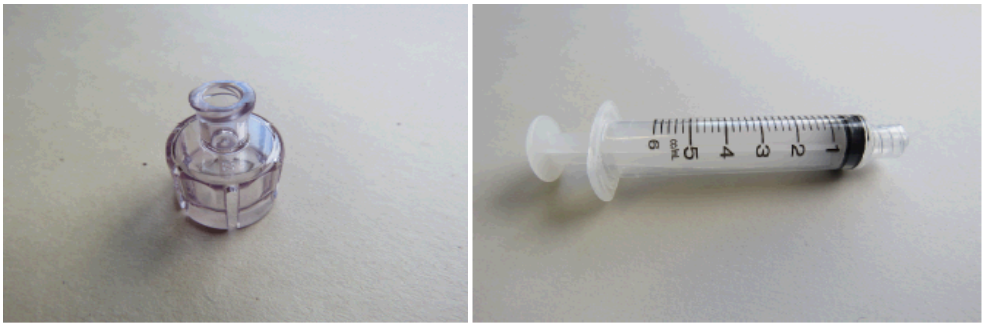


Figure 61. CABENUVA Safety Needle

Figure 62. CABENUVA Copack Images 3 mL (Left) and 2 mL (Right)

Table 220. CABENUVA Constituent Parts Description

	Tradename and Identifier	Description	Material of Construction (Product Contact)	Packaging	Manufacturer	Device Classification	510(k) Reference	Reference
Vial Adapter	Vial Adapter (b) (4)	Sterile, single-use, 13 mm vial adapter with an integrated luer connection	Body: (b) (4)	Single pre-packaged in (b) (4) blister pack with (b) (4) (b) (4) labelled with shelf-life	(b) (4)	Class II (b) (4)	(b) (4)	3.1.1
Syringe	(b) (4)	Sterile, single-use, 5 mL syringe	Barrel & Plunger: (b) (4) Plunger Gasket: (b) (4)	Single pre-packaged blister pack, (b) (4) labelled with shelf-life	(b) (4)	Class II (b) (4)	(b) (4)	3.1.2
Safety Needle	(b) (4)	Sterile, single-use, 23G 1.5-inch safety needle	Cannula: Stainless steel Safety Sheath: (b) (4)	Single pre-packaged blister pack, (b) (4) labelled with shelf-life	(b) (4)	Class II (b) (4)	(b) (4)	3.1.3

Vial Adapter

The vial adapter is a fluid transfer device that facilitates the withdrawal of liquid drug products from vials into syringes for dosing, without coring or fragmentation of the rubber stopper. The vial adapter has an integrated plastic spike on the 'vial end' and luer fitting on the 'syringe end'. Once attached onto the vial, the spike punctures the stopper, and the drug product can be aspirated by attaching a luer syringe onto the luer fitting and pulling back the syringe plunger. The fluid contact path is sterile.

5ml Syringe

Two sterile single-use 5-mL syringes are included in each copack to enable aspiration and administration of the two-drug injectable dosing regimen. The syringe is graduated in alignment with the dosing requirements. The syringe has an integrated plastic luer fitting for connection to the vial adapter (for aspiration) and needle (for administration).

Safety Needle

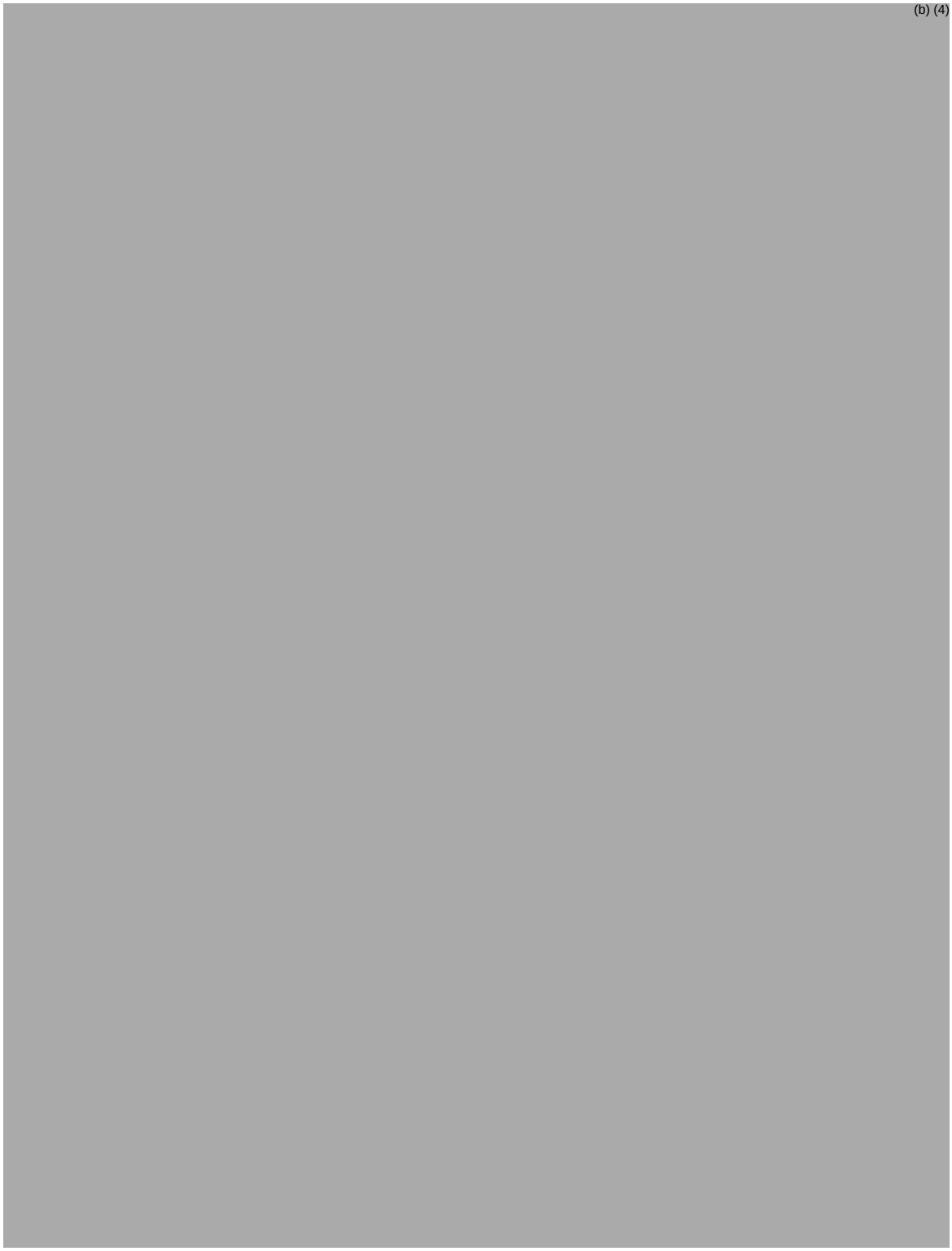
Two sterile single-use 23G 1.5-inch safety needles are included in each copack to enable administration of the two-drug injectable dosing regimen. The safety needle is a needle with an attached plastic sheath which functions as a sharps injury prevention feature. After use of the needle for injection of the drug product, the needle is locked into the sheath via manual activation, which prevents sharps exposure after dosing is completed. The needle has an integrated plastic luer fitting for connection to the syringe.

20.4.4.2. Steps for Using the Device

The Instructions for Use enclosed in the kit includes the instructions to be used by the healthcare practitioner in the preparation and administration of each drug product in the two drug injectable dose regimen. A summary of the instructions follows:

Figure 63. CABENUVA Instructions for Use

(b) (4)



20.4.4.3. Device Description Interactive Review

CDRH sent Device Description Interactive Review questions to the Applicant	☐ Yes ☒ No

20.4.5. Filing Review

CDRH performed filing review	☒
CDRH was not consulted prior to the filing date; therefore, CDRH did not perform a filing review	☐

Filing Review Summary/Conclusions	
Acceptable for filing: ☒ Yes ☐ No ☐ N/A	74-day letter or RTF deficiencies: ☐ Yes ☐ No ☒ N/A
Facilities inspection recommendation: ☐ (PAI) Pre-approval inspection ☐ Postapproval inspection ☐ Routine surveillance ☒ No inspection	
Site(s) needing inspection	
Reviewer conclusion	
Refuse to file deficiencies: None 74-day letter deficiencies: None	

Table 221. Filing Review Checklist

		Present		
Description		**Yes**	**No**	**N/A**
Description of device constituent		X		
Device constituent labeling		X		
Letters of authorization		X		
Essential performance requirements defined by the Applicant		X		
Design requirements specifications included in the NDA/BLA by the Applicant		X		
Design verification data included in the NDA/BLA or adequately cross-referenced to a master file.		X		
Risk analysis supplied in the NDA/BLA by the Applicant		X		
Traceability between resign requirements, risk control measures and V&V activities		X		
Verification/ validation check	Full test reports for verification and validation testing	X		
	Engineering performance (must include safety assurance case for infusion pumps)	X		
	Reliability	X		
	Biocompatibility-completed in 510k review			X
	Sterility -completed in 510k review			X
	Software			X
	Cybersecurity			X
	Electrical safety			X
	EMC/RF wireless			X
	MR compatibility			X
	Human factors	X		
	Shelf life, aging and transportation	X		
	Clinical validation	X		
	Human factors validation			X
Quality systems/ manufacturing controls check	Description of device manufacturing process	X		
	Description of quality systems (drug cGMP-based, device QSR-based, both)	X		
	CAPA procedure	X		
	Control strategy provided for EPRs	X		

Reviewer comment: The Applicant has provided adequate device constituent documentation for filing.

20.4.5.1. Facilities Information

No CDRH quality systems or facilities review required.

All of the device constituent parts are 510(k) cleared and are well understood with basic technology and have a low-risk of device related injuries or malfunction.

20.4.5.2. Filing Review Interactive Review

CDRH sent Interactive Filing Review questions to the Applicant	☐ Yes ☒ No

20.4.6. Design Control Summary

Device Description Review Summary/Conclusion		
Filing deficiencies: ☐ Yes ☒ No ☐ N/A	Midcycle deficiencies: ☐ Yes ☒ No ☐ N/A	Final deficiencies ☐ Yes ☒ No ☐ N/A
Reviewer conclusion Midcycle comments: No deficiencies Final review comments: The Applicant has provided adequate information		
Materials reviewed Document title: NDA 212888	Location: 3.2.R, 3.2.P.2.2	

20.4.6.1. Summary of Design Control Activities

Risk analysis attributes	**Yes**	**No**	**N/A**
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, postmarket data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design inputs/outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
Design verification/validation attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial		X	
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer comment: The Applicant has provided adequate design control activities.

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

20.4.6.4. Design Control Interactive Review

CDRH sent Design Control Interactive Review questions to the Applicant	☐ Yes ☒ No

20.4.7. Risk Analysis

Risk Analysis Review Summary Conclusion		
Filing deficiencies: ☐ Yes ☒ No ☐ N/A	Midcycle deficiencies: ☐ Yes ☒ No ☐ N/A	Final deficiencies ☐ Yes ☒ No ☐ N/A

Reviewer conclusion
Midcycle comments: No deficiencies

Final review comments:

Materials reviewed
Document title: NDA 212888 Location: 3.2.R-risk assessment

20.4.7.1. Risk Management Plan

The device constituent parts in the copack kit combination product will be prepared and the medication administered by a healthcare professional. They are well known, commonly used devices with low risks. The Applicant provided the following risk assessment of using the device constituent parts incorrectly.

Figure 64. CABENUVA Risk Acceptance Matrix

Risk acceptance matrix

	None	Discomfort	Minor	Medical Attention	Permanent	Life threat	Not known
Improbable	A	A	A	A	A	A	A
Unlikely	A	A	A	A	A	U1	K/G
Remote	A	A	A	A	U1	U2	K/G
Occasional	A	A	A	U1	U2	U3	K/G
Probable	A	A	U1	U2	U3	U4	K/G
Frequent	A	U1	U2	U3	U4	U5	K/G
Not known	A	K/G	K/G	K/G	K/G	K/G	K/G

Term	Definition
A	Risk acceptable.
U1 to U5	Risk unacceptable. Will require risk benefit-justification after the exhaustion of all risk mitigation strategies
K/G	Risk unacceptable due to lack of knowledge. Further work required to understand risk

Reviewer comments: The risk assessment of the device constituent parts was based on the human factors study. The Applicant's risk assessment is adequate.

20.4.7.2. Hazard Analysis and Risk Summary Report

Figure 65. Risk Summary of Device Constituent Parts

ID	Process Step	Cause of failure	Chain of events	Effect (Hazard)	*Severity*	*Occurrence*	Existing controls (justification for occurrence score)	Risk Level
							the dose, and to check that a full dose has been draw prior to injection.	
17	Preparation of vials	Failure to clean top of vial with alcohol swab	Microbial contamination of product	Delivery of non sterile dose	Medical Attention	Unlikely	Limited time for microbial growth between vial preparation and delivery	A
18	Transfer of dose to syringe	Spike breakage	Unable to transfer medicine to syringe	CAB Failure to deliver effective dose (once)	Medical Attention	Improbable	Not seen on the 13mm vial adaptor in any HF studies.	A
19	Transfer of dose to syringe	Spike breakage	Unable to transfer medicine to syringe	RPV Failure to deliver effective dose (once)	Medical Attention	Improbable	Not seen on the 13mm vial adaptor in any HF studies.	A
20	Transfer of dose to syringe	Spike cause leakage path in septum	Cabotegravir leakage onto skin	Cabotegravir Dermal exposure	None	Unlikely	HCP should be wearing gloves. IFU states gloves required.	A
21	Transfer of dose to syringe	Spike cause leakage path in septum	Rilpivirine leakage onto skin	RPV Dermal contact	None	Unlikely	HCP should be wearing gloves.	A
22	Transfer of dose to syringe	Spike cause leakage path in septum	Cabotegravir loss of drug product	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	HF studies show this is not an issue	A
23	Transfer of dose to syringe	Spike cause leakage path in septum	Rilpivirine loss of drug product	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	HF studies show this is not an issue	A
24	Transfer of dose to syringe	Drop component	Component breaks	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	Stock of products available at treatment centre. Off the shelf components used. Possibility to use other needles, this does not affect PK data	A
25	Transfer of dose to syringe	Drop component	Component breaks	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	Stock of products available at treatment	A

							centre. Off the shelf components used. Possibility to use other needles, this does not affect PK data	
26	Transfer of dose to syringe	Failure to inject air into vial	More difficult to transfer dose to syringe	CAB Failure to deliver effective dose (once)	Medical Attention	Remote	(b) (4) IFU provided. HCP should check dose before injecting. HF studies show that this is not an issue.	A
27	Transfer of dose to syringe	Failure to inject air into vial	More difficult to transfer dose to syringe	RPV Failure to deliver effective dose (once)	Medical Attention	Remote	(b) (4) IFU provided. HCP should check dose before injecting. HF studies show that this is not an issue.	A
28	Transfer of dose to syringe	Back pressure in vial	Syringe is filled, not disconnected from vial adaptor for some time, back pressure reduces volume in syringe, syringe dose not checked before injection, lower volume delivered	CAB Failure to deliver effective dose (multiple times)	Permanent	Unlikely	(b) (4) IFU provided and has been updated to state that HCP should check the syringe before administering the dose.	A
29	Transfer of dose to syringe	Back pressure in vial	Syringe is filled, not disconnected from vial adaptor for some time, back pressure reduces volume in syringe, syringe dose not checked before injection, lower volume delivered	RPV Failure to deliver effective dose (multiple times)	Permanent	Unlikely	(b) (4) IFU provided and has been updated to state that HCP should check the syringe before administering the dose.	A
30	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	Cabotegravir Dermal exposure	None	Remote	(b) (4) Standard luer lock	A
31	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	RPV Dermal contact	None	Remote	(b) (4) Standard luer lock components being used.	A
32	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	Cabotegravir Mucus membrane exposure	Discomfort	Remote	(b) (4) Standard luer lock components being used.	A
33	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	RPV Ocular contact	Discomfort	Remote	(b) (4) Standard luer lock components being used.	A
34	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Standard luer lock components being used. Not	A

35	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Standard luer lock components being used. Not seen as an issue during HF tests.	A
36	Prepare syringe	Syringe prepared too early	Sedimentation in syringe failure to deliver dose	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Sedimentation expected to take over 2 hours	A
37	Prepare syringe	Syringe prepared too early	Sedimentation in syringe failure to deliver dose	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Sedimentation expected to take over 2 hours	A
38	Prepare syringe	Syringe prepared too early	Exposure to light (Rilpivirine)	RPV delivery of degraded drug	Permanent	Improbable	IFU provided. Pack has closable lid feature. Injection should happen shortly after being drawn into syringe. As advised by (b) (4)	A
39	Dose delivery	Incorrect injection depth	Dose delivered subcutaneously	Cabotegravir Dose delivered subcutaneously	Minor	Occasional	(b) (4)	A
40	Dose delivery	Incorrect injection depth	Dose delivered subcutaneously	RPV Subcutaneous injection	Minor	Occasional	(b) (4)	A
41	Dose delivery	Failure to aspirate before injecting	Injection into blood vessel	Cabotegravir Dose delivered intravenously	Permanent	Unlikely	(b) (4)	A
42	Dose delivery	Failure to aspirate before injecting	Injection into blood vessel	RPV Intravenous injection	Permanent	Unlikely		A

							(b) (4)	
43	Dose delivery	Injection into dorsogluteal site	Injection in dorsogluteal site, incorrect techniques used, sciatic nerve hit	Nerve damage from injection	Permanent	Unlikely	(b) (4) Instructions state ventrogluteal site injection is preferred. Injury to sciatic nerve unlikely (b) (4) (b) (4) Dorsogluteal site is still safe if correct technique used.	A
44	Disposal	Fail to activate needle safety system	Failure to put used needle into sharps bin. Non-patient receives contaminated needle stick injury	Cross contamination	Permanent	Unlikely	Most HCPs activated the safety after use and all disposed of in sharps bin.	A
45	Disposal	Wrong technique used to activate needle safety system	HCP receives contaminated needle stick injury	Cross contamination	Permanent	Unlikely	(b) (4) (b) (4) In HF tests when unsure they just disposed of used needle into the sharps bin. Needle safety system is compliant with ISO standard.	A
46	Dose delivery	Dose delivered orally	Syringe used as a dosing syringe and dose delivered orally	Cabotegravir Oral exposure	Discomfort	Improbable	(b) (4) IFU provided.	A
47	Dose delivery	Dose delivered orally	Syringe used as a dosing syringe and dose delivered orally	CAB Failure to deliver effective dose (multiple times)	Permanent	Improbable	(b) (4) IFU provided.	A
48	Dose delivery	Dose delivered orally	Syringe used as a dosing syringe and dose delivered orally	RPV Oral dose	Discomfort	Improbable	(b) (4) IFU provided.	A

49	Dose delivery	Dose delivered orally	Syringe used as a dosing syringe and dose delivered orally	RPV Failure to deliver effective dose (multiple times)	Permanent	Improbable	(b) (4). IFU provided.	A
50	Transfer of dose to syringe	Use needle rather than vial adaptor for dose transfer	Needle becomes blunted	Injection with blunted needle	Discomfort	Unlikely	(b) (4). IFU provided.	A
51	Transfer of dose to syringe	Drawing up from both vials	Confusion over treatment and HCP attempts to mix the products	CAB Failure to deliver effective dose (multiple times)	Permanent	Unlikely	Not seen in HF or clinical studies. (b) (4) HCP should be aware of the treatment.	A
52	Transfer of dose to syringe	Drawing up from both vials	Confusions over treatment and HCP attempts to mix the products	RPV Failure to deliver effective dose (multiple times)	Permanent	Unlikely	Not seen in HF or clinical studies. (b) (4) HCP should be aware of the treatment.	A
53	Prepare syringe	Inadequate needle used	Too short a needle used results in subcutaneous injection of CAB	Cabotegravir Dose delivered subcutaneously	Minor	Unlikely	(b) (4) Not seen in the Clinical Trials. Needles are provided within the pack given to HCP.	A
54	Prepare syringe	Inadequate needle used	Too short a needle used results in subcutaneous injection of RPV	RPV Subcutaneous injection	Minor	Unlikely	(b) (4) Not seen in the Clinical Trials. Needles are provided within the pack given to HCP.	A
55	Prepare syringe	Inadequate needle used	Large needle gauge used, suspension blocks needle	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Not seen in the Clinical Trials. Needles are provided within the pack given to HCP.	A
56	Prepare syringe	Inadequate needle used	Large needle gauge used, suspension blocks needle	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Not seen in the Clinical Trials. Needles are provided within the pack given to HCP.	A

57	Dose delivery	Injection into non patient	HCP accidental needle stick during needle insertion	Needlestick injury (Sterile)	Minor	Unlikely	(b) (4) Components have needle protection for after use. Not seen in any of the HF studies	A
58	Dose delivery	Injection into non patient	HCP accidental needle stick during needle insertion, and injects CAB	Cabotegravir Single dose delivered to non patient	Discomfort	Improbable	(b) (4) Components have needle protection for after use. Not seen in any of the HF studies	A
59	Dose delivery	Injection into non patient	HCP accidental needle stick during needle insertion, and injects RPV	RPV Delivery to non-patient	Minor	Improbable	(b) (4) Components have needle protection for after use. Not seen in any of the HF studies	A
60	Dose delivery	Patient with High BMI	Incorrect needle used, results in incorrect injection depth	Cabotegravir Dose delivered subcutaneously	Minor	Unlikely	Phase 3 studies have not noted this to date. IFU advises HCP to be aware of this.	A
61	Dose delivery	Patient with High BMI	Incorrect needle used, results in incorrect injection depth	RPV Subcutaneous injection	Minor	Unlikely	Phase 3 studies have not noted this to date. IFU advises HCP to be aware of this.	A
62	Supply and storage	Wrong pack selected	Maintenance rather than starter	CAB Failure to deliver effective dose (multiple times)	Permanent	Improbable	Not seen in HF studies	A
63	Supply and storage	Wrong pack selected	Maintenance rather than starter	RPV Failure to deliver effective dose (multiple times)	Permanent	Improbable	Not seen in HF studies	A
64	Supply and storage	Wrong pack selected	Starter rather than maintenance	Cabotegravir Overdose (2 vial of loading phase)	Minor	Unlikely	Not seen in HF studies	A
65	Supply and storage	Wrong pack selected	Starter rather than maintenance	RPV overdose	Minor	Unlikely	Not seen in HF studies	A
66	Supply and storage	User splits pack	Various scenarios	CAB Failure to deliver effective	Permanent	Unlikely	Combination product stated on packaging.	A

				dose (multiple times)			IFU provided. Not common practice to break up drug product packs. Not seen in HF tests	
67	Transfer of dose to syringe	Vial adaptor contacted	Vial adaptor spike or luer lock left out of packaging and becomes contaminated	Delivery of non sterile dose	Medical Attention	Unlikely	Minimal time for microbial growth. HCP should be wearing gloves. Correct procedure explained in IFU.	A
68	Transfer of dose to syringe	CAB mixed into RPV vial	HCP misunderstands, thinks that the vials need to be mixed together, HCP put CAB into the RPV vial to mix	CAB Failure to deliver effective dose (multiple times)	Permanent	Unlikely	IFU provided. Not seen in HF.	A
69	Preparation of vials	Drug expired	HCP does not check the expiry date and the expiry date has past leading to injection of ineffective dose	CAB Failure to deliver effective dose (once)	Medical Attention	Improbable	It has been observed through HF studies that HCP's always check the date and it is part of their training.	A
70	Preparation of vials	Drug expired	HCP does not check the expiry date and the expiry date has past leading to injection of ineffective dose	RPV Failure to deliver effective dose (once)	Medical Attention	Improbable	It has been observed through HF studies that HCP's always check the date and it is part of their training.	A
71	Dose delivery	Second injection not delivered	HCP fails to continue to the second injection of the treatment	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) IFU states to continue to the second injection once the first is complete.	A
72	Dose delivery	Second injection not delivered	HCP fails to continue to the second injection of the treatment	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) IFU states to continue to the second injection once the first is complete.	A

Reviewer comments: The risk analysis/assessment was complete and adequate.

20.4.7.3. Risk Analysis Interactive Review

CDRH sent Risk Analysis Interactive Review questions to the Applicant	☒ Yes ☐ No

20.4.8. Design Verification Review

Design Verification Review Summary/Conclusion		
Filing deficiencies:	Midcycle deficiencies:	Final deficiencies
☐ Yes ☒ No ☐ N/A	☒ Yes ☐ No ☐ N/A	☐ Yes ☒ No ☐ N/A

Reviewer conclusion

Midcycle comments: 2 IRs were sent to the Applicant on 9-20-2019. See IRs and responses under Section 20.4.13.2.

Final review comments: The Applicant has provided complete and adequate test reports/information

Materials reviewed

Document title: NDA 212888 Location: P.2.2, P.2.6, and P.5.4

20.4.8.1. Performance/Engineering Verification

Table 222. Essential Performance Requirement Evaluation

Test	Acceptance Criteria	Sample Size (# of units)	Mean Result	Minimum - Maximum (Std. Deviation)	Overall Result
Leakage test for syringe-needle connection[1] (mm)	The plunger displacement remains less than or equal to (b) (4) mm when subjected to an injection force of (b) (4) N after attachment of the safety needle to the syringe.	30	0.040	(b) (4) (0.020)	Pass
Vial adapter attachment/detachment force (N)	The force required to attach the vial adapter onto the vial shall not exceed (b) (4) N.	30	25.62	(b) (4) (1.73)	Pass
	The force required to disconnect the vial adapter from the vial shall be greater than (b) (4) N when applied axially.	30	16.15	(b) (4) (1.97)	Pass
Unscrewing torque test (Nm)	The unscrewing torque required to disconnect the vial adapter from the syringe shall be equal to or greater than (b) (4) Nm as per (b) (4)	30	0.060	(b) (4) (0.006)	Pass
Separation force test (N)	The force required to separate the syringe from the vial adapter in the axial direction shall exceed (b) (4) N as per (b) (4)	30	165 N	(b) (4) (13)	Pass
Stress cracking test[1]	The syringe to vial adapter connection shall not break or leak when tested according to (b) (4) stress cracking.	30	No visual cracks observed after 48 hours	N/A	Pass
Unscrewing torque test (Nm)	The unscrewing torque required to disconnect the safety needle from the syringe shall be equal to or greater than (b) (4) Nm as per (b) (4)	30	0.074	(b) (4) (0.009)	Pass
Separation force test (N)	The force required to separate the syringe from the needle shall exceed (b) (4) N as per (b) (4)	30	58.8	(b) (4) (3.6)	Pass
Stress cracking test[1]	The syringe to needle connection shall not break or leak when tested according to (b) (4) stress cracking.	30	No visual cracks observed after 48 hours	N/A	Pass

Table 223. Stress Cracking Test and Leakage Test Results Following Storage at 25°C/60% RH

Test	Acceptance Criteria	Sample Size (# of units)	Timepoint (months)			
			Initial	1.5	3	6
Syringe to Vial Adapter connection - Stress Cracking	No visual cracks shall be visible 48 hours after stress crack testing	30	Pass	Pass	Pass	Pass
Syringe to Needle connection - Stress Cracking	No visual cracks shall be visible 48 hours after stress crack testing	30	Pass	Pass	Pass	Pass
Syringe to Needle connection - Leakage test in use condition (simulation of injection)	Plunger displacement (b) (4) mm after 48 hours	30	Pass	Pass	Pass	Pass

Table 224. Injectability Force for Rilpivirine Extended-Release Suspension for Injection Following Storage at 25°C/60% RH

Test	Acceptance Criteria	Sample Size (# of units)	Timepoint (months)	Mean Result	Minimum-Maximum (Std. Deviation)	Overall Result
Injection force (N) 2-mL fill presentation	Average injection force of each measurement (b) (4) N	30	Initial	15.6	(b) (4) (0.6)	Pass
			1.5	15.4		(0.7)	Pass
			3	15.7		(0.7)	Pass
			6	16.0		(0.7)	Pass
Injection force (N) 3-mL fill presentation	Average injection force of each measurement (b) (4) N	30	Initial	16.2		(0.8)	Pass
			1.5	15.2		(0.6)	Pass
			3	16.1		(0.6)	Pass
			6	14.9		(0.7)	Pass

Reviewer comment: The design verification test reports are adequate. The Applicant completed the functional performance tests that CDRH recommended in previous communications. Individual device components were tested and cleared under their 510k submissions.

Table 225. Design Functional Requirements (DFR) Evaluation

Design Input	Design Output	Verification Method	Results/ Deviations	Adequately Verified (Y/N)	Validated Through Clinical, Human Factors, or Other	Adequately Validated (Y/N/NA)
Dose accuracy	Aligned to drug product specification for extractable volume	Compliance to (b) (4)	Delivered volume contents from syringe, 2 mL and 2 mL	Y	Y- human factors	Y
Absence of leakage	Aligned to drug product specification for extractable volume	Compliance to (b) (4)	No leakage	Y	Y - human factors	Y
Vial, vial adaptor, syringe and needle compatibility	Aligned to drug product specification for extractable volume	Compliance to (b) (4)	All device constituent parts are compatible	Y	Y - human factors	Y
Injection force	Less than (b) (4) N (max value)	Compliance to (b) (4)	(b) (4) N	Y	Y - human factors	Y

Table 226. Syringeability Data for Cabotegravir Injectable Suspension

Fill Presentation	Batch Number	Storage Condition	Time (months)	Syringeability		
				Breakloose Force (N)	Average Glide Force (N)	Maximum Glide Force (N)
Acceptance Criteria				NGT (b) (4)	NGT (b) (4)	NGT (b) (4)
2-mL	172405685	Initial	0	(b) (4)		
		40°C/75% RH	1			
			3			
3-mL	172406948	Initial	0			
		40°C/75% RH	1			
			3			

Reviewer comment: Documentation supporting the validation of administration of the copack is provided in m3.2.R. Attachment_Human Factors Validation.

20.4.8.2. Design Verification Interactive Review

CDRH sent Design Verification Interactive Review questions to the Applicant	☒ Yes ☐ No

	Date Sent:9-20-2019 **Date/Sequence Received:9-27-2019**
Information request #1	You have not provided the lot release specifications for all the device constituent parts of your combination product. The lot release specifications should include all the essential performance requirements for the combination product. The essential performance requirements for the vial adapter, syringe and safety needle include: Dose accuracy Break loose/glide force vial/adapter compatibility Adapter/syringe compatibility
Applicant response	See Applicant's complete response under Section 20.4.13.2.
Reviewer comments	Adequate response, deficiency resolved.
Response adequate	☒ Yes ☐ No, see IR # sent on **(date)**

	Date Sent:9-20-2019	**Date/Sequence Received:9-27-2019**
Information request #2	Please provide traceability documentation. A traceability matrix should be provided to ensure 1) the design outputs are adequately verified to meet the design inputs and 2) the finished combination product is validated to meet the user needs. It is highly recommended that the essential performance requirements (EPRs) are highlighted for ease of review.	
Applicant response	See Applicant's complete response under Section 20.4.13.2.	
Reviewer comments	Adequate response, deficiency resolved.	
Response adequate	☒ Yes ☐ No, see IR # sent on **(date)**	

20.4.8.3. Discipline Specific Subconsulted Reviews

☒ No additional discipline-specific subconsults were requested

☐ The following additional discipline-specific subconsults were requested

Table 227. Discipline-Specific Design Verification/Validation Adequately Addressed

	Consult Needed				
Discipline	**Yes**	**No**	**N/A**	**Consultant**	**Section**
Engineering (materials, mechanical, general)			X		
Biocompatibility			X		
Sterility			X		
Software/cybersecurity			X		
Electrical safety/EMC			X		
Human factors			X		10
Clinical			X		

20.4.9. Clinical Validation Review

Clinical Verification Review Summary/Conclusion		
Filing deficiencies: ☐ Yes ☒ No ☐ N/A	Midcycle deficiencies: ☐ Yes ☒ No ☐ N/A	Final deficiencies ☐ Yes ☒ No ☐ N/A

Reviewer conclusion

Midcycle comments: Information was adequate.

Final review comments: Information was adequate

Materials reviewed

Document title: NDA 212888 – clinical studies Location: 1.11

20.4.9.1. Review of Clinical Studies

☐ There are no clinical studies for review.

☒ There are clinical studies for review.

The Applicant used information gathered from the phase 3 clinical study to determine what device constituent parts to use in the to be marketed copack kit. The following is a summary:

Table 228. Phase 3 Clinical Trials vs. Commercial Copack

		Phase 3 Clinical Trials	Commercial Co-Pack
Initiation Dose	Dose[1]	600 mg/3 mL dose of Cabotegravir Injectable Suspension 900 mg/3 mL dose of Rilpivirine Extended-release Suspension for Injection	
	Vials	2 x 2-mL vials[2] of each suspension required to deliver the intended doses	Separate, single-use 3-mL vial of each suspension to deliver the intended doses included in the co-pack
Continuation Dose	Dose[1]	400 mg/2 mL dose of Cabotegravir Injectable Suspension 600 mg/2 mL dose of Rilpivirine Extended-release Suspension for Injection	
	Vials	Separate, single-use vial of each suspension to deliver the intended doses	Separate, single-use vial of each suspension to deliver the intended doses included in the co-pack
Vial adapters		Aspiration device (if applicable, typically a needle) sourced by clinical sites	Included in the co-pack
Syringes		Sourced by clinical sites	Included in the co-pack
Needles		Sourced centrally or locally	Included in the co-pack[3]

A review of syringes and needles utilized for dosing in the phase 3 ATLAS clinical study (protocol 201585) of Cabotegravir Injection Suspension, 200 mg/mL and Rilpivirine Extended-Release Suspension for Injection 300 mg/mL was completed in order to inform device selection for the commercial copack.

Syringe: The primary syringe attribute assessed as a design input was the materials of construction. Both glass and plastic syringes were utilized for dosing in clinical trials. In a representative sampling of Cabotegravir Injection Suspension, 200 mg/mL (n=1314) and Rilpivirine Extended-Release Suspension for Injection 300 mg/mL (n=1313) injections, approximately 98.5% were delivered using a plastic syringe and approximately 1.5% were delivered with a glass syringe. Of the injections delivered with a glass syringe, greater than 70% were restricted to one country (non-United States).

Needle: Needle attributes assessed as design inputs were the needle length and needle gauge. Needle length was evaluated for potential impact to exposure, as well as suitability to deliver an IM injection across the weight and BMI range of patients. Needle gauge was primarily considered in relation to syringeability and pain perception.

Needle length: In the phase 3 ATLAS clinical study (Protocol 201585), needle lengths ranging from 1-inch to greater than 2-inch were utilized for dosing Cabotegravir Injection Suspension, 200 mg/mL (n=3488) and Rilpivirine Extended-Release Suspension for Injection 300 mg/mL (n=3490) as presented in Table 229. The data indicated that approximately 91% of the injections were dosed with 1.5 to <2-inch needle. A 1.5-inch needle length was selected for the copack to administer both Cabotegravir Injection Suspension, 200 mg/mL and Rilpivirine Extended-Release Suspension for Injection300 mg/mL. The use of alternate needle lengths is permitted at the discretion of the healthcare practitioner based on patient need.

Table 229. Needle Lengths Used for Injections

		Cabotegravir Injection Suspension, 200 mg/mL	Rilpivirine 300 mg/mL Extended-release Suspension for Injection
Subjects (n)		303	303
Injections (n)		3488	3490
Needle Length (in)	1 - < 1.5	147 (4%)	148 (4%)
	1.5 - < 2	3175 (91%)	3176 (91%)
	≥ 2	166 (5%)	166 (5%)

Needle gauge: In the phase 3 ATLAS clinical study (Protocol 201585), needle gauges ranging from (b) (4) were utilized for dosing Cabotegravir Injection Suspension, 200 mg/mL (n=3488), and needle gauges from (b) (4) were utilized for dosing Rilpivirine Extended-Release Suspension for Injection 300 mg/mL (n=3490). As presented in Table 230, needle gauges used ranged from (b) (4) for both drug products. A needle gauge of 23G was selected for the copack to administer both Cabotegravir Injection Suspension, 200 mg/mL and Rilpivirine Extended-Release Suspension for Injection 300 mg/mL.

Table 230. Needle Gauges Used for Injections

		Cabotegravir Injection Suspension, 200 mg/mL	Rilpivirine 300 mg/mL Extended-release Suspension for Injection
Subjects (n)		303	303
Injections (n)		3488	3490
Needle Gauge	(b) (4)	7 (<1%)	10 (<1%)
		1409 (40%)	2018 (58%)
		117 (3%)	153 (4%)
		1335 (38%)	1307 (37%)
		0 (0%)	0 (0%)
		620 (18%)	2 (<1%)

Reviewer comment: The Applicant used information gathered in the phase 3 clinical study to determine what devices to use in their copack. The Applicant followed CDRH's recommendations from previous communications and used 510(k) cleared devices and a needle with a safety feature in their to be marketed copack kit.

20.4.9.2. Clinical Validation Interactive Review

CDRH sent Design Validation Interactive Review questions to the Applicant	☐ Yes ☒ No

20.4.10. Human Factors Validation Review

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☒

20.4.11. Labeling

Labeling Review Summary/Conclusion		
Filing deficiencies: ☐ Yes ☒ No ☐ N/A	Midcycle deficiencies: ☐ Yes ☒ No ☐ N/A	Final deficiencies ☐ Yes ☒ No ☐ N/A

Reviewer conclusion

Midcycle comments: The device labeling and instructions for use is complete and adequate.

Final review comments: The device labeling and instructions for use is complete and adequate.

Materials reviewed

Document title: NDA 212888 Location: 1.14.1, 2, and 3

20.4.11.1. General Labeling Review

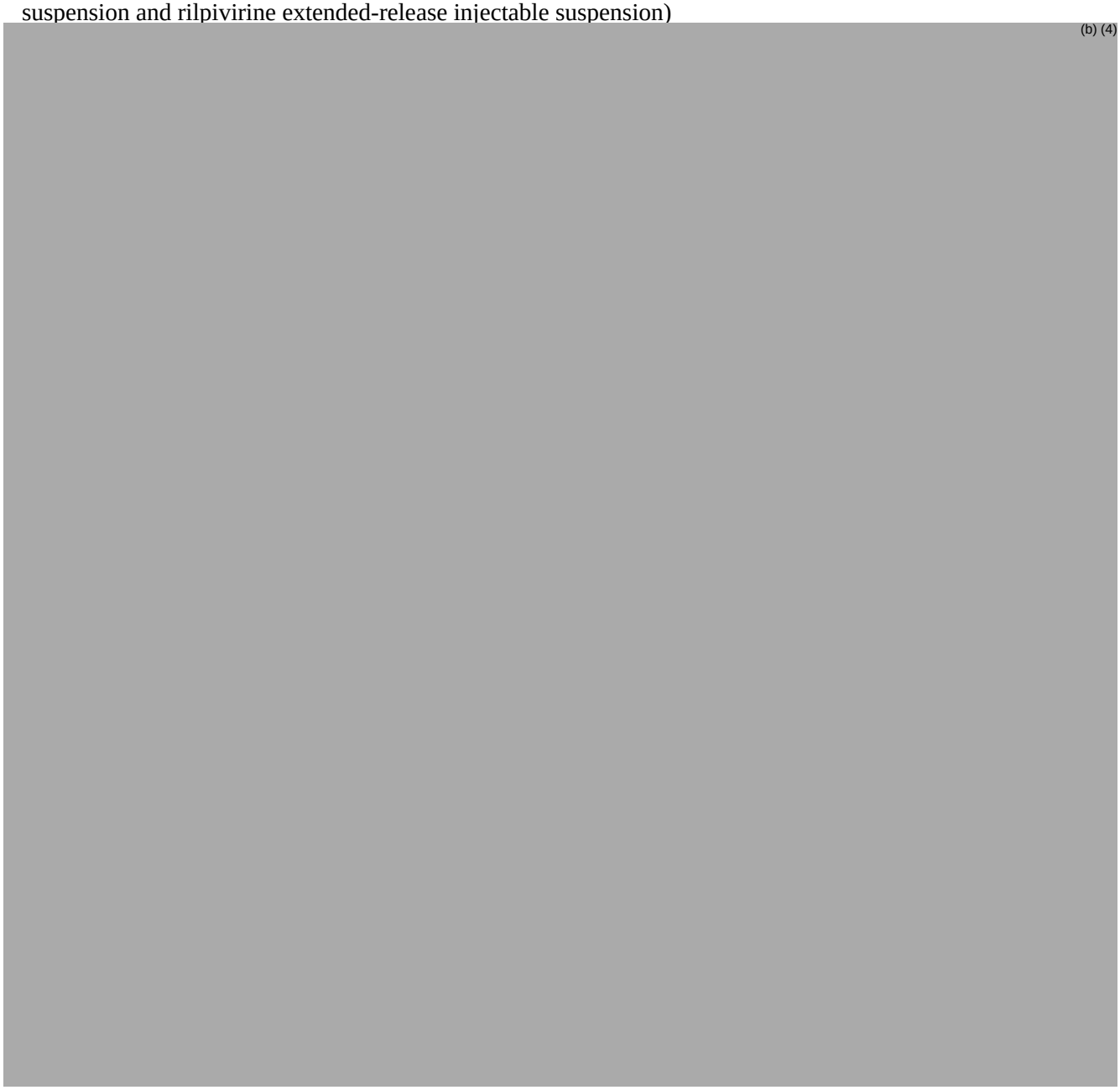
The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

	Adequate?		
Device Labeling Review Checklist	**Yes**	**No**	**N/A**
Indications for use or intended use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/combination product name and labeling is consistent with the type of device constituent	X		
Prescriptive statement/symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for use	X		
Final instructions for use validated through human factors	X		
Electrical safety labeling/symbols			X
EMC labeling/symbols			X
Software version labeling			X
MRI labeling/symbols			X
RF/wireless labeling/symbols			X

Reviewer comments: The device labeling is complete and adequate.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)



20.4.11.3. Labeling Interactive Review

CDRH sent Labeling Interactive Review questions to the Applicant	☐ Yes ☒ No

20.4.12. Quality Systems/Manufacturing Controls

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☒

No CDRH quality systems or facilities review required.

All of the device constituent parts are 510(k) cleared and are well understood with basic technology and have a low-risk of device related injuries or malfunction.

20.4.13. Appendix A (Information Requests)

20.4.13.1. Filing/74-Day Information Requests

None.

20.4.13.2. Midcycle Information Requests

CDRH Question 1-Sent on September 20, 2019

You have not provided the lot release specifications for all the device constituent parts of your combination product. The lot release specifications should include all the essential performance requirements for the combination product. The essential performance requirements for the vial adapter, syringe and safety needle include:

- Dose accuracy
- Break loose/glide force vial/adapter compatibility
- Adapter/syringe compatibility

Applicant's Response Received September 27, 2019:

Clarification of Essential Performance Requirements

Based on the Agency's recommendation (IND 109,678 preliminary meeting comments, pre-NDA type B meeting, 28 January 2019), the Applicant designated the following essential performance requirements (EPR) for the combination product (hereafter referred to as copack):

- Dose accuracy
- Absence of leakage
- Device compatibility

This information is presented in section 4.2.1 of m3.2.R_Attachment_Devices of NDA 212888.

Break loose/glide force has not been designated as an EPR for this copack. The rationale is based on the fact that drug product is filled into the syringe at the point of use, and as such, the syringe is not subject to a peak break loose followed by a glide force as opposed to a drug product, such as a prefilled syringe, where these forces may be impacted by the long-term storage of the drug product in the syringe.

Injection force has also not been designated as an EPR for this copack. Rather, the appropriate injection force for this copacked product is based on the force needed to expel each drug product from the respective syringe after the drug product has been withdrawn into the syringe.

While break loose/glide force is not an EPR for this product presentation, injection force has been verified during development. As presented in section 4.2.2 of m3.2.R_Attachment_Devices, this has been considered as an additional performance requirement. Further detail is included in the traceability matrix requested in question 2 of this information request.

Device Constituent Parts of the Copack

The Applicant confirms adequate controls are in place to ensure that the device components of the copack demonstrate acceptable performance for the defined EPRs. These controls include testing performed by the Applicant during development of the copack, as well as testing performed by the device manufacturers to ensure lot-to-lot consistency of the prepacked, presterilized medical devices.

The devices are sourced from their original manufacturers in their original (presterilized) blister packaging, with manufacturer-provided information such as lot number and expiration date. The devices are independently registered and marketed as stand-alone devices. It is noted that in order for these devices to be used in the commercial clinical environment, where healthcare practitioners may choose devices manufactured by alternate manufacturers to facilitate drug delivery for independently marketed drug products, conformance to international standards is utilized in order to ensure compatibility. The Applicant has confirmed the intended use of the devices to include compliance with such applicable international standards (including ISO 80369 for the luer connections), as is detailed below in Table 231.

The Applicant acknowledges its accountability for the intercompatibility I usability of the constituents (i.e., devices together with drug products) as used to prepare and administer the drug products to patients, and as such has confirmed suitability through verification and validation testing, as well as a supplier audit program and incoming component specifications.

Control Strategy

(b) (4)

5 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

20.4.13.3. Interactive Information Requests

None.

21. Data Integrity-Related Consults (OSI, Other Inspections)

21.1. Clinical Inspection Summary

Date	10/28/2019
From	Karen Bleich, M.D., Reviewer Aisha Johnson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jacquelyn Rosenberger, Pharm.D, Regulatory Project Manager Mark Needles, M.D., Clinical Reviewer Yuliya Yasinskaya, M.D., Team Leader Division of Anti-Viral Drug Products
NDA/BLA #	NDA 212887 and NDA 212888
Applicant	ViiV Healthcare Co.
Drug	Vocabria (cabotegravir) tablets for oral use (NDA 212887) and Cabenuva (co-packaged cabotegravir and rilpivirine) suspension for IM injection (NDA 212888)
NME (Yes/No)	Yes
Review classification	Priority
Proposed indication(s)	Vocabria: For use in combination with rilpivirine for short- term treatment of HIV-1 infection in adults who are virologically suppressed. Cabenuva: For treatment of HIV-1 infection in adults who are virologically suppressed.
Consultation request date	5/6/2019
Summary goal date	10/29/2019
Action goal date	12/29/2019
PDUFA date	12/29/2019

21.1.1. Overall Assessment of Findings and Recommendations

The data from study 201584 (FLAIR) and study 201585 (ATLAS) were submitted to the Agency in support of NDA 212887 and NDA 212888. A total of four clinical investigator sites were selected for audit: Dr. Miguel Gorgolas Hernandez-Morales (protocol 201584/site 225283), Dr. Maria Del Mar Masia (protocol 201584/site 225120 and protocol 201585/site 225163), Dr. Christopher Bettacchi (protocol 201584/site 222234 and protocol 201585/site 222290), and Dr. Franco Antonia Felizarta (protocol 201584/site 222193 and protocol 201585/site 222276).

Inspections of selected clinical investigator sites from studies 201584 and 201585 identified nine unreported adverse events in seven subjects at two of the sites in Spain. Based on the reports of the inspections, communication with the field inspector, and communication with the Applicant, it was determined that the cause of the underreporting was that the adverse events reports became available to the investigators and the Applicant after the submission of the NDA. The

adverse events were identified upon review of a newly available electronic medical record system that captured primary care visits in Spain. The review of the primary care EMR occurred after the submission of the NDA. The unreported AEs consisted of events that were reported by study subjects to their care provider and were not also reported by the study subjects to the clinical investigator. The unreported AEs were classified as nonserious and were assessed as unrelated to the study drug by the clinical investigators.

The Applicant is in the process of evaluating if any additional unreported adverse events exist at other study sites in Spain related to the integration of the primary care EMR after the NDA submission. The Applicant reports that a final review of the issue and corrective and preventive action plan in expected to be in place by October 31st, 2019.

There was no under reporting of adverse events that were disclosed by subjects to the clinical investigators, which was the primary mechanism for AE reporting in the 201584 and 201585 studies. The unreported AEs do not appear to have been unreported because of any deficiency in study conduct. The inspections demonstrated no additional significant findings related to data integrity or human subject protection.

Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these clinical investigator sites submitted by the Applicant appear acceptable in support of the proposed indication.

21.1.2. Background

ViiV Healthcare Co. seeks approval to market VOCABRIA and CABENUVA for the treatment of HIV-1 infection in adults who are virologically suppressed. VOCABRIA is an oral formulation of cabotegravir, to be taken with oral RPV and is intended for OLI for IM use of CABENUVA. CABENUVA is an IM formulation that consists of copackaged CAB and RPV and is administered monthly.

The clinical data to support the use of CAB/RPV (as oral tablets or as IM injections) is based on the 48-week results of two phase 3 studies: study 201584 (FLAIR) and study 201585 (ATLAS). Both studies compared the safety and efficacy of monthly IM injections of CABENUVA as compared to standard daily oral triple therapy for HIV-1.

In the FLAIR study, antiretroviral-naïve adults with HIV-1 were enrolled and were given a standard daily oral triple therapy regimen for an induction period. Subjects who achieved viral suppression were subsequently eligible to enter a maintenance phase in which subjects were randomized to either the IM formulation of the study drug (preceded by an OLI) or to continue their oral antiretroviral regimen.

In the ATLAS study, adult subjects with HIV-1 with a suppressed viral load on a stable antiretroviral regiment were eligible for enrollment. Subjects were randomized to either the IM formulation of the study drug (preceded by an OLI) or to continue their oral antiretroviral regimen.

In both studies, the primary endpoint was the number of cases of virologic failure at 48 weeks. The studies are summarized below:

Table 237. Study 201584 (FLAIR)

Title of study	A phase III, randomized, multi-center, parallel-group, open-label study evaluating the efficacy, safety, and tolerability of long-acting intramuscular cabotegravir and rilpivirine for maintenance of virologic suppression following switch from an integrase inhibitor single tablet regimen in HIV-1 infected antiretroviral therapy naïve adult participants: Week 48 – Primary endpoint
Number of subjects	629
Main criteria for inclusion	Anti-retroviral-naïve adults with HIV-1
Treatment administration	
Induction phase	All subjects received abacavir/dolutegravir/lamivudine (ABC/DTG/3TC) for 20 weeks
Maintenance phase	Subjects who achieved viral suppression were randomized (1:1) to Arm 1 or Arm 2
Arm 1	Cabotegravir and rilpivirine (daily oral lead in for 4 weeks, followed by monthly IM formulation)
Arm 2	Remain on daily oral induction regiment
Study sites	108 sites in 11 countries (Canada, France, Germany, Italy, Japan, Netherlands, Russia, South Africa, Spain, United Kingdom, and U.S)
Study period	October 27th, 2016 – August 30th, 2018
Primary objective	To demonstrate the non-inferior antiviral activity of switching to IM cabotegravir + rilpivirine every 4 weeks compared to continuation of continued/current antiretroviral regimen over 48 weeks in HIV-1 antiretroviral naïve subjects
Primary efficacy endpoint	Proportion of subjects with a virologic failure endpoint as per FDA Snapshot algorithm at Week 48

Table 238. Study 201585 (ATLAS)

Title of study	A Phase III, randomized, multicenter, parallel-group, noninferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current INI-, NNRTI-, or PI-based antiretroviral regimen in HIV-1 injected adults who are virologically suppressed
Number of subjects	616
Main criteria for inclusion	Adults with HIV-1 on stable antiretroviral regimen with suppressed viral load
Treatment administration	Subjects randomized 1:1 to Arm 1 or Arm 2
Arm 1	Cabotegravir and rilpivirine (daily oral lead in for 4 weeks, followed by monthly IM formulation)
Arm 2	Remain on current antiretroviral therapy (at time of enrollment)
Study sites	115 sites in 13 countries (Argentina, Australia, Canada, France, Germany, Italy, Mexico, Korea, Russia, South Africa, Spain, Sweden, and the U.S.)
Study period	October 28th, 2016 – May 29th, 2018
Primary objective	To demonstrate the non-inferior antiviral activity of switching to IM CAB + RPV every 4 weeks (monthly) compared to continuation of CAR over 48 weeks in HIV-1 infected ART- experienced subjects
Primary efficacy endpoint	Proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL per the Snapshot Algorithm at Week 48.

Rationale for Site Selection

Sites were chosen for inspection based primarily upon enrollment of relatively large numbers of subjects and participation in both the FLAIR and ATLAS studies.

21.1.3. Results (by Site)

Dr. Miguel Gorgolas Hernandez-Morales, Madrid, Spain (Protocol 201584 (FLAIR) Site 225283)

The inspection of Dr. Hernandez-Morales' site was conducted from July 22, 2019 – July 26, 2019. At the time of the inspection, the study was in long-term follow-up (closed to enrollment). The site screened 21 subjects and enrolled 16 subjects.

The inspection included a review of documents related to the site's training program, ethics committee approval and correspondences, informed consent, site monitoring, and financial disclosures. A comprehensive review of the source document records for all enrolled subjects was performed. The data listings submitted in the NDA were verified by comparison with the source data at the site, including protocol deviations, primary efficacy endpoint test results, enrollment criteria, and adverse events.

Adverse events were identified in the source records that were not included in the site data listings provided to the Agency by the Applicant. The cause of the omission was that the adverse events were identified in primary care electronic medical records and these records became available to the Applicant and the clinical investigator after the submission of the NDA. The inspector verified that the adverse events in the site's source documents had been entered into the study eCFR retrospectively. The unreported events from Dr. Hernandez-Morales' site are listed in Table 239.

Table 239. Adverse Events at Study Site 225283 (FLAIR Study) Not Included in NDA Submission (Adapted From Applicant's Response to Information Request 10/17/2019)

Subject Number	Treatment Assignment	AE Term	Start Date	End Date	AE Severity
(b) (6)	Induction phase WD	Atopic eczema		(b) (6)	Mild or grade 1
	Induction phase WD	Cold			Mild or grade 1
	Induction phase WD	Sinusitis			Mild or grade 1
(b) (6)	ABC/DTG/3TC	Physical aggression			Mild or grade 1
	ABC/DTG/3TC	Pediculosis pubis			Mild or grade 1

No additional significant deficiencies or inconsistencies between source records and submitted NDA data were identified at the site. No FDA Form 483 was issued at the end of the inspection.

Dr. Maria Del Mar Masia, Elche, Spain (Protocol 201584 (FLAIR) Site 225120 and Protocol 201585 (ATLAS) Site 225163)

The inspection of Dr. Masia's site was conducted from July 29, 2019 – August 2, 2019. At the time of the inspection, the FLAIR study was in long-term follow-up (closed to enrollment) and the ATLAS study was completed. The site screened 16 subjects and enrolled 11 subjects for the FLAIR study. For the ATLAS study, the site screened six subjects and enrolled five subjects.

The inspection included a review of documents for both studies related to the site's training program, ethics committee approval and correspondences, site monitoring, investigational product accountability, and financial disclosures.

A comprehensive review of the source document records for all enrolled subjects for both studies was performed. The data listings submitted in the NDA were verified by comparison with the source data at the site, including consent, entry criteria, primary endpoint data, and adverse events.

Adverse events were identified in the source records for both studies that were not included in the site data listings provided to the Agency by the Applicant. The cause of the omission was that the adverse events were found in primary care electronic medical records and these records became available to the Applicant and the investigator after the submission of the NDA. The inspector verified that the adverse events in the site's source documents had been entered into the study eCFR retrospectively. The unreported adverse events from Dr. Masia's site for the FLAIR study and for ATLAS study are listed in Table 240 and Table 241, respectively.

Table 240. Adverse Events at Study Site 225120 (FLAIR Study) Not Included in NDA Submission (Adapted From Applicant's Response to Information Request 10/17/2019)

Subject Number	Treatment Assignment	AE Term	Start Date	End Date	AE Severity
(b) (6)	Cabotegravir and rilpivirine	Foot pain		(b) (6)	Moderate or grade 2
	Cabotegravir and rilpivirine	Proctitis			Moderate or grade 2
(b) (6)	Cabotegravir and rilpivirine	bloody exudate			Mild or grade 1

Table 241. Adverse Events at Study Site 225163 (ATLAS Study) Not Included in NDA Submission (Adapted From Applicant's Response to Information Request 10/17/2019)

Subject Number	Treatment Assignment	AE Term	Start Date	End Date	AE Severity
(b) (6)	Cabotegravir and rilpivirine	Abdominal pain		(b) (6)	Mild or grade 1

No additional significant deficiencies or inconsistencies between source records and submitted NDA data were identified at the site. No FDA form 483 was issued at the end of the inspection.

Dr. Christopher Bettacchi, Dallas, Texas (Protocol 201584 (FLAIR) Site 222234 and Protocol 201585 (ATLAS) Site 222290)

The inspection of Dr. Bettacchi's site was conducted from August 5, 2019 – August 9, 2019. At the time of the inspection, the FLAIR study was in long-term follow-up (closed to enrollment)

and the ATLAS study was completed. The site screened 24 subjects and enrolled 17 subjects for the FLAIR study. For the ATLAS study, the site enrolled three subjects.

The inspection included a review of documents related to the site's training program, IRB approval and correspondences, informed consent, site monitoring, investigational product accountability, protocols, and financial disclosures for both studies.

A comprehensive review of the source document records for all 17 subjects enrolled in FLAIR and all 3 subjects enrolled in ATLAS was performed. The data listings submitted in the NDA were verified by comparison with the source data at the site, including primary efficacy endpoint results, adverse events, protocol deviations, and concomitant medications.

No significant deficiencies were identified at the site and no significant inconsistencies between source records and submitted NDA data were identified. No FDA form 483 was issued at the end of the inspection.

Dr. Franco Antonio Felizarta, Bakersfield, California (Protocol 201584 (FLAIR) Site 222193 and Protocol 201585 (ATLAS) Site 222276)

The inspection of Dr. Felizarta's site was conducted from June 16, 2019 – June 21, 2019. At the time of the inspection, the FLAIR study was in long-term follow-up (closed to enrollment) and the ATLAS study was completed. The site screened 19 subjects and enrolled 16 subjects for the FLAIR study. For the ATLAS study, the site screened 12 subjects and enrolled 6 subjects.

The inspection included a review of documents related to the site's training programs, IRB approval and correspondences, site monitoring, investigational product accountability, and financial disclosures for both trials. Informed consent documents were reviewed for all enrolled subjects in both trials.

A comprehensive review of the source document records was performed for six subjects in the FLAIR study and for four subjects in the ATLAS study, including the primary efficacy endpoint test result, adverse events, and eligibility criteria. The data listings submitted in the NDA were verified by comparison to the data in the source documents for the selected subjects.

No significant deficiencies were identified at the site and no significant inconsistencies between source records and submitted NDA data were identified. No FDA form 483 was issued at the end of the inspection.

Karen Bleich, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation Office of Scientific Investigations

Concurrence:

Aisha Johnson, M.D. Acting Team Leader
Good Clinical Practice Assessment Branch
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Kassa Ayalew, M.D., M.P.H Branch Chief
Good Clinical Practice Assessment Branch
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Office of Scientific Investigations

22. Labeling Summary of Considerations and Key Additional Information

Prescribing Information Labeling Review

Applicant's proposed labels for CABENUVA and VOCABRIA, submitted on April 29, 2019, were compared with final agreed upon labeling for both applications. This review summarizes the major label changes and provides a cross reference to other sections of the integrated review for additional details and rationale for the labeling changes. Most of the changes outlined below apply to both CABENUVA and VOCABRIA. However, the two labels have different levels of detail and different subsection numbers. For this reason, if the change only applies to one label it is noted in the review below.

General Changes to Prescribing Information

- Cross reference to CABENUVA, VOCABRIA or EDURANT labels were added to the USPI to inform the healthcare provider (HCP) to read the other labels for additional detail. This was necessary because VOCABRIA and EDURANT are used as an oral-lead prior to CABENUVA treatment and are also the same components as CABENUVA so there are many sections of the USPI with overlap of information that may be pertinent for the HCP to be aware of but cannot be concisely summarized in all the labels.
- When referencing the other drug's name in the label, both the proprietary and (nonproprietary) names were included the first time the other drugs were mentioned but only the proprietary name of the other drug was included for the rest of the section for ease of review.
- In section 6 of the VOCABRIA USPI [redacted] (b) (4) was included instead of week 48 data with the injectable formulations. Section 14 [redacted] (b) (4) were removed and replaced with cross reference to the CABENUVA USPI. [redacted] (b) (4) [redacted] were not included VOCABRIA label and a cross reference was made to CABENUVA because [redacted] (b) (4) [redacted] and are more appropriate to include in the CABENUVA label.
- Highlights and table of contents for both USPI were updated for consistency with changes in the full prescribing information.

1 INDICATIONS AND USAGE

Indications was modified to add “on a stable antiretroviral regimen with no history of treatment failure” for consistency with other HIV antiretrovirals as well as accurately describe the patient population from FLAIR and ATLAS trials.

2 DOSAGE AND ADMINISTRATION

2.1 Adherence to CABENUVA (CABENUVA USPI)

This subsection was created to alert the HCP to consider careful patient selection due to risk of viral rebound and potential development of resistance in the event of nonadherence and noncompliance to CABENUVA.

2.3 Intramuscular Injection Dosing with CABENUVA (CABENUVA USPI)

Clarification was added to specify the IM injections should be at separate gluteal injection sites “on opposite sides or 2 cm apart.”

While there is no significant effect of food on the PK of CAB, for simplicity and consistency with phase 3 studies, labeling was modified to state that oral CAB and oral RPV should be taken at approximately the same time each day with a meal (subsection 2.1 in VOCABRIA) or should be taken once daily with a meal (subsection 2.3 in CABENUVA).

2.4 Missed Injections (CABENUVA USPI)

Additional information on how to address missed injections for:

- Planned missed injections (oral dosing to replace up to two consecutive monthly injections; and
- Unplanned missed injections were added.

See Section II.5 for additional details.

2.5 Administration Instructions (CABENUVA USPI)

- To ensure needle length is sufficient to reach the gluteus muscle, recommendation to use longer needle, which may not be included in the dosing kit for patients with BMI greater than 30 kg/m^2 was added. See Section II.6.4.4 for additional details.
- Information from section 16 of the USPI on the stability of the vials in the carton at room temperature for up to 6 hours and in a syringe for up to 2 hours was to this section per guidance for industry *Dosage and Administration Section of the Labeling for Human Prescription Drug and Biological Products – Content and Format* (March 2010)[46] to provide storage conditions needed to maintain stability of the product.

3 DOSAGE FORMS AND STRENGTHS (CABENUVA USPI)

Description of the two difference dose kits were changed to include emphasis on the dosage of each component of CABENUVA, 400 mg/600 mg and 600 mg/900 mg instead of the (b) (4)

5 WARNINGS AND PRECAUTIONS

5.2 Post-Injection Reactions (CABENUVA USPI)

This section was created to further describe post injection-related adverse reactions and to provide management recommendation for patients who experience these reactions. See Section II.7.7.4 for additional details.

5.3 Depressive Disorders (VOCABRIA USPI)

This section was created to warn HCP about the risk of depressive disorders associated with VOCABRIA. The phase 2 data for oral CAB showed depressive disorders were related to CAB in the absence of RPV. The following text was added. See Section II.7.6.6 for additional detail.

Depressive disorders (including depressed mood, depression, mood altered, mood swings) have been reported with VOCABRIA *[see Adverse Reactions (6.1)]*. Promptly evaluate patients with depressive symptoms to assess whether the symptoms are related to VOCABRIA and to determine whether the risks of continued therapy outweigh the benefits.

5.6 Long-Acting Properties and Potential Associated Risks with CABENUVA (CABENUVA USPI)

This section was created to warn HCP that residual concentration of CAB+RPV may remain in the systemic circulation of up to 12 months or longer and that careful selection of patients who agree to the required monthly injection dosing schedule is imperative. See Section I.2 for additional detail.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience (CABENUVA USPI)

- Table 3 which list most common adverse reactions from FLAIR and ATLAS trials was divided to include all grades and at least grade 2 for both CAB+RPV arm and for the current antiretroviral regimen arm. See Section II.7.6.5 for additional detail.
- Under *Local Injection Site Reactions* subsection, another subsection entitled "*Other Injection-Associated Adverse Reactions"* was added to highlight an increased incidence of pyrexia (8%) in the CAB+RPV arm in addition to report of musculoskeletal pain and vasovagal reactions reported in CAB+RPV arm. See Section II.7.7.4 for additional detail.
- Less common adverse reactions: See Section II.7.6.5, Table 24 for list of less common adverse reactions. Weight increase is an important risk with certain INSTIs, including with CAB+RPV. See Section II.7.7.5 for additional detail on weight increase.

- Laboratory findings: [redacted] was deleted from laboratory findings. Serum cortisol changes from baseline was added from the EDURANT labeling. See Section II.7.6.7 for details on laboratory findings.

6.2 Postmarketing Experience (CABENUVA USPI)

Nephrotic syndrome was added per consistency with EDURANT (rilpivirine) USPI.

7 DRUG INTERACTIONS

7.3 Potential for Other Drugs to Affect CABENUVA (CABENUVA USPI) and 7.2 Potential for Other Drugs to Affect VOCABRIA (VOCABRIA USPI)

- Due to drug interactions specific to oral cabotegravir and oral rilpivirine and not relevant to the injectables (such as interactions affecting oral absorption), reference to the VOCABRIA and EDURANT labels was added.
- Clinically insignificant drug interaction information from in vitro studies or PBPK modeling was moved to subsection 12.3 of the USPI.

7.4 Established and Other Potentially Significant Drug Interactions (CABENUVA USPI)

Under macrolides or ketolide antibiotics, to clarify the macrolide-RPV interaction consists of both a PK and PD component, the clinical comment was modified to alert HCPs of that macrolides are associated with risk of Torsade de Points. In addition, [redacted] was deleted because [redacted]. See Section II.8.2 for additional detail.

7.5 Drugs without Clinically Significant Interactions (CABENUVA USPI)

Due to the presence of residual concentrations after discontinuation, clarification was added that the listed ARVs lacking interactions with CAB or RPV may be given after discontinuation of CAB or RPV.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary/Clinical Consideration/Data:

- Information on risk of neural tube defects (NTDs) associated with another integrase inhibitors was added. See Section II.7.7.3 for additional detail.
- Long-acting properties of CABENUVA and the potential for prolonged fetal exposure to CABENUVA during pregnancy are highlighted in this section.
- In animal reproduction studies, the delay in onset of parturition and the increase in stillbirths and neonatal deaths in rats was added. In addition, exposure multiples and presentation of data were updated. See Section II.8.4 for additional details.

8.6 Renal Impairment

The following recommendation for patients with ESRD was added: In patients with end-stage renal disease not on dialysis, effects on the PK of CAB or RPV are unknown. As CAB and RPV are greater than 99% protein bound, dialysis is not expected to alter exposures of cabotegravir or rilpivirine. See Section II.8.1.3 for additional details.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

- The table of PK parameters was expanded to include PK parameters after oral administration and after the initial injection.
- Due to uncertainty in measurement of IC_{50} and K_i in vitro, the statement that AUC of OAT1/3 substrates may be increased was added. See Section 14.3.1 for additional details.

12.4 Microbiology

See Section II.7.7.1 for additional detail on labeling changes to microbiology subsection.

Antiviral Activity in Cell Culture

The statement that antiviral activity of RPV was not antagonistic when combined with NNRTIs, NRTIs, PI, CCR5 coreceptor antagonist, or INSTI was added including examples of drugs from each class.

Resistance

Cell Culture: Additional integrase substitutions selected in viruses harboring integrase substitutions associated were added to provide a more complete list of substitutions associated with CAB resistance.

Clinical Trials: Data from phase 2 and 3 clinical trials (207966, LATTE, and LATTE-2) were provided to provide a more thorough list of substitutions associated with CAB resistance and to show that virologic failures in phase 2 trials included subtypes A1, A, B and C.

Association of Subtype A1 and Baseline L74I Substitution in Integrase With Cabotegravir plus Rilpivirine Virologic Failure

This section was added to provide information on the association of subtype A1 and baseline integrase L74I with virologic failure to cabotegravir plus rilpivirine in a clear and logical format.

Cross-Resistance

Provided INSTI substitutions that confer cross-resistance to cabotegravir.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Exposure multiples were added for the 2-year mouse and rat carcinogenicity studies with CAB.

14 CLINICAL STUDIES

14.1 Clinical Trials in Adults

- [redacted] deleted and only efficacy results from individual trials were presented separately. [redacted]
- [redacted] was deleted. See Sections 15.1.15 and 15.2.6.8 for additional detail.

17 PATIENT COUNSELING INFORMATION

- Additional detail on adverse reactions following injections was added with cross reference to Warnings and Precautions (5.2) and Adverse Reactions (6.1). (CABENUVA USPI)
- Drug Interactions: Statement that CABENUVA is an extended-release injectable which may be systemically present for 12 months or longer was added. (CABENUVA USPI)
- Adherence to CABENUVA: this subheader was added with reference to Dosage and Administration (2.1) and Warnings and Precautions (5.6) warning about the importance of adherence to scheduled visit. (CABENUVA USPI)
- Depressive disorder: this subheader was added with reference to Warnings and Precautions (5.6) and Adverse Reactions (6.1) for additional details. (VOCABRIA USPI)

23. Postmarketing Requirements and Commitments

No PMR and commitments will be requested outside of PMR under PREA. Refer to Section II.8.3 for PREA PMRs.

24. Financial Disclosure

Table 242. Covered Clinical Studies: FLAIR, ATLAS

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 164 for the two phase 3 trials		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 12		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 16 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Applicant of covered study: Two phase 3 trials (focus for this form) but the disclosure covers two phase 2 and two phase 3 trials		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 36		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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(b) (4)

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26. Review Team Acknowledgments

Table 243. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Andrew Gentles, PharmD, BCPS AQ-ID
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Table 244. Additional Reviewers of Application

Office or Discipline	Name(s)
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- **CMC ATL(s)**	Erika Englund, PhD David Claffey, PhD
- **Drug Product**	Peter Guerrieri, PhD Balajee Shanmugam, PhD
- **Drug Substance**	Kabir Shahjahan, PhD Haripada Sarker, PhD
- **Environmental Analysis**	Raanan Bloom, PhD Scott Furness, PhD
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VOCABRIA (cabotegravir) Tablets and CABENUVA (cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension)

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OPQ = Office of Pharmaceutical Quality
OMPI = Office of Medical Policy Initiatives
OPDP = Office of Prescription Drug Promotion
DMPP = Division of Medical Policy Programs
PLT = Patient Labeling Team
OSE = Office of Surveillance and Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
OSI = Office of Scientific Investigations
DRISK = Division of Risk Management
DEPI = Division of Epidemiology
CDRH = Center for Devices and Radiologic Health
DAGRID = Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices
COA = Clinical Outcomes Assessment
DNP = Division of Neurology Products

Table 245. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Debra Birnkrant, MD	OA/DAV	Enter sections. ☐ Authored ☒ Approved Section 1 and Section II
Division Director	**Signature:**		
Clinical	Kimberly Struble, PharmD	OA/DAV	Enter sections. ☒ Authored Section I: Executive summary, Benefit-Risk Conclusions ☒ Approved Section II: Interdisciplinary assessment, Appendix 15 and 17
Cross-Disciplinary Team Lead	**Signature: See DARRTS Memo**		
Clinical	Yodit Belew, MD	OA/DAV	Enter sections. ☒ Authored Authored Section I: Benefit-Risk Section II: Section 7 Appendix 17 ☒ Approved Sections II, Appendix 15, 17
Primary Reviewer	**Signature: See DARRTS Memo**		
Pharmacology/Toxicology	Hanan Ghantous, PhD, DABT	OA/DPT-ID	Enter sections. ☐ Authored ☐ Approved
Team Leader	**Signature: See DARRTS Memo**		
Pharmacology/Toxicology	David McMillan, PhD, DABT	OA/DPT-ID	Enter sections. ☒ Authored Sections 7.1 and 13.1 ☐ Approved
Reviewer	**Signature: See DARRTS Memo**		

Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Pharmacology/Toxicology	Ilona Bebenek, PhD, DABT	OA/DPT-ID	Enter sections. ☒ Authored Sections 7.2 and 13.2 ☐ Approved
Reviewer	**Signature: See DARRTS Memo**		
Clinical Virology	Julian O'Rear, PhD	OA/DAV	Enter sections. ☐ Authored ☐ Approved
Team Leader	**Signature: See DARRTS Memo**		
Clinical Virology	Lisa Naeger, PhD	OA/DAV	Enter sections. ☐ Authored ☐ Approved
Reviewer	**Signature: See DARRTS Memo**		
Clinical Virology	Michael Thomson, PhD	OA/DAV	Enter sections. ☐ Authored ☐ Approved
Reviewer	**Signature: See DARRTS Memo**		
Clinical Pharmacology	Vikram Arya, PhD	OCP/DCP4	Enter sections. ☐ Authored ☐ Approved
Team Leader	**Signature: See DARRTS Memo**		
Clinical Pharmacology	Mario Sampson, PhD	OCP/DCP4	Enter sections. ☐ Authored ☐ Approved
Reviewer	**Signature: See DARRTS Memo**		
Statistical	Thamban Valappil, PhD	OB/DBIV	Enter sections. ☐ Authored ☐ Approved
Team Leader	**Signature: See DARRTS Memo**		
Statistical	Hengrui Sun, DrPH	OB/DBIV	Enter sections. ☒ Authored Sections 6.3, 6.4, 6.5, and Appendix 16 ☐ Approved

Discipline and Title or Role	**Reviewer Name**	**Office/Division**	**Sections Authored/ Acknowledged/ Approved[1]**
Reviewer	**Signature: See DARRTS Memo**		
	Andrew Gentles, PharmD, BCPS AQ-ID	OA/DAV	Summary of Regulatory History ☒ Authored ☐ Approved
Project Manager	**Signature:**		

[1] Include "IA" for authors who contributed to the Integrated Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary.

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/s/

ANDREW A GENTLES
12/19/2019 12:02:51 PM

JOHN J FARLEY
12/19/2019 01:21:22 PM
My signature indicates that I have considered the assessments and recommendations expressed by all parties included in this Integrated Review in determining the regulatory action.

KIMBERLY A STRUBLE
12/19/2019 01:23:26 PM