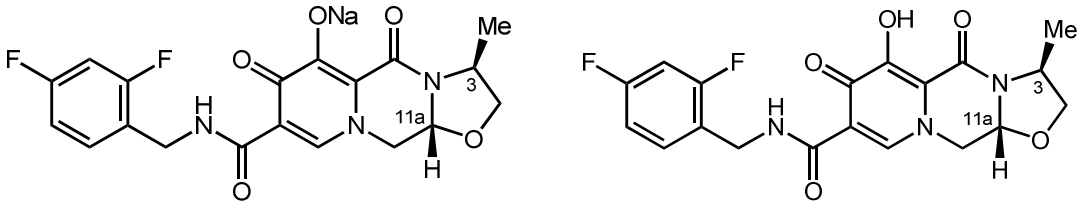
MODULE 2.6.1. INTRODUCTION

1. INTRODUCTION

Cabotegravir (CAB, GSK1265744) is a novel, potent and selective HIV Integrase Strand Transfer Inhibitor (INSTI) being developed by ViiV Healthcare (ViiV) for the treatment and prevention of HIV-1 infection. CAB (see Figure 1.1 below) is being developed for both oral administration (as the sodium salt) and as a long acting (LA) injectable formulation (as the free acid), to be co-administered with rilpivirine.

Figure 1.1 Structure of CAB (sodium salt and free acid)



Sodium salt Free acid

The proposed indication for CAB tablets/CAB injection is for use in combination with RPV for patients with HIV-1 infection who are virologically suppressed (HIV-1 RNA <50 c/mL) and have no known or suspected resistance to either CAB or RPV.

The proposed oral CAB regimen for HIV-1-infected subjects is CAB 30 mg once daily + oral RPV 25 mg once daily for approximately 1 month (at least 28 days) to assess tolerability to CAB and is referred to as Oral Lead In (OLI). LA (long acting) CAB injection is indicated in combination with RPV LA injection for treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 c/mL) without prior treatment failure and have no known or suspected resistance to either CAB or RPV. The dosing regimens for CAB and RPV is shown in Table 1.1 and Table 1.2 below.

Table 1.1 Proposed CAB LA Monthly Dosing Regimen, When Used with RPV

Dosing Schedule	Drug	OLI	Initiation Injection	Continuation Injection
		For 1 Month (at Least 28 Days)	At Month 2	At Month 3 and Onward
Monthly	CAB	30 mg once daily with a meal	3 mL (600 mg)	2 mL (400 mg) monthly
	RPV	25 mg once daily with a meal	3 mL (900 mg)	2 mL (600 mg) monthly

Note: In Clinical Study 201584 and Clinical Study 201585 protocols, the 3 mL injections were referred to as "First Injections (Loading Dose)" and the 2 mL injections were referred to as "Maintenance Injections."

Table 1.2 Proposed CAB LA Every 2 Months Dosing Regimen, When Used with RPV

Dosing Schedule	Drug	OLI	Initiation Injections (1 Month Apart)	Continuation Injections (2 Months Apart)
		For 1 Month (at Least 28 Days)	At Month 2 and Month 3	At Month 5 and Onward
Every 2 months	CAB	30 mg once daily with a meal	3 mL (600 mg)	3 mL (600 mg) every 2 months
	RPV	25 mg once daily with a meal	3 mL (900 mg)	3 mL (900 mg) every 2 months

For therapeutic administration, CAB has been formulated for oral administration at a dose of 30 mg/day tablet (equivalent to 0.6 mg/kg/day for a 50 kg person). For the parenteral formulation, CAB LA was formulated as an injectable suspension containing 200 mg/mL of CAB free acid at a dose 400 mg/month (2 mL for continuation injection) (equivalent to 8.0 mg/kg/month for a 50 kg person). The systemic exposure in HIV-1 infected patients after administration of the maximum recommended therapeutic oral dose of 30 mg/day and following a 400 mg IM monthly dose is shown in Table 1.3. These values are considered the maximum exposure to CAB that is likely to occur in humans during therapy and are used throughout m2.6 as a comparison to the highest exposures achieved in nonclinical species that resulted in no observed adverse effects.

Table 1.3 CAB Exposure Values Following Administration of Proposed CAB + RPV Regimen in HIV-1-infected Subjects used for Comparison to Nonclinical Exposures

Clinical Study Report	Method of Administration	C_{max} (μg/mL)	AUC_{0-t} (μg.h/mL)
2018N384611	Oral Lead-in [a]	8.1	146
2018N384611	Monthly Injection [b]	4.2	2461

Key:
a. Mean exposure (C_{max} and AUC_{0-24}) following CAB 30 mg PO once daily (POPPK analysis).
b. Mean exposure (C_{max} and AUC_{0-t}) month 3 onward following a 400 mg IM monthly dose (POPPK analysis).

Nonclinical studies conducted to support the development of CAB include primary pharmacology studies which demonstrated the inhibition of integrase activity and HIV-1 replication in vitro as well as studies to determine the potential for HIV resistance to develop via mutations. Secondary pharmacologic activity was assessed, and safety pharmacology studies were conducted to investigate any untoward pharmacologic actions of cabotegravir on the respiratory, cardiovascular, central and peripheral nervous systems.

The absorption, distribution, metabolism and excretion of CAB were investigated to characterize the disposition of CAB in the toxicology test species, and a full toxicological evaluation was performed which included the toxicokinetics of CAB.

The CAB clinical route of administration is intended to be both oral and injectable (via IM) for the LA formulation. To support oral administration, CAB was evaluated in repeat dose oral toxicity studies of up to 26 weeks duration in Sprague Dawley rats, 39 weeks duration in cynomolgus monkeys, 13 weeks in CD-1 mice, and 13 days in Dutch-belted rabbits. Reproductive and developmental toxicity studies were conducted using oral administration to Sprague Dawley rats and Dutch-belted rabbits. Genotoxicity, carcinogenicity, and immunotoxicity studies were also conducted as well as skin and ocular irritancy and skin sensitization studies. To support LA administration, subcutaneous (SC) and IM studies of up to 13 weeks duration in the rat were also performed.

All pivotal safety pharmacology and toxicology studies were conducted in an Organisation for Economic and Cooperation and Development (OECD) member country in accordance with the OECD Test Guidelines and the Principles of Good Laboratory Practice (GLP). Investigations undertaken to establish suitable doses for use in the toxicity and pharmacokinetic studies were performed in accordance with the general principles of GLP.

The impurity profile of the batches of test material used in the definitive investigations was consistent with that used in the clinical evaluation of CAB and that proposed for use in CAB 30 mg tablets and 400 mg IM injection formulation. Tables detailing the batches

of CAB used in safety studies, together with information on the methods of formulation, are presented in the Written Summaries [m2.6.2 and m2.6.6].

A full description of the pharmacology, pharmacokinetics and toxicology studies using CAB is provided in proceeding sections [m2.6.2 to m2.6.7]. The corresponding company reports are located in m4.2, Study Reports.

MODULE 2.6.2. PHARMACOLOGY WRITTEN SUMMARY

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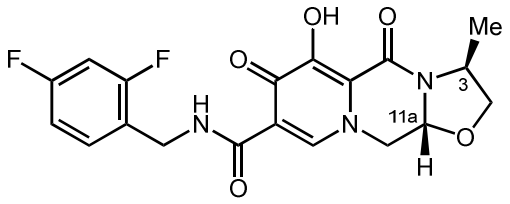
1. BRIEF SUMMARY

Cabotegravir (also referred to as GSK1265744, or simply as CAB) is a potent integrase strand transfer inhibitor (INSTI) which inhibits the integrase catalyzed viral DNA strand transfer. It has been developed as a sterile long-acting parenteral (LAP) suspension formulation intended for intramuscular (IM) or subcutaneous (SC) administrations, and as an oral formulation for the treatment of human immunodeficiency virus-1 (HIV-1) infection.

A range of in vitro investigations has been conducted to characterize the primary pharmacology (virology) of CAB with respect to the treatment of HIV [see m2.7.2.4 for a study list and full discussion of these studies]. In vitro secondary pharmacology studies using CAB have been conducted, and a battery of safety pharmacology studies has also been performed using the in vitro hERG assay and in vivo oral studies in Sprague Dawley rats and cynomolgus monkeys. For reference, the chemical structure of CAB free acid is shown in Figure 1.1.

Figure 1.1 Structure of CAB



In study reports, the parent form of CAB was designated as GSK1265744A, and the sodium salt was designated as GSK1265744B. However, for clarity and consistency, these compounds are referred to simply as CAB throughout this sectional summary. The specific salt form of CAB used in each study is denoted in Table 3.1 and Table 4.1. The sodium salt is the form proposed for oral administration by tablets in humans, and the free acid is proposed for the long acting parenteral formulation use in humans. All doses and concentrations (including analyte concentrations in plasma) are expressed in terms of the parent compound, referred to as CAB throughout m2.6.

The secondary pharmacology studies described in this section were conducted in accordance with accepted practice and in general agreement with the principles of Good Laboratory Practice (GLP). All pivotal safety pharmacology and toxicology studies were conducted in an Organisation for Economic and Cooperation and Development (OECD) member country in accordance with the OECD Test Guidelines and the Principles of Good Laboratory Practice (GLP).

A listing of each of the pharmacology studies conducted with CAB, together with the location of the reports within Module 4 and their GLP status, is provided in Table 3.1 and Table 4.1. Tabulations of the safety pharmacology studies are provided in m2.6.3. Studies that were undertaken with CAB but are not included in this submission are addressed in Appendix 1.

The impurity profiles of the drug substance batches used in the nonclinical safety pharmacology studies [see m2.6.7, Table 4.1] were comparable to the impurity profile of the material used in clinical investigations and that proposed for use in the marketed product. Drug substance batch numbers and details of the formulations used in the safety pharmacology studies are presented in Table 4.2.

A summary of the findings from the secondary pharmacodynamics and safety pharmacology studies conducted with CAB is provided below. In Sections 2 to 5, a discussion of the design and findings from these studies is presented. An overall assessment of the findings from the pharmacological investigations is provided in Section 6, Discussion and Conclusion.

Secondary pharmacodynamics

- In a panel of 93 enzymes, receptors, ion channels, transporters and isolated tissue assays to evaluate the potential for CAB-related off-target activity, the only significant activity (>50% binding inhibition) noted was at the melanocortin (MC4) receptor (53% binding inhibition at 10 μM).

Safety pharmacology

- In conscious telemetered male monkeys, CAB at 1000 mg/kg (C_{max} of 67 μg/mL; AUC_{0-24} 1051 μg.h/mL) produced a mild, transient increase in mean arterial pressure (3.7 to 8.6%) and a transient increase in heart rate (16 to 23%) during the first 2 hours after dosing.

Pharmacodynamic drug interactions

- No specific nonclinical pharmacodynamic drug interaction studies have been conducted for CAB [see m2.7.2.4 for studies in which CAB was tested with other drugs].

2. VIROLOGY (PRIMARY PHARMACODYNAMICS)

A range of in vitro studies has been conducted to investigate the virology (primary pharmacodynamics) of CAB. A study list and full discussion of these studies are provided within Clinical Pharmacology, Other Studies, m2.7.2.4. A brief overview of these studies is presented below.

CAB is a potent in vitro inhibitor of HIV integrase and inhibits the integrase catalyzed viral DNA strand transfer with IC_{50} values in the nanomolar range (3.0 to 13 nM). CAB is a potent antiviral agent when tested in a variety of in vitro assays against the HIV-1 strains Ba-L and NL432 in human peripheral bone marrow cells (PBMC; IC_{50} = 0.22 and 0.53 nM, respectively), and against the HIV-1 strain IIIB in MT-4 cells (IC_{50} = 0.57 and 2.1 nM, respectively) and in the PHIV assay (IC_{50} = 0.74 nM). Additionally, the IC_{50} values of CAB for viral replication of National Institute of Health (NIH) reference strains consisting of 24 strains of HIV-1 and 4 strains of HIV-2 in PBMC assays and for 3 HIV-1 strains in monocyte-derived macrophage assays were also in the low nanomolar concentration range, like that seen with HIV-1 strains Ba-L and NL432. In vitro studies suggested an approximate average of 408-fold shift in IC_{50} of CAB in the presence of 100% human serum (by method of extrapolation), and the PA-IC_{50} was estimated to be 102 nM in HIV-1 IIIB infected MT4 cells. In vitro cytotoxicity studies provided a selectivity index of ≥10,000 for CAB compared with the HIV-1 antiviral potency in PBMCs. In a viral integrase susceptibility assay using the integrase coding region from 13 clinically diverse subtype B isolates, CAB demonstrated antiviral potency like that observed for laboratory strains, with a mean IC_{50} of 1.3 nM.

CAB showed anti-HIV activity (susceptibility) equivalent to wild type virus (fold change [FC] <5) against 22 of 25 INI-resistant mutant viruses with single mutations. Of the 17 INI-resistant mutant viruses with 2 or more mutations, 8 showed susceptibility to CAB (FC<5). Exposure of MT-2 cells infected with HIV-1 IIIB to CAB for up to 112 days did not produce any highly resistant mutants (>10-fold increase in IC_{50}). No amino acid substitutions in the integrase region were selected when passaging the wild type HIV-1 NL-432 in the presence of 6.4 nM CAB through 56 days.

3. SECONDARY PHARMACODYNAMICS

Studies were performed with CAB to investigate potential off-target activity of dolutegravir against a broad panel of proteins, and to determine the potential effects on a variety of isolated tissues in functional activity assessments. A listing of the studies undertaken, and the location of the company reports within this application, is presented in Table 3.1.

3.1. In Vitro Studies

3.1.1. Radioligand binding and enzyme assays

The secondary pharmacology potential of CAB was evaluated for possible interactions with 16 enzyme assays and 65 physiological receptors, ion channels and transporter binding sites [Report RH2007/00209, m4.2.1.2].

CAB at 10 μM did not significantly affect (defined as ≥50%) 80 of the 81 in vitro assays. The only effect greater than 50% was a 53% inhibition of binding in the melanocortin 4 (MC4) receptor binding assay.

3.1.2. Functional tissue assays

The secondary pharmacology potential of CAB was also evaluated for possible interactions in 12 isolated tissue assays [Report RH2007/00209, m4.2.1.2].

CAB at up to 100 μM did not significantly affect any of the 12 tissue assays.

Table 3.1 List of Secondary Pharmacodynamic Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Selectivity profile: In vitro profiling against a panel of receptors, channels and enzymes	Receptors, ion channels, transporters and enzymes	In vitro	A	No	[redacted]	RH2007/00209	m4.2.1.2
In vitro isolated tissue assay	Isolated tissues	In vitro	A	No	[redacted]	RH2007/00209	m4.2.1.2

Key:
A = GSK1265744A, the parent form.

Testing Facility:
[redacted] = [redacted] - Taiwan [redacted].

Note: Early screening assays undertaken to identify pharmacological targets of opportunity, and internal update/status reports, have not been included in this listing. However, this information has been reviewed within GSK and is considered to have no bearing on safety.

4. SAFETY PHARMACOLOGY

A battery of safety pharmacology studies has been performed including an in vitro hERG study and in vivo studies in Sprague Dawley rats and cynomolgus monkeys following oral administration. A list of these studies, together with their report locations within this submission, is presented in Table 4.1. The tabulated summaries for the safety pharmacology studies are presented in m2.6.3, Pharmacology Tabulated Summary, of this submission.

All safety pharmacology studies were conducted with the sodium salt of CAB except for the neurobehavioral study in which the parent was administered. In the in vivo studies in rats and monkeys, CAB was administered by oral gavage in a formulation comprising aqueous 0.5% w/w hydroxypropylmethylcellulose (HPMC) in 0.1% w/w Tween 80. A list of the batches of CAB used in each of the safety pharmacology studies is shown in Table 4.2.

Table 4.1 List of Safety Pharmacology Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Neurobehavioral study[a]	Rat (Sprague Dawley)	5M	Oral (gavage)	A	30, 100, 300	5 days	Yes	GSK	RD2006/01741 (R41937)	m4.2.3.2
Respiratory study	Rat (Sprague Dawley)	4M[b]	Oral (gavage)	B	30, 100, 300	Single	Yes	GSK	CD2007/00268 (G07103)	m4.2.1.3
hERG assay	HEK293 cells	NA	In vitro	B	5.28, 17.6 μM	NA	Yes	GSK	FD2007/00242 (V27748)	m4.2.1.3
Cardiovascular function	Monkey (cynomolgus)	4M[b]	Oral	B	8, 25, 1000	Single	Yes	GSK	CD2007/00707 (G07232)	m4.2.1.3

Key:
a = Neurobehavioral assessments were performed as part of the 14 day toxicity study in rats on Day 5.
b = Latin square crossover dosing design.
HEK293 = Transformed human embryonic kidney cells.
A = GSK1265744A, the parent form.
B = GSK1265744B, the sodium salt.

Testing Facility:
GSK = GlaxoSmithKline

4.1. Overt Central and Peripheral Effects

4.1.1. Rat

As part of the rat 14-day oral toxicity study (see m2.6.6, Section 3.3.1.1), the first 5 male rats from each dosing group given 30, 100 or 300 mg/kg CAB were assessed for effects on neurobehavioral function (functional observational battery), reflecting central and peripheral nervous system activity [Report RD2006/01741, m4.2.3.2]. A tabulated summary of this study and noteworthy findings is presented in m2.6.3, Table 4.1.

No effects occurred throughout the assessment interval of up to 25 hours following dosing on Day 5. Systemic exposure (C_{max} and AUC_{0-24}) in male rats given a single oral dose of 300 mg/kg was 35.8 μg/mL and 708 μg.h/mL, respectively (Day 1 systemic exposure).

4.2. Actions on Respiratory System

4.2.1. Rat

Single oral doses of CAB at 30, 100 or 300 mg/kg were administered to male rats (n=4; Latin square crossover design with 7 days between doses) [Report CD2007/00268, m4.2.1.3]. CAB was prepared in a vehicle of 0.5% (w/w) HPMC with 0.1% (w/w) Tween™ 80 in purified water. Ventilatory function (tidal volume, respiratory rate and minute volume), a measure of airway resistance (total pulmonary resistance) and body temperature were monitored for up to 7 days after dosing in conscious rats. A tabulated summary of this study and noteworthy findings is presented in m2.6.3, Table 4.1.

CAB did not produce any effect on respiratory functional parameters (respiratory rate, tidal volume, minute volume, pulmonary resistance) or body temperature when monitored throughout the day of dosing and up to 7 days after dosing. A dose of 300 mg/kg was associated with a mean C_{max} and AUC_{0-24} of 35.8 μg/mL and 708 μg.h/mL, respectively (Day 1 systemic exposure data in males from the rat 14-day oral toxicity study, m2.6.6, Section 3.3.1.1).

4.3. Actions on Cardiovascular System

4.3.1. In vitro

4.3.1.1. hERG assay

The effect of CAB at concentrations of 5.28 μM and the maximum soluble concentration of 17.61 μM (2.14 and 7.14 μg/mL, respectively) on hERG tail current was studied in HEK-293 cells which had been stably transfected with hERG cDNA [Report FD2007/00242, m4.2.1.3]. A tabulated summary of this study and noteworthy findings is presented in m2.6.3, Table 4.1.

No difference from vehicle was seen at either concentration of CAB, indicating that there was no effect on hERG channel tail current.

4.3.2. In vivo

4.3.2.1. Monkey

In a cardiovascular study in conscious, non-restrained male monkeys (n = 4, Latin square crossover design with 7 days between doses), single oral doses of CAB were administered at either 8, 25, or 1000 mg/kg [Report CD2007/00707, m4.2.1.3]. Arterial pressures, heart rate, body temperature and electrocardiographic intervals and waveforms were monitored for up to 76 hours after dosing. A tabulated summary of this study and noteworthy findings is presented in m2.6.3, Table 4.1.

At 1000 mg/kg, CAB produced a mild, transient increase in mean arterial pressure (3.7 to 8.6%) and a transient increase in heart rate (16 to 23%) during the first 2 hours after dosing. No ECG waveform or interval changes were associated with these pressure and heart rate changes and no effects occurred at doses of 8 and 25 mg/kg (mean C_{max} of 20.8 µg/mL and AUC_{0-24} of 233 µg.h/mL at 25 mg/kg from Day 1 systemic exposure data in male monkeys used in the 14-day oral toxicity study). In addition, following repeat dosing in male and female monkeys at the same doses in a 14-day toxicity study, CAB produced no effects on ECG tracings (see m2.6.6, Section 3.4.1.2).

A dose of 1000 mg/kg was associated with an exposure of C_{max} 67.0 µg/mL and AUC_{0-24} of 1051 µg.h/mL (Day 1 systemic exposure data in males in the monkey 14-day oral toxicity study).

Table 4.2 Batch Numbers of CAB and Formulations Used in Safety Pharmacology Studies

Study Type	Report No. (Study No.)	Species or Assay	Duration of Dosing	Salt Form	Batch or Lot Number(s)	Formulation	Concentration (mg/mL)
Neurobehavioral assessments	RD2006/01741 (R41937)	Rat	Single	A	[redacted]	1	3, 10, 30
Single dose respiratory study	CD2007/00268 (G07103)	Rat	Single	B	[redacted]	1	3, 10, 30
hERG assay	FD2007/00242 (V27748)	HEK293 cells	NA	B	[redacted]	2	2.142 and 7.14 μg/mL (5.283, 17.61 μM)
Single dose cardiovascular study	CD2007/00707 (G07232)	Monkey	Single	B	[redacted]	1	1, 3.125, 125

Key:
A = GSK1265744A, the parent form.
B = GSK1265744B, the sodium salt.
HEK293 = Human embryonic kidney cells.

Formulation Code:
1 = Aqueous 5% w/w hydroxypropylmethylcellulose with 0.1% w/w Tween™ 80.
2 = Dimethylsulfoxide (DMSO).

5. PHARMACODYNAMIC DRUG INTERACTIONS

Studies conducted with CAB in combination with other antivirals are summarized in m2.7.2.4, Special Studies. Various in vitro assays have demonstrated CAB is a highly specific and selective HIV-1 integrase inhibitor. CAB, tested in 16 enzyme assays, 65 physiological receptors, ion channel and transporter binding assays, and 12 isolated tissue assays, did not show any significant activity at any of the pharmacological targets, with the exception of a significant in vitro receptor binding inhibition at the MC4 receptor. However, no significant dose-related effects occurred on body weight and food consumption in the rat study (up to 26 weeks) and monkey study (up to 39 weeks), indicating the lack of apparent biological activity at the MC4 receptor.

Based on the data available for CAB, the potential for pharmacodynamic drug interactions is unlikely.

6. DISCUSSION AND CONCLUSION

CAB is a potent and selective in vitro inhibitor of HIV INSTI and inhibits the integrase catalyzed viral DNA strand transfer [see Clinical m2.7.2.4].

The secondary pharmacology potential of CAB was evaluated for possible interactions with 16 enzyme assays and 65 physiological receptor and ion channel and transporter binding sites and 12 isolated tissue assays. CAB at 10 μM did not significantly affect (defined as ≥50%) 80 of the 81 in vitro assays, and at up to 100 μM did not significantly affect any of the 12 tissue assays. The only effect greater than 50% was a 53% inhibition of binding in the melanocortin (MC4) receptor binding assay. No dose-related significant effects occurred on body weight and food consumption in the repeat dose toxicity studies in the rat (up to 26 weeks) and monkey (up to 39 weeks), indicating the lack of apparent biological activity at the MC4 receptor.

In conscious telemetered male monkeys, a CAB dose of 1000 mg/kg (C_{max} of 67 μg/mL; AUC_{0-24} 1051 μg.h/mL) produced a mild, transient increase in mean arterial pressure (3.7 to 8.6%) and a transient increase in heart rate (16 to 23%) during the first 2 hours after dosing. No ECG waveform or interval changes were associated with these pressure and heart rate changes and no effects occurred at doses of 8 and 25 mg/kg (C_{max} 20.8 μg/mL; AUC_{0-24} 233 μg.h/mL). In addition, no ECG changes occurred in male or female monkeys given up to 1000 mg/kg/day for at least 14 consecutive days. CAB at 7.14 μg/mL (the maximum concentration limited by solubility), also equivalent to 17.61 μM, caused no inhibition of hERG channel tail current in HEK-293 cells stably transfected with hERG cDNA, indicating a low probability for interaction at the hERG channel.

No respiratory effects occurred in conscious telemetered male rats in safety pharmacology studies at doses up to 300 mg/kg (C_{max} of 35.8 μg/mL; AUC_{0-24} 708 μg.h/mL). No neurobehavioral effects occurred in male rats on Day 5 of the 14 day oral toxicity study at doses up to 300 mg/kg (C_{max} of 35.8 μg/mL; AUC_{0-24} 708 μg.h/mL).

In summary, the results from primary, secondary, and safety pharmacology studies support the use of CAB for both oral and parenteral administration to patients in accordance with the proposed indication.

APPENDIX 1. ADDITIONAL INFORMATION

Early screening assays undertaken to identify pharmacological targets of opportunity, and internal/status company reports, have not been provided in this sectional summary. However, this information has been reviewed by the Sponsor and is considered to have no bearing on safety.

MODULE 2.6.3. PHARMACOLOGY TABULATED SUMMARY

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1. PHARMACOLOGY: OVERVIEW FOR CAB

The reports for virology studies (assessing primary pharmacodynamics) are in Module 5.3.5.4 together with the clinical virology reports.

Table 1.1 List of Secondary Pharmacodynamic Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Selectivity profile: In vitro profiling against a panel of receptors, channels and enzymes	Receptors, ion channels, transporters and enzymes	In vitro	A	No	[redacted]	RH2007/00209	m4.2.1.2
In vitro isolated tissue assay	Isolated tissues	In vitro	A	No	[redacted]	RH2007/00209	m4.2.1.2

Key:
A = GSK1265744A, the free acid.

Testing Facility:
[redacted] = [redacted] - Taiwan [redacted].

Note: Early screening assays undertaken to identify pharmacological targets of opportunity, and internal update/status reports, have not been included in this listing. However, this information has been reviewed within GSK and is considered to have no bearing on safety.

Table 1.2 List of Safety Pharmacology Studies Performed with CAB

Type of Study	Species (Strain)/ Test System	No./Sex/ Group	Method of Administration	Form	Dose (mg/kg) or Concentration	Duration of Dosing	GLP	Testing Facility	Report No. (Study No.)	Location in CTD
Neurobehavioral study[a]	Rat (Sprague Dawley)	5M	Oral (gavage)	A	30, 100, 300	5 days	Yes	GSK	RD2006/01741 (R41937)	m4.2.3.2
Respiratory study	Rat (Sprague Dawley)	4M[b]	Oral (gavage)	B	30, 100, 300	Single	Yes	GSK	CD2007/00268 (G07103)	m4.2.1.3
hERG assay	HEK293 cells	NA	In vitro	B	5.28, 17.6 μM	NA	Yes	GSK	FD2007/00242 (V27748)	m4.2.1.3
Cardiovascular function	Monkey (cynomolgus)	4M[b]	Oral	B	8, 25, 1000	Single	Yes	GSK	CD2007/00707 (G07232)	m4.2.1.3

Key:
a = Neurobehavioral assessments were performed as part of the 14 day toxicity study in rats on Day 5.
b = Latin square crossover dosing design.
HEK293 = Transformed human embryonic kidney cells.
A = GSK1265744A, the parent form.
B = GSK1265744B, the sodium salt.

Testing Facility:
GSK = GlaxoSmithKline

2. VIROLOGY (PRIMARY PHARMACODYNAMICS)

Not applicable.

3. SECONDARY PHARMACODYNAMICS

Not applicable.

4. SAFETY PHARMACOLOGY

Table 4.1 Safety Pharmacology Studies with CAB

Organ Systems Evaluated	Species (Strain)	Method of Admin.	Doses[a] (mg/kg)	No. Per Sex Per Group	Noteworthy Findings	GLP Compliant	Report No. (Study No.)
Neurobehavioral study	Rat (Sprague Dawley)	Oral (gavage)	30, 100, 300 for 5 days	5M	None.	Yes	RD2006/01741 (R41937)
Single dose respiratory study	Rat (Sprague Dawley)	Oral (gavage)	30, 100, 300	4M	None.	Yes	CD2007/00268 (G07103)
hERG assay	HEK-293 cells	In vitro	5.28, 17.6 μM	NA	None.	Yes	FD2007/00242 (V27748)
Single dose cardiovascular study	Monkey (cynomolgus)	Oral (gavage)	8, 25, 1000	4M	A dose of 1000 mg/kg produced a mild, transient increase in mean arterial pressure (3.7 to 8.6%) and a transient increase in heart rate (16 to 23%) during the first 2 hours after dosing. No ECG waveform or interval changes were associated with these pressure and heart rate changes and no effects occurred at doses of 8 and 25 mg/kg.	Yes	CD2007/00707 (G07232)

Key:
a = Single dose unless specified otherwise.

5. PHARMACODYNAMIC DRUG INTERACTIONS

Not applicable.