

1. NAME OF THE MEDICINAL PRODUCT

Vocabria Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains cabotegravir sodium equivalent to 30 mg cabotegravir.

Excipient with known effect

Each film-coated tablet contains 155 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White, oval, film-coated tablets (approximately 8.0 mm by 14.3 mm), debossed with 'SV CTV' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vocabria tablets are indicated in combination with rilpivirine tablets for the 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 antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class (see sections 4.2, 4.4 and 5.1) for:

- oral lead-in to assess tolerability of Vocabria and rilpivirine prior to administration of long acting cabotegravir injection plus long acting rilpivirine injection.
- oral therapy for adults who will miss planned dosing with cabotegravir injection plus rilpivirine injection.

4.2 Posology and method of administration

Vocabria should be prescribed by physicians experienced in the management of HIV infection.

Vocabria tablets are indicated for the short-term treatment of HIV in combination with rilpivirine tablets, therefore, the prescribing information for rilpivirine tablets should be consulted for recommended dosing.

Prior to starting Vocabria, healthcare professionals should carefully select patients who agree to the required monthly injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses (see section 4.4).

Posology

Adults

Oral lead in

Prior to the initiation of cabotegravir injection, Vocabria tablets together with rilpivirine tablets should be taken for approximately one month (at least 28 days) to assess tolerability to cabotegravir and rilpivirine (see section 4.4). One Vocabria 30 mg tablet should be taken with one rilpivirine 25 mg tablet, once daily.

Table 1 Recommended Dosing Schedule in Adult Patients

	ORAL LEAD-IN
Medicinal Product	During month 1
Vocabria	30 mg once daily
Rilpivirine	25 mg once daily

Oral dosing for missed injections of cabotegravir

If a patient plans to miss a scheduled injection visit by more than 7 days, oral therapy (one Vocabria 30 mg tablet and one rilpivirine 25 mg tablet once daily) may be used to replace up to 2 consecutive monthly injection visits or one, every 2 month injection visit. For oral therapy durations greater than two months, an alternative oral regimen is recommended.

The first dose of oral therapy should be taken one month (+/- 7 days) after the last injection doses of cabotegravir and rilpivirine for patients being given monthly injections. For patients being given every 2-month injections, the first dose of oral therapy should be taken 2 months (+/- 7 days) after the last injection doses of cabotegravir and rilpivirine. Injection dosing should be resumed on the day oral dosing completes.

Missed doses

If the patient misses a dose of Vocabria tablets, the patient should take the missed dose as soon as possible, providing the next dose is not due within 12 hours. If the next dose is due within 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

If a patient vomits within 4 hours of taking Vocabria tablets, another Vocabria tablet should be taken. If a patient vomits more than 4 hours after taking Vocabria tablets, the patient does not need to take another dose of Vocabria until the next regular scheduled dose.

Elderly

No dose adjustment is required in elderly patients. There are limited data available on the use of cabotegravir in patients aged 65 years and over (see section 5.2).

Renal impairment

No dosage adjustment is required in patients with mild to severe renal impairment (CrCL <30 mL/min and not on dialysis [see section 5.2]). Cabotegravir has not been studied in patients with end-stage renal disease on renal replacement therapy. As cabotegravir is greater than 99% protein bound, dialysis is not expected to alter exposures of cabotegravir. If administered in a patient on renal replacement therapy, cabotegravir should be used with caution.

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). Cabotegravir has not been studied in patients with severe hepatic impairment (Child-Pugh score C [see section 5.2]).

If administered in a patient with severe hepatic impairment, cabotegravir should be used with caution.

Paediatric population

The safety and efficacy of Vocabria in children and adolescents aged under 18 years have not been established. No data is available.

Method of administration

Oral use.

Vocabria tablets may be taken with or without food. When taken at the same time as rilpivirine tablets, Vocabria tablets should be taken with a meal.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use with rifampicin, rifapentine, carbamazepine, oxcarbazepine, phenytoin or phenobarbital (see section 4.5).

4.4 Special warnings and precautions for use

Baseline factors associated with virological failure

Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥ 30 kg/m². Available data suggest that virologic failure occurs more often when these patients are treated according to the every 2 month dosing regimen as compared to the monthly dosing regimen. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI ≥ 30 kg/m² or HIV-1 A6/A1 subtype (see section 5.1).

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with integrase inhibitors including cabotegravir. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Vocabria and other suspected medicinal products should be discontinued immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated. (See sections 4.2 and 5.1).

Hepatotoxicity

Hepatotoxicity has been reported in a limited number of patients receiving Vocabria with or without known pre-existing hepatic disease (see section 4.8). Administration of cabotegravir oral lead-in was used in clinical studies to help identify patients who may be at risk of hepatotoxicity.

Monitoring of liver chemistries is recommended and treatment with Vocabria should be discontinued if hepatotoxicity is suspected.

HBV/HCV co-infection

Patients with hepatitis B co-infection were excluded from studies with Vocabria. It is not recommended to initiate Vocabria in patients with hepatitis B co-infection. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus.

Limited data is available in patients with hepatitis C co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection

Interactions with medicinal products

Caution should be given to prescribing Vocabria tablets with medicinal products that may reduce its exposure (see section 4.5).

Polyvalent cation containing antacids are recommended to be taken at least 2 hours before and 4 hours after taking Vocabria tablets (see section 4.5).

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated, and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

Patients should be advised that Vocabria or any other antiretroviral therapy do not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Vocabria tablets, in combination with rilpivirine tablets, are indicated for the treatment of HIV-1, therefore, the prescribing information for rilpivirine tablets should be consulted for associated interactions.

Effect of other agents on the pharmacokinetics of cabotegravir

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 and to a lesser extent by UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9

are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy (see section 4.3 and table 2 below). In poor metabolizers of UGT1A1, representing a maximum clinical UGT1A1 inhibition, the mean AUC, C_{max} and C_{tau} of oral cabotegravir increased by up to 1.5-fold. The impact of an UGT1A1 inhibitor may be slightly more pronounced, however, considering the safety margins of cabotegravir, this increase is not expected to be clinically relevant. No dosing adjustments for Vocabria are, therefore, recommended in the presence of UGT1A1 inhibitors (e.g. atazanavir, erlotinib, sorafenib).

Cabotegravir is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), however, because of its high permeability, no alteration in absorption is expected when co-administered with either P-gp or BCRP inhibitors.

Effect of cabotegravir on the pharmacokinetics of other medicinal products

In vivo, cabotegravir did not have an effect on midazolam, a cytochrome P450 (CYP) 3A4 probe. *In vitro*, cabotegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

In vitro, cabotegravir inhibited the organic anion transporters (OAT) 1 (IC₅₀=0.81 µM) and OAT3 (IC₅₀=0.41 µM). Therefore, caution is advised when co-dosing with narrow therapeutic index OAT1/3 substrate drugs (e.g. methotrexate).

Based on the *in vitro* and clinical drug interaction profile, cabotegravir is not expected to alter concentrations of other anti-retroviral medications including protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, entry inhibitors and ibalizumab.

The drug interaction data provided in Table 2 is obtained from studies with oral cabotegravir (increase is indicated as “↑”, decrease as “↓”, no change as “↔”, area under the concentration versus time curve as “AUC”, maximum observed concentration as “C_{max}”, concentration at end of dosing interval as “C_τ”).

Table 2 Drug Interactions

Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
<i>HIV-1 Antiviral medicinal products</i>		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C _{max} ↑ 4% C _τ ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dose adjustment of Vocabria tablets is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	Cabotegravir ↔ AUC ↑ 12% C _{max} ↑ 5% C _τ ↑ 14% Rilpivirine ↔ AUC ↓ 1% C _{max} ↓ 4% C _τ ↓ 8%	Rilpivirine did not significantly change cabotegravir plasma concentration. No dose adjustment of Vocabria tablets is necessary when co-administered with rilpivirine.
<i>Anticonvulsants</i>		
Carbamazepine Oxcarbazepine	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated (see section 4.3).

Phenytoin Phenobarbital		
<i>Antacids</i>		
Antacids (e.g. magnesium, aluminium, or calcium)	Cabotegravir ↓	Co-administration of antacid supplements has the potential to decrease oral cabotegravir absorption and has not been studied. Antacid products containing polyvalent cations are recommended to be administered at least 2 hours before or 4 hours after oral Vocabria (see section 4.4).
<i>Antimycobacterials</i>		
Rifampicin	Cabotegravir ↓ AUC ↓ 59% C _{max} ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration which is likely to result in loss of therapeutic effect. Dosing recommendations for co-administration of Vocabria with rifampicin have not been established and co-administration of Vocabria with rifampicin is contraindicated (see section 4.3).
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated (see section 4.3).
Rifabutin	Cabotegravir ↓ AUC ↓ 21% C _{max} ↓ 17% C _τ ↓ 8%	Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required. Prior to initiation of oral cabotegravir therapy, the prescribing information for cabotegravir injection should be consulted regarding concomitant use with rifabutin.
<i>Oral Contraceptives</i>		
Ethinyl estradiol (EE) and Levonorgestrel (LNG)	EE ↔ AUC ↑ 2% C _{max} ↓ 8% C _τ ↔ 0% LNG ↔ AUC ↑ 12% C _{max} ↑ 5% C _τ ↑ 7%	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with Vocabria tablets.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are a limited amount of data from the use of cabotegravir in pregnant women. The effect of Vocabria on human pregnancy is unknown.

Cabotegravir was not teratogenic when studied in pregnant rats and rabbits but, exposures higher than the therapeutic dose showed reproductive toxicity in animals (see section 5.3). The relevance to human pregnancy is unknown.

Vocabria tablets are not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus.

Breast-feeding

It is expected that cabotegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans.

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

There are no data on the effects of cabotegravir on human male or female fertility. Animal studies indicate no effects of cabotegravir on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that dizziness, fatigue and somnolence has been reported during treatment with Vocabria. The clinical status of the patient and the adverse reaction profile of Vocabria should be borne in mind when considering the patient's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction (ARs) from monthly dosing studies were headache (up to 12%) and pyrexia⁴ (10%).

The most frequently reported ARs, considered by the investigator as causally related, from ATLAS-2M every 2 month dosing were headache (7%) and pyrexia⁴ (7%).

Tabulated list of adverse reactions

The ARs identified for cabotegravir and rilpivirine are listed in Table 3 by body system organ class and frequency. Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ to $< 1/1\ 000$), very rare ($< 1/10\ 000$).

Table 3 Tabulated summary of adverse reactions¹

MedDRA System Organ Class (SOC)	Frequency Category	ARs for Vocabria + rilpivirine regimen
Immune system disorders	Uncommon	Type I hypersensitivity*
Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
	Uncommon	Suicide attempt; Suicidal ideation (particularly in patients with a pre-existing history of psychiatric illness)
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence

Gastrointestinal disorders	Common	Nausea Vomiting Abdominal pain ² Flatulence Diarrhoea
Hepatobiliary Disorders	Uncommon	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash ³
	Uncommon	Urticaria* Angioedema*
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Pyrexia ⁴
	Common	Fatigue Asthenia Malaise
Investigations	Common	Weight increased
	Uncommon	Transaminase increased Blood bilirubin increased

¹ The frequency of the identified ARs are based on all reported occurrences of the events and are not limited to those considered at least possibly related by the investigator.

² Abdominal pain includes the following grouped MedDRA preferred term: upper abdominal pain.

³ Rash includes the following grouped MedDRA preferred terms: rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic.

⁴ Pyrexia includes the following grouped MedDRA preferred terms: feeling hot, body temperature increased. The majority of pyrexia events were reported within one week of injections.

* Please refer to section 4.4

Description of selected adverse reactions

Weight increased

At the Week 48 time point, subjects in studies FLAIR and ATLAS, who received Vocabria plus rilpivirine gained a median of 1.5 kg in weight; subjects continuing on their current antiretroviral therapy (CAR) gained a median of 1.0 kg (pooled analysis). In the individual studies FLAIR and ATLAS, the median weight gains in the Vocabria plus rilpivirine arms were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR arms.

At the 48 week timepoint, in ATLAS-2M the median weight gain in both the monthly and 2-monthly Vocabria plus rilpivirine dosing arms was 1.0 kg.

Changes in laboratory chemistries

Small, non-progressive increases in total bilirubin (without clinical jaundice) were observed with treatment with Vocabria plus rilpivirine. These changes are not considered clinically relevant as they likely reflect competition between cabotegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1).

Elevated transaminases (ALT/AST) were observed in subjects receiving Vocabria plus rilpivirine during clinical studies. These elevations were primarily attributed to acute viral hepatitis. A few subjects on oral therapy had transaminase elevations attributed to suspected drug-related hepatotoxicity; these changes were reversible upon discontinuation of treatment (see section 4.4).

Elevated lipases were observed during clinical trials with Vocabria plus rilpivirine; Grade 3 and 4 lipase increases occurred at a higher incidence with Vocabria plus rilpivirine compared with CAR. These elevations were generally asymptomatic and did not lead to Vocabria plus rilpivirine discontinuation. One case of fatal pancreatitis with Grade 4 lipase and confounding factors (including history of pancreatitis) has been reported in study ATLAS-2M, for which causality to the injection regimen could not be ruled out.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

Additionally, you should also report to GSK Israel (il.safety@gsk.com)

4.9 Overdose

There is no specific treatment for Vocabria overdose. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Cabotegravir is known to be highly protein bound in plasma; therefore, dialysis is unlikely to be helpful in removal of medicinal product from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, integrase inhibitor, ATC code: J05AJ04

Mechanism of action

Cabotegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Pharmacodynamic effects

Antiviral activity in cell culture

Cabotegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of cabotegravir necessary to reduce viral replication by 50 percent (EC₅₀) values of 0.22 nM in peripheral blood mononuclear cells (PBMCs), 0.74 nM in 293T cells and 0.57 nM in MT-4 cells. Cabotegravir demonstrated antiviral activity in cell culture against a panel of 24 HIV-1 clinical isolates (three in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC₅₀ values ranging from 0.02 nM to 1.06 nM for HIV-1. Cabotegravir EC₅₀ values against three HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM. No clinical data is available in patients with HIV-2.

Antiviral Activity in combination with other antiviral medicines

No medicines with inherent anti-HIV activity were antagonistic to cabotegravir's antiretroviral activity

(*in vitro* assessments were conducted in combination with rilpivirine, lamivudine, tenofovir and emtricitabine).

Resistance in vitro

Isolation from wild-type HIV-1 and activity against resistant strains: Viruses with >10-fold increase in cabotegravir EC₅₀ were not observed during the 112-day passage of strain IIIB. The following integrase (IN) mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the presence of cabotegravir: Q146L (fold-change [FC] range 1.3-4.6), S153Y (FC range 2.8-8.4), and I162M (FC = 2.8). As noted above, the detection of T124A is selection of a pre-existing minority variant that does not have differential susceptibility to cabotegravir. 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 of cabotegravir through Day 56.

Among the multiple mutants, the highest FC was observed with mutants containing Q148K or Q148R. E138K/Q148H resulted in a 0.92-fold decrease in susceptibility to cabotegravir but E138K/Q148R resulted in a 12-fold decrease in susceptibility and E138K/Q148K resulted in an 81-fold decrease in susceptibility to cabotegravir. G140C/Q148R and G140S/Q148R resulted in a 22- and 12-fold decrease in susceptibility to cabotegravir, respectively. While N155H did not alter susceptibility to cabotegravir, N155H/Q148R resulted in a 61-fold decrease in susceptibility to cabotegravir. Other multiple mutants, which resulted in a FC between 5 and 10, are: T66K/L74M (FC=6.3), G140S/Q148K (FC=5.6), G140S/Q148H (FC=6.1) and E92Q/N155H (FC=5.3).

Resistance in vivo

The number of subjects who met Confirmed Virologic Failure (CVF) criteria was low across the pooled FLAIR and ATLAS trials. In the pooled analysis, there were 7 CVFs on cabotegravir plus rilpivirine (7/591, 1.2%) and 7 CVFs on current antiretroviral regimen (7/591, 1.2%). The three CVFs on cabotegravir plus rilpivirine in FLAIR with resistance data had Subtype A1. In addition, 2 of the 3 CVFs had treatment-emergent integrase inhibitor resistance associated substitution Q148R while one of the three had G140R with reduced phenotypic susceptibility to cabotegravir. All 3 CVFs carried one rilpivirine resistance-associated substitution: K101E, E138E/A/K/T or E138K, and two of the three showed reduced phenotypic susceptibility to rilpivirine. The 3 CVFs in ATLAS had subtype A, A1 and AG. One of the three CVFs carried the INI resistance-associated substitution N155H at failure with reduced cabotegravir phenotype susceptibility. All three CVFs carried one rilpivirine resistance-associated substitution at failure: E138A, E138E/K or E138K, and showed reduced phenotypic susceptibility to rilpivirine. In two of these three CVFs, the rilpivirine resistance-associated substitutions observed at failure were also observed at baseline in PBMC HIV-1 DNA. The seventh CVF (FLAIR) never received an injection.

The substitutions associated with resistance to long-acting cabotegravir injection, observed in the pooled ATLAS and FLAIR trials were G140R (n=1), Q148R (n=2), and N155H (n=1).

In the ATLAS-2M study 10 subjects met CVF criteria through Week 48: 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm. Eight subjects met CVF criteria at or before the Week 24 timepoint.

At Baseline in the Q8W arm, 5 subjects had rilpivirine resistance-associated mutations of Y181Y/C + H221H/Y, Y188Y/F/H/L, Y188L, E138A or E138E/A and 1 subject contained cabotegravir resistance mutation, G140G/R (in addition to the above Y188Y/F/H/L rilpivirine resistance-associated mutation). At the suspected virologic failure (SVF) timepoint in the Q8W arm, 6 subjects had rilpivirine resistance-associated mutations with 2 subjects having an addition of K101E and 1 subject having an addition of E138E/K from Baseline to SVF timepoint. Rilpivirine FC was above the biological cut-off for 7 subjects and ranged from 2.4 to 15. Five of the 6 subjects with rilpivirine resistance-associated substitution, also had INSTI resistance-associated substitutions, N155H (n=2); Q148R; Q148Q/R+N155N/H (n=2). INSTI substitution, L74I, was seen in 4/7 subjects. The Integrase genotype and phenotype assay failed for one subject and cabotegravir phenotype was unavailable for another.

FCs for the Q8W subjects ranged from 0.6 to 9.1 for cabotegravir, 0.8 to 2.2 for dolutegravir and 0.8 to 1.7 for bictegravir.

In the Q4W arm, neither subject had any rilpivirine or INSTI resistance-associated substitutions at Baseline. One subject had the NNRTI substitution, G190Q, in combination with the NNRTI polymorphism, V189I. At SVF timepoint, one subject had on-treatment rilpivirine resistance-associated mutations, K101E + M230L and the other retained the G190Q + V189I NNRTI substitutions with the addition of V179V/I. Both subjects showed reduced phenotypic susceptibility to rilpivirine. Both subjects also had INSTI resistance-associated mutations, either Q148R + E138E/K or N155N/H at SVF and 1 subject had reduced susceptibility to cabotegravir. Neither subject had the INSTI substitution, L74I. FCs for the Q4W subjects were 1.8 and 4.6 for cabotegravir, 1.0 and 1.4 for dolutegravir and 1.1 and 1.5 for bictegravir.

Clinical efficacy and safety

The efficacy of Vocabria plus rilpivirine has been evaluated in two Phase III randomised, multicentre, active-controlled, parallel-arm, open-label, non-inferiority studies, FLAIR (study 201584) and ATLAS (study 201585). The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

Patients virologically suppressed (on prior dolutegravir based regimen for 20 weeks)

In FLAIR, 629 HIV-1-infected, antiretroviral treatment (ART)-naïve subjects received a dolutegravir integrase strand transfer inhibitor (INSTI) containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 2 other nucleoside reverse transcriptase inhibitors if subjects were HLA-B*5701 positive). Subjects who were virologically suppressed (HIV-1 RNA <50 copies per mL, n=566) were then randomised (1:1) to receive either the Vocabria plus rilpivirine regimen or remain on the current antiretroviral (CAR) regimen. Subjects randomised to receive the Vocabria plus rilpivirine regimen, initiated treatment with oral lead-in dosing with one 30 mg Vocabria tablet plus one 25 mg rilpivirine tablet, daily, for at least 4 weeks, followed by treatment with Vocabria injection (month 1: 600 mg injection, month 2 onwards: 400 mg injection) plus rilpivirine injection (month 1: 900 mg injection, month 2 onwards: 600 mg injection) every month for an additional 44 weeks. This study was extended to 96 weeks.

Patients virologically suppressed (stable on prior ARV therapy for at least 6 months)

In ATLAS, 616 HIV-1-infected, ART-experienced, virologically-suppressed (for at least 6 months) subjects (HIV-1 RNA <50 copies per mL) were randomised (1:1) and received either the Vocabria plus rilpivirine regimen or remained on the CAR regimen. Subjects randomised to receive the Vocabria plus rilpivirine regimen, initiated treatment with oral lead-in dosing with one 30 mg Vocabria tablet plus one 25 mg rilpivirine tablet, daily for at least 4 weeks, followed by treatment with Vocabria injection (month 1: 600 mg injection, month 2 onwards: 400 mg injection) plus rilpivirine injection (month 1: 900 mg injection, month 2 onwards: 600 mg injection) every month for an additional 44 weeks. In ATLAS, 50%, 17%, and 33% of subjects received an NNRTI, PI, or INI (respectively) as their baseline third treatment medicine class prior to randomisation and this was similar between treatment arms.

Pooled data

At baseline, in the pooled analysis, for the Vocabria plus rilpivirine arm, the median age of subjects was 38 years, 27% were female, 27% were non-white, 1% were ≥ 65 years and 7% had CD4+ cell count less than 350 cells per mm³; these characteristics were similar between treatment arms.

The primary endpoint of both studies was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at week 48 (snapshot algorithm for the ITT-E population).

In a pooled analysis of the two pivotal studies, Vocabria plus rilpivirine was non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL (1.9% and 1.7% respectively) at

Week 48. The adjusted treatment difference between Vocabria plus rilpivirine and CAR (0.2; 95% CI: -1.4, 1.7) for the pooled analysis met the non-inferiority criterion (upper bound of the 95% CI below 4%).

The primary endpoint and other week 48 outcomes, including outcomes by key baseline factors, for FLAIR and ATLAS are shown in Tables 4 and 5.

Table 4 Virologic Outcomes of randomised treatment of FLAIR and ATLAS at 48 Weeks (Snapshot analysis)

	FLAIR		ATLAS		Pooled Data	
	Vocabria + RPV N=283	CAR N=283	Vocabria + RPV N=308	CAR N=308	Vocabria +RPV N=591	CAR N=591
HIV-1 RNA\geq50 copies/mL\dagger (%)	6 (2.1)	7 (2.5)	5 (1.6)	3 (1.0)	11 (1.9)	10 (1.7)
Treatment Difference % (95% CI)*	-0.4 (-2.8, 2.1)		0.7 (-1.2, 2.5)		0.2 (-1.4, 1.7)	
HIV-1 RNA <50 copies/mL (%)	265 (93.6)	264 (93.3)	285 (92.5)	294 (95.5)	550 (93.1)	558 (94.4)
Treatment Difference % (95% CI)*	0.4 (-3.7, 4.5)		-3.0 (-6.7, 0.7)		-1.4 (-4.1, 1.4)	
No virologic data at Week 48 window (%)	12 (4.2)	12 (4.2)	18 (5.8)	11 (3.6)	30 (5.1)	23 (3.9)
Reasons						
Discontinued study/study drug due to adverse event or death (%)	8 (2.8)	2 (0.7)	11 (3.6)	5 (1.6)	19 (3.2)	7 (1.2)
Discontinued study/study drug for other reasons (%)	4 (1.4)	10 (3.5)	7 (2.3)	6 (1.9)	11 (1.9)	16 (2.7)
Missing data during window but on study (%)	0	0	0	0	0	0

* Adjusted for baseline stratification factors.

\dagger Includes subjects who discontinued for lack of efficacy, discontinued while not suppressed.

N = Number of subjects in each treatment group, CI = confidence interval, CAR = current antiviral regimen.

Table 5 Proportion of subjects with plasma HIV-1 RNA \geq 50 copies/mL at Week 48 for key baseline factors (Snapshot Outcomes).

Baseline factors		Pooled Data from FLAIR and ATLAS	
		Vocabria+RPV N=591 n/N (%)	CAR N=591 n/N (%)
Baseline CD4+ (cells/ mm³)	<350	0/42	2/54 (3.7)
	\geq 350 to <500	5/120 (4.2)	0/117
	\geq 500	6/429 (1.4)	8 / 420 (1.9)

Gender	Male	6/429 (1.4)	9/423 (2.1)
	Female	5/162 (3.1)	1/168 (0.6)
Race	White	9/430 (2.1)	7/408 (1.7)
	Black African/American	2/109 (1.8)	3/133 (2.3)
	Asian/Other	0/52	0/48
BMI	<30 kg/m ²	6/491 (1.2)	8/488 (1.6)
	≥30 kg/m ²	5/100 (5.0)	2/103 (1.9)
Age (years)	<50	9/492 (1.8)	8/466 (1.7)
	≥50	2/99 (2.0)	2/125 (1.6)
Baseline antiviral therapy at randomisation	PI	1/51 (2.0)	0/54
	INI	6/385 (1.6)	9/382 (2.4)
	NNRTIs	4/155 (2.6)	1/155 (0.6)

BMI= body mass index

PI= Protease inhibitor

INI= Integrase inhibitor

NNRTI= non-nucleoside reverse transcriptase inhibitor

In both the FLAIR and ATLAS studies, treatment differences across baseline characteristics (CD4+ count, gender, race, BMI, age, baseline third agent treatment class) were comparable.

In the FLAIR study at 96 Weeks, the results remained consistent with the results at 48 Weeks. The proportion of subjects having plasma HIV-1 RNA ≥50 c/mL in Vocabria plus rilpivirine (n=283) and CAR (n=283) was 3.2% and 3.2% respectively (adjusted treatment difference between Vocabria plus rilpivirine and CAR [0.0; 95% CI: -2.9, 2.9]). The proportion of subjects having plasma HIV-1 RNA <50 c/mL in Vocabria plus rilpivirine and CAR was 87% and 89%, respectively (adjusted treatment difference between Vocabria plus rilpivirine and CAR [-2.8; 95% CI: -8.2, 2.5]).

Every 2 month dosing

Patients virologically suppressed (stable on prior ARV therapy for at least 6 months)

The efficacy and safety of Vocabria injection given every 2 months, has been evaluated in one Phase IIIb randomised, multicentre, parallel-arm, open-label, non-inferiority study, ATLAS-2M (207966). The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

In ATLAS-2M, 1045 HIV-1 infected, ART experienced, virologically suppressed subjects were randomised (1:1) and received a Vocabria plus rilpivirine injection regimen administered either every 2 months or monthly. Subjects initially on non-cabotegravir/rilpivirine treatment received oral lead-in treatment comprising one 30 mg Vocabria tablet plus one 25 mg rilpivirine tablet, daily, for at least 4 weeks. Subjects randomised to monthly Vocabria injections (month 1: 600 mg injection, month 2 onwards: 400 mg injection) and rilpivirine injections (month 1: 900 mg injection, month 2 onwards: 600 mg injection) received treatment for an additional 44 weeks. Subjects randomised to every 2 month Vocabria injections (600 mg injection at months 1, 2, 4 and every 2 months thereafter) and rilpivirine injections (900 mg injection at months 1, 2, 4 and every 2 months thereafter) received treatment for an additional 44 weeks. Prior to randomisation, 63%, 13% and 24% of subjects received Vocabria plus rilpivirine for 0 weeks, 1 to 24 weeks and >24 weeks, respectively.

At baseline, the median age of subjects was 42 years, 27% were female, 27% were non-white, 4% were ≥ 65 years and 6% had a CD4+ cell count less than 350 cells per mm³; these characteristics were similar between the treatment arms.

The primary endpoint in ATLAS-2M was the proportion of subjects with a plasma HIV-1 RNA ≥ 50 c/mL at Week 48 (snapshot algorithm for the ITT-E population).

In ATLAS-2M, Vocabria and rilpivirine administered every 2 months was non-inferior to Vocabria and rilpivirine administered every month on the proportion of subjects having plasma HIV-1 RNA ≥ 50 c/mL (1.7% and 1.0% respectively) at Week 48. The adjusted treatment difference between Vocabria and rilpivirine administered every 2 months and every month (0.8; 95% CI: -0.6, 2.2) met the non-inferiority criterion (upper bound of the 95% CI below 4%).

Table 6 Virologic Outcomes of Randomised Treatment of ATLAS-2M at 48 Weeks (Snapshot analysis)

	2 month Dosing (Q8W)	Monthly Dosing (Q4W)
	N=522 (%)	N=523 (%)
HIV-1 RNA ≥ 50 copies/mL[†] (%)	9 (1.7)	5 (1.0)
Treatment Difference % (95% CI)*	0.8 (-0.6, 2.2)	
HIV-1 RNA <50 copies/mL (%)	492 (94.3)	489 (93.5)
Treatment Difference % (95% CI)*	0.8 (-2.1, 3.7)	
No virologic data at week 48 window	21 (4.0)	29 (5.5)
Reasons:		
Discontinued study due to AE or death (%)	9 (1.7)	13 (2.5)
Discontinued study for other reasons (%)	12 (2.3)	16 (3.1)
On study but missing data in window (%)	0	0

* Adjusted for baseline stratification factors.

[†] Includes subjects who discontinued for lack of efficacy, discontinued while not suppressed.

N = Number of subjects in each treatment group, CI = confidence interval, CAR = current antiviral regimen.

Table 7 Proportion of Subjects with Plasma HIV-1 RNA ≥ 50 copies/mL at Week 48 for key baseline factors (Snapshot Outcomes).

Baseline factors		Number of HIV-1 RNA ≥ 50 c/mL/Total Assessed (%)	
		2 Month Dosing (Q8W)	Monthly dosing (Q4W)
Baseline CD4+ cell count (cells/mm ³)	<350	1/ 35 (2.9)	1/ 27 (3.7)
	350 to <500	1/ 96 (1.0)	0/ 89
	≥ 500	7/391 (1.8)	4/407 (1.0)
Gender	Male	4/385 (1.0)	5/380 (1.3)
	Female	5/137 (3.5)	0/143
Race	White	5/370 (1.4)	5/393 (1.3)
	Non-White	4/152 (2.6)	0/130

	Black/African American	4/101 (4.0)	0/90
	Non-Black/African American	5/421 (1.2)	5/421 (1.2)
BMI	<30 kg/m ²	3/409 (0.7)	3/425 (0.7)
	≥30 kg/m ²	6/113 (5.3)	2/98 (2.0)
Age (years)	<35	4/137 (2.9)	1/145 (0.7)
	35 to <50	3/242 (1.2)	2/239 (0.8)
	≥50	2/143 (1.4)	2/139 (1.4)
Prior exposure CAB/RPV	None	5/327 (1.5)	5/327 (1.5)
	1-24 weeks	3/69 (4.3)	0/68
	>24 weeks	1/126 (0.8)	0/128

BMI= body mass index

In the ATLAS-2M study, treatment differences on the primary endpoint across baseline characteristics (CD4+ lymphocyte count, gender, race, BMI, age and prior exposure to cabotegravir/rilpivirine) were not clinically meaningful.

The efficacy results at Week 96 are consistent with the results of the primary endpoint at Week 48. Vocabria plus rilpivirine injections administered every 2 months is non-inferior to Vocabria and rilpivirine administered every month. The proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 96 in Vocabria plus rilpivirine every 2 months dosing (n=522) and Vocabria plus rilpivirine monthly dosing (n=523) was 2.1% and 1.1% respectively (adjusted treatment difference between Vocabria plus rilpivirine every 2 months dosing and monthly dosing [1.0; 95% CI: -0.6, 2.5]). The proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 96 in Vocabria plus rilpivirine every 2 months dosing and Vocabria plus rilpivirine monthly dosing was 91% and 90.2% respectively (adjusted treatment difference between Vocabria plus rilpivirine every 2 months dosing and monthly dosing [0.8; 95% CI: -2.8, 4.3]).

The efficacy results at Week 152 are consistent with the results of the primary endpoint at Week 48 and at Week 96. Vocabria plus rilpivirine injections administered every 2 months is non-inferior to Vocabria and rilpivirine administered every month. In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 152 in Vocabria plus rilpivirine every 2 months dosing (n=522) and Vocabria plus rilpivirine monthly dosing (n=523) was 2.7% and 1.0% respectively (adjusted treatment difference between Vocabria plus rilpivirine every 2 months dosing and monthly dosing [1.7; 95% CI: 0.1, 3.3]). In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 152 in Vocabria plus rilpivirine every 2 months dosing and Vocabria plus rilpivirine monthly dosing was 87% and 86% respectively (adjusted treatment difference between Vocabria plus rilpivirine every 2 months dosing and monthly dosing [1.5; 95% CI: -2.6, 5.6]).

Post-hoc analyses

Multivariable analyses of pooled phase 3 studies (ATLAS through 96 weeks, FLAIR through 124 weeks and ATLAS-2M through 152 weeks) examined the influence of various factors on the risk of CVF. The baseline factors analysis (BFA) examined baseline viral and participant characteristics, and dosing regimen; and the multivariable analysis (MVA) included the baseline factors and incorporated

post-baseline predicted plasma drug concentrations on CVF using regression modelling with a variable selection procedure. Following a total of 4291 person-years, the unadjusted CVF incidence rate was 0.54 per 100 person-years; 23 CVFs were reported (1.4% of 1651 individuals in these studies).

The BFA demonstrated rilpivirine resistance mutations (incidence rate ratio IRR=21.65, p<0.0001), HIV-1 subtype A6/A1 (IRR=12.87, p<0.0001), and body mass index IRR=1.09 per 1 unit increase, p=0.04; IRR=3.97 of ≥ 30 kg/m², p=0.01) were associated with CVF. Other variables including Q4W or Q8W dosing, female gender, or CAB/INSTI resistance mutations had no significant association with CVF. A combination of at least 2 of the following key baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥ 30 kg/m² (see Table 8).

Table 8 Virologic outcomes by presence of key baseline factors of rilpivirine resistance mutations, Subtype A6/A1¹ and BMI ≥ 30 kg/m²

Baseline Factors (number)	Virologic Successes (%) ²	Confirmed Virologic Failure (%) ³
0	844/970 (87.0)	4/970 (0.4)
1	343/404 (84.9)	8/404 (2.0) ⁴
≥ 2	44/57 (77.2)	11/57 (19.3) ⁵
TOTAL (95% Confidence Interval)	1231/1431 (86.0) (84.1%, 87.8%)	23/1431 (1.6) ⁶ (1.0%, 2.4%)

¹ HIV-1 subtype A1 or A6 classification based on Los Alamos National Library panel from HIV Sequence database (June 2020)

² Based on the FDA Snapshot algorithm of RNA <50 copies/mL at Week 48 for ATLAS, at Week 124 for FLAIR, at Week 152 for ATLAS-2M.

³ Defined as two consecutive measurements of HIV RNA ≥ 200 copies/mL.

⁴ Positive Predictive Value (PPV) <2%; Negative Predictive Value (NPV) 98.5%; sensitivity 34.8%; specificity 71.9%

⁵ PPV 19.3%; NPV 99.1%; sensitivity 47.8%; specificity 96.7%

⁶ Analysis dataset with all non-missing covariates for baseline factors (out of a total of 1651 individuals).

In patients with at least two of these risk factors, the proportion of subjects who had a CVF was higher than observed in patients with none or one risk factor, with CVF identified in 6/24 patients [25.0%, 95% CI (9.8%, 46.7%)] treated with the every 2 months dosing regimen and 5/33 patients [15.2%, 95% CI (5.1%, 31.9%)] treated with the monthly dosing regimen.

5.2 Pharmacokinetic properties

Cabotegravir pharmacokinetics is similar between healthy and HIV-infected subjects. The PK variability of cabotegravir is moderate. In Phase I studies in healthy subjects, between-subject CVb% for AUC, C_{max}, and C_{tau} ranged from 26 to 34% across healthy subject studies and 28 to 56% across HIV-1 infected subject studies. Within-subject variability (CVw%) is lower than between-subject variability.

Table 9 Pharmacokinetic parameters following cabotegravir orally once daily

Dosing Phase	Dosage Regimen	Geometric Mean (5 th , 95 th Percentile) ^a		
		AUC _(0-tau) ^b (µg•h/mL)	C _{max} (µg/mL)	C _{tau} (µg/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)

^a Pharmacokinetic parameter values based on pooled FLAIR and ATLAS individual post-hoc estimates from cabotegravir population pharmacokinetic model (n = 581)

^b tau is dosing interval: 24 hours for oral administration.

^c Oral lead-in pharmacokinetic parameter values represent steady-state.

Absorption

Cabotegravir is rapidly absorbed following oral administration, with median T_{max} at 3 hours post dose for tablet formulation. With once daily dosing, pharmacokinetic steady-state is achieved by 7 days. Cabotegravir may be administered with or without food. Food increased the extent of absorption of cabotegravir. Bioavailability of cabotegravir is independent of meal content: high fat meals increased cabotegravir AUC_(0-∞) by 14% and increased C_{max} by 14% relative to fasted conditions. These increases are not clinically significant.

The absolute bioavailability of cabotegravir has not been established.

Distribution

Cabotegravir is highly bound (>99%) to human plasma proteins, based on *in vitro* data. Following administration of oral tablets, the mean apparent oral volume of distribution (V_z/F) in plasma was 12.3 L. In humans, the estimate of plasma cabotegravir V_c/F was 5.27 L and V_p/F was 2.43 L. These volume estimates, along with the assumption of high bioavailability, suggest some distribution of cabotegravir to the extracellular space.

Cabotegravir is present in the female and male genital tract. Median cervical and vaginal tissue:plasma ratios ranged from 0.16 to 0.28 and median rectal tissue:plasma ratios were ≤0.08 following a single 400 mg intramuscular injection (IM) at 4, 8, and 12 weeks after dosing.

Cabotegravir is present in cerebrospinal fluid (CSF). In HIV-infected subjects receiving a regimen of cabotegravir injection plus rilpivirine injection, the cabotegravir CSF to plasma concentration ratio [median (range)] (n=16) was 0.003(range: 0.002 to 0.004) one week following a steady-state long acting cabotegravir (Q4W or Q8W) injection. Consistent with therapeutic cabotegravir concentrations in the CSF, CSF HIV-1 RNA (n=16) was <50 c/mL in 100% and <2 c/mL in 15/16 (94%) of subjects. At the same time point, plasma HIV-1 RNA (n=18) was <50 c/mL in 100% and <2 c/mL in 12/18 (66.7%) of subjects.

In vitro, cabotegravir was not a substrate of organic anion transporting polypeptide (OATP) 1B1, OATP2B1, OATP1B3 or organic cation transporter (OCT1).

Biotransformation

Cabotegravir is primarily metabolised by UGT1A1 with a minor UGT1A9 component. Cabotegravir is the predominant circulating compound in plasma, representing > 90% of plasma total radiocarbon. Following oral administration in humans, cabotegravir is primarily eliminated through metabolism; renal elimination of unchanged cabotegravir is low (<1% of the dose). Forty-seven percent of the total oral dose is excreted as unchanged cabotegravir in the faeces. It is unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronide conjugate, which can be further degraded to form the parent compound in the gut lumen. Cabotegravir was observed to be present in duodenal bile samples. The glucuronide metabolite was also present in some but not all of the duodenal bile samples.

Twenty-seven percent of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (75% of urine radioactivity, 20% of total dose).

Cabotegravir is not a clinically relevant inhibitor of the following enzymes and transporters: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B15, and UGT2B17, P-gp, BCRP, Bile salt export pump (BSEP), OCT1, OCT2, OATP1B1, OATP1B3, multidrug and toxin extrusion transporter (MATE) 1, MATE 2-K, multidrug resistance protein (MRP) 2 or MRP4.

Elimination

Cabotegravir has a mean terminal half-life of 41 h and an apparent clearance (CL/F) of 0.21 L per hour.

Polymorphisms

In a meta-analysis of healthy and HIV-infected subject trials, subjects with UGT1A1 genotypes conferring poor cabotegravir metabolism had a 1.3- to 1.5-fold mean increase in steady-state cabotegravir AUC, C_{max} , and C_{tau} compared with subjects with genotypes associated with normal metabolism via UGT1A1. These differences are not considered clinically relevant. No dose adjustment is required in subjects with UGT1A1 polymorphisms.

Special patient populations

Gender

Population pharmacokinetic analyses revealed no clinically relevant effect of gender on the exposure of cabotegravir, therefore no dose adjustment is required on the basis of gender.

Race

Population pharmacokinetic analyses revealed no clinically relevant effect of race on the exposure of cabotegravir, therefore no dosage adjustment is required on the basis of race.

Body Mass Index (BMI)

Population pharmacokinetic analyses revealed no clinically relevant effect of BMI on the exposure of cabotegravir, therefore no dose adjustment is required on the basis of BMI.

Elderly

Population pharmacokinetic analysis of cabotegravir revealed no clinically relevant effect of age on cabotegravir exposure. Pharmacokinetic data for cabotegravir in subjects of >65 years old are limited.

Renal impairment

No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCL <30 mL/min and not on dialysis) and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to severe renal impairment (not on dialysis). Cabotegravir has not been studied in patients on dialysis.

Hepatic impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of cabotegravir has not been studied.

5.3 Preclinical safety data

Carcinogenesis and mutagenesis

Cabotegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Cabotegravir was not carcinogenic in long term studies in the mouse and rat.

Reproductive toxicology studies

No effect on male or female fertility was observed in rats treated with cabotegravir at oral doses up to 1000 mg/kg/day (>20 times the exposure in humans at the maximum recommended dose).

In an embryo-foetal development study there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits up to a maternal toxic dose of 2,000 mg/kg/day (0.66 times the exposure in humans at the MRHD) or to pregnant rats at doses up to 1,000 mg/kg/day (>30 times the exposure in humans at the MRHD). In rats, alterations in foetal growth (decreased body weights) were observed at 1,000 mg/kg/day. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in foetal tissue.

In rat pre- and post-natal (PPN) studies cabotegravir reproducibly induced a delayed onset of parturition, and an increase in the number of stillbirths and neonatal mortalities at 1,000 mg/kg/day (>30 times the exposure in humans at the MRHD). A lower dose of 5 mg/kg/day (approximately 10 times the exposure in humans at the MRHD) cabotegravir was not associated with delayed parturition or neonatal mortality. In rabbit and rat studies there was no effect on survival when foetuses were delivered by caesarean section. Given the exposure ratio, the relevance to humans is unknown.

Repeated dose toxicity

The effect of prolonged daily treatment with high doses of cabotegravir has been evaluated in repeat oral dose toxicity studies in rats (26 weeks) and in monkeys (39 weeks). There were no drug-related adverse effects in rats or monkeys given cabotegravir orally at doses up to 1,000 mg/kg/day or 500 mg/kg/day, respectively.

In a 14 day and 28 day monkey toxicity study, gastro-intestinal (GI) effects (body weight loss, emesis, loose/watery faeces, and moderate to severe dehydration) were observed and was the result of local drug administration and not systemic toxicity.

In a 3 month study in rats, when cabotegravir was administered by monthly sub-cutaneous (SC) injection (up to 100 mg/kg/dose); monthly IM injection (up to 75 mg/kg/dose) or weekly SC injection (100 mg/kg/dose), there were no adverse effects noted and no new target organ toxicities (at exposures >30 times the exposure in humans at the MRHD of 400 mg IM dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Lactose monohydrate
Sodium starch glycolate (Type A)
Hypromellose 2910, 3 mPa*s
Magnesium stearate

Tablet coating

Hypromellose 2910, 3 mPa*s (E464)

Titanium dioxide (E171)

Macrogol 400 (E1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

White HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closures, with a polyethylene faced induction heat seal liner. Each bottle contains 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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8. LICENSE HOLDER AND IMPORTER

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