

Attachment 1: AusPAR - Vocabria and Cabenuva - cabotegravir and cabotegravir/rilpivirine - ViiV Healthcare Pty Ltd - PM-2019-04281-1-2 and PM-2019-04280-1-2 FINAL 3 May 2021. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## AUSTRALIAN PRODUCT INFORMATION

### VOCABRIA (cabotegravir) film-coated tablets

#### 1 NAME OF THE MEDICINE

Cabotegravir (as cabotegravir sodium)

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VOCABRIA tablet contains 30 mg cabotegravir (as cabotegravir sodium).

Cabotegravir is a white to almost white solid.

##### List of excipients with known effect

VOCABRIA tablets contain lactose monohydrate.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

#### 3 PHARMACEUTICAL FORM

VOCABRIA tablets are white, oval, film-coated, tablets, 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) and have no known or suspected resistance to either cabotegravir or rilpivirine (see sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials) for:

- oral lead in to assess tolerability of cabotegravir prior to administration of cabotegravir prolonged-release suspension for injection plus rilpivirine prolonged-release suspension for injection.
- oral therapy for adults who will miss planned dosing with cabotegravir prolonged-release suspension for injection.

##### 4.2 DOSE AND METHOD OF ADMINISTRATION

VOCABRIA should be prescribed by a physician experienced in the management of HIV infection.

VOCABRIA is indicated for the treatment of HIV-1 in combination with rilpivirine, therefore, the product information for rilpivirine should be consulted for recommended dosing.

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## Adults

### **Oral lead-in dosing**

VOCABRIA tablets are recommended for approximately one month (at least 28 days) in virologically suppressed patients prior to the initiation of cabotegravir injections, a component of CABENUVA (cabotegravir and rilpivirine prolonged release suspensions for injection), to assess tolerability to cabotegravir. One VOCABRIA tablet (30 mg) should be taken with one rilpivirine tablet (25 mg) once daily.

The final oral dose should be taken on the same day injections with CABENUVA are started.

### **Missed doses**

#### Missed VOCABRIA film-coated tablet

If a patient misses an oral dose of VOCABRIA, the patient should take the missed dose as soon as possible

#### Oral dosing for missed injections of CABENUVA

If a deviation of more than 7 days from a scheduled injection visit cannot be avoided, oral therapy (one VOCABRIA tablet [30 mg] and one rilpivirine tablet [25 mg] once daily) may be used to replace up to 2 consecutive monthly injection visits. For oral therapy durations greater than two months, an alternative oral regimen is recommended.

The first dose of oral therapy should be taken approximately one month after the last injection dose of cabotegravir or rilpivirine. Injection dosing should be resumed on the day oral dosing completes.

### **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 PHARMACOKINETIC PROPERTIES, Special patient populations).

### **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 PHARMACOKINETIC PROPERTIES, Special patient populations).

### **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 PHARMACOKINETIC PROPERTIES, Special patient populations).

### **Paediatric and adolescent population**

The safety and efficacy of VOCABRIA in children and adolescents aged under 18 years has not been established.

### **Method of Administration**

Oral use.

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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

VOCABRIA is contraindicated in patients:

- with known hypersensitivity to cabotegravir or to any of the excipients listed in section 6.1.
- receiving rifampicin, rifapentine, phenytoin, phenobarbital carbamazepine and oxcarbazepine (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

VOCABRIA is only indicated for treatment of HIV-1 in combination with rilpivirine, therefore, the prescribing information for rilpivirine should also be consulted.

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

#### Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with other integrase inhibitors. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. While no such reactions have been observed to date in association with VOCABRIA, physicians should remain vigilant and should discontinue VOCABRIA and other suspected medicinal products 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. Administration of oral lead-in is recommended to help identify patients who may be at risk of a hypersensitivity reaction (see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION, 4.3 CONTRAINDICATIONS and prolonged-release properties of cabotegravir injection below).

#### Hepatotoxicity

Hepatotoxicity has been reported in a limited number of patients receiving cabotegravir with or without known pre-existing hepatic disease (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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

#### Risk of resistance following treatment discontinuation

To minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive, antiretroviral regimen no later than one month after the final injection of cabotegravir when dosed monthly and no later than two months after the final injection of cabotegravir when dosed every 2 months..

If virologic failure is suspected, an alternative regimen should be adopted as soon as possible.

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### **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  $\geq 30$  kg/m<sup>2</sup>. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI  $\geq 30$  kg/m<sup>2</sup> or HIV-1 A6/A1 subtype (see section 5.1 PHARMACODYNAMIC PROPERTIES).

### **Interactions with medicinal products**

Caution should be given to prescribing VOCABRIA with medicinal products that may reduce its exposure (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

### **Opportunistic infections**

Patients receiving VOCABRIA or any other antiretroviral therapy 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.

### **Transmission of Infection**

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

### **Concomitant treatment with rilpivirine**

VOCABRIA is indicated for the treatment of HIV-1 in combination with rilpivirine, therefore, the product information for rilpivirine injection should be consulted.

### **Use in hepatic impairment**

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

### **Use in renal impairment**

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

### **Use in the elderly**

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

### **Paediatric use**

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

### **Effects on laboratory tests**

Small, non-progressive increases in total bilirubin (without clinical jaundice) were observed with treatment with cabotegravir 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).

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Elevated transaminases (ALT/AST) were observed in subjects receiving cabotegravir plus rilpivirine during the clinical studies. These elevations were primarily attributed to acute viral hepatitis. A few subjects had transaminase elevations attributed to suspected drug-related hepatotoxicity.

Asymptomatic creatine phosphokinase (CPK) elevations mainly in association with exercise, have also been reported with cabotegravir plus rilpivirine treatment.

#### **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

VOCABRIA, in combination with rilpivirine, is indicated for the treatment of HIV-1, therefore, the product information for rilpivirine should be consulted for associated interactions.

##### **Effect of other medicinal products on the pharmacokinetics of cabotegravir**

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 with some contribution from 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 CONTRAINDICATIONS).

Simulations using physiologically based pharmacokinetic (PBPK) modelling show that no clinically significant interaction is expected following co-administration of cabotegravir with medicines that inhibit UGT enzymes.

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

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. 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.

Cabotegravir inhibited the organic anion transporters (OAT) 1 ( $IC_{50}=0.81 \mu M$ ) and OAT3 ( $IC_{50}=0.41 \mu M$ ) *in vitro*, however, based on PBPK modelling no interaction with OAT substrates is expected at clinically relevant concentrations.

*In vitro*, cabotegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

Based on these data and the results of drug interaction studies, cabotegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of these enzymes or transporters.

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

No drug interaction studies have been performed with cabotegravir injection. The drug interaction data provided in Table 1 is obtained from studies with oral cabotegravir.

**Table 1: 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 <sub>max</sub> ↑ 4% C <sub>T</sub> ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dose adjustment of VOCABRIA is necessary when co-administered with etravirine.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	Cabotegravir ↔ AUC ↑ 12% C <sub>max</sub> ↑ 5% C <sub>T</sub> ↑ 14%  Rilpivirine ↔ AUC ↓ 1% C <sub>max</sub> ↓ 4% C <sub>T</sub> ↓ 8%	Rilpivirine did not significantly change cabotegravir plasma concentration. No dose adjustment of VOCABRIA is necessary when co-administered with rilpivirine.
<i>Anticonvulsants</i>		
Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentration. Concomitant use is contraindicated (see Section 4.3 CONTRAINDICATIONS).
<i>Antimycobacterials</i>		
Rifampicin	Cabotegravir ↓ AUC ↓ 59% C <sub>max</sub> ↓ 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 CONTRAINDICATIONS)
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated (see Section 4.3 CONTRAINDICATIONS).
Rifabutin	Cabotegravir AUC ↓ 21% C <sub>max</sub> ↓ 17% C <sub>T</sub> ↓ 8%	Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required.
<i>Oral contraceptives</i>		
Ethinyl estradiol (EE) and Levonorgestrel (LNG)	EE ↔ AUC ↑ 2% C <sub>max</sub> ↓ 8%	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.



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Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
	C <sub>T</sub> ↔ 0%	
	LNG ↔	

Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no change ; AUC = area under the concentration versus time curve ; C<sub>max</sub> = maximum observed concentration; C<sub>T</sub> = concentration at end of dosing interval.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on 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.

Cabotegravir when administered orally to male and female rats at 1,000 mg/kg/day (>30 times the exposure in humans at the Maximum Recommended Human Dose [MHRD] of 30 mg oral or 400 mg intramuscular (IM) dose) for up to 26 weeks did not cause adverse effects on male or female reproductive organs or spermatogenesis. No functional effects on male or female mating or fertility were observed in rats given cabotegravir at doses up to 1,000 mg/kg/day.

### Use in pregnancy

#### (Pregnancy Category B1)

There are no studies of cabotegravir in pregnant women. The effect of VOCABRIA on human pregnancy is unknown.

VOCABRIA should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection, therefore, consideration should be given to the potential for fetal exposure during pregnancy (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cabotegravir crossed the placenta in pregnant rats and could be detected in fetal tissues. Cabotegravir was not teratogenic in rats at oral doses up to 1000 mg/kg/day (>30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose) but caused a delay in delivery that was associated with reduced survival and viability of rat offspring; there was no effect on survival at birth when fetuses were delivered by caesarean section. Exposures at the NOAEL were at least 11 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose. The relevance to human pregnancy is unknown.

To monitor maternal-fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established (<http://www.apregistry.com>) for cabotegravir. This is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products. For rilpivirine, sufficient first trimester exposures are available to allow detection of at least a two-fold increase in risk of overall birth defects.

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### **Use in lactation**

Health experts recommend that where possible HIV 1 infected women should not breastfeed their infants in order to avoid transmission of HIV-1. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

It is expected that cabotegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans. Cabotegravir may be present in human milk for up to 12 months or longer after the last cabotegravir injection.

### **4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

There have been no studies to investigate the effect of cabotegravir on driving performance or the ability to operate machinery. The clinical status of the patient and the adverse event profile of VOCABRIA should be borne in mind when considering the patient's ability to drive or operate machinery.

### **4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)**

#### **Clinical trial data**

The safety assessment of VOCABRIA in HIV-1-infected, virologically suppressed patients is based on pooled primary Week 48 analyses of data from two international, multicenter open-label studies, FLAIR and ATLAS and one Phase IIIb international, multicentre open-label study, ATLAS-2M.

In FLAIR and ATLAS, a total of 1,182 HIV-1 infected patients were randomized to receive either a cabotegravir plus rilpivirine regimen or remain on their baseline antiretroviral regimen. Patients randomized to receive the cabotegravir plus rilpivirine regimen, initiated treatment with daily oral lead-in dosing with one 30 mg cabotegravir tablet plus one 25 mg rilpivirine tablet (EDURANT) for at least 4 weeks followed by treatment with cabotegravir injection plus rilpivirine injection for at least an additional 44 weeks.

In ATLAS-2M, 1045 HIV-1 infected, ART experienced, virologically suppressed subjects were randomised and received a cabotegravir plus rilpivirine injection regimen administered either every 2 months or monthly. Subjects initially on non-CAB/RPV treatment received oral lead-in treatment comprising one cabotegravir 30 mg tablet (VOCABRIA) plus one rilpivirine 25 mg tablet (EDURANT), daily, for at least 4 weeks. Subjects randomised to monthly cabotegravir injections and rilpivirine injections received treatment for an additional 44 weeks. Subjects randomised to every 2 month cabotegravir injections and rilpivirine injections received treatment for an additional 44 weeks.

#### **Adverse events**

For many of the adverse events listed in Table 2, it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process

The most common adverse events reported in >10% of subjects in the group that received VOCABRIA in the FLAIR and ATLAS studies were injection site pain, nasopharyngitis, upper



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respiratory tract infection, headache, diarrhoea, injection site nodule and injection site induration.

**Table 2: Summary of adverse events reported in ≥3% of subjects in any treatment group by overall frequency in ATLAS and FLAIR (Week 48 pooled analysis)**

Preferred Term <sup>□</sup>	Cabotegravir plus rilpivirine <sup>¶</sup> N=591 <sup>¶</sup> n(%) <sup>□</sup>	Current antiretroviral therapy <sup>¶</sup> N=591 <sup>¶</sup> n(%) <sup>□</sup>
<b>Infections and Infestations<sup>□</sup></b>		
Nasopharyngitis <sup>□</sup>	108(18%) <sup>□</sup>	90(15%) <sup>□</sup>
Upper respiratory tract infection <sup>□</sup>	70(12%) <sup>□</sup>	53(9%) <sup>□</sup>
Influenza <sup>□</sup>	42(7%) <sup>□</sup>	34(6%) <sup>□</sup>
Respiratory tract infection, viral <sup>□</sup>	24(4%) <sup>□</sup>	29(5%) <sup>□</sup>
Pharyngitis <sup>□</sup>	23(4%) <sup>□</sup>	21(4%) <sup>□</sup>
Gastroenteritis <sup>□</sup>	20(3%) <sup>□</sup>	21(4%) <sup>□</sup>
<b>Gastrointestinal disorders<sup>□</sup></b>		
Diarrhoea <sup>□</sup>	54(9%) <sup>□</sup>	40(7%) <sup>□</sup>
Nausea <sup>□</sup>	30(5%) <sup>□</sup>	16(3%) <sup>□</sup>
Haemorrhoids <sup>□</sup>	20(3%) <sup>□</sup>	5(<1%) <sup>□</sup>
<b>Nervous system disorders<sup>□</sup></b>		
Headache <sup>□</sup>	73(12%) <sup>□</sup>	38(6%) <sup>□</sup>
Dizziness <sup>□</sup>	24(4%) <sup>□</sup>	8(1%) <sup>□</sup>
<b>Musculoskeletal and connective tissue disorders<sup>□</sup></b>		
Back pain <sup>□</sup>	43(7%) <sup>□</sup>	23(4%) <sup>□</sup>
<b>General disorders and administration site conditions<sup>□</sup></b>		
Injection site pain <sup>□</sup>	458(77%) <sup>□</sup>	- <sup>□</sup>
Injection site nodule <sup>□</sup>	81(14%) <sup>□</sup>	- <sup>□</sup>
Injection site induration <sup>□</sup>	68(12%) <sup>□</sup>	- <sup>□</sup>
Injection site swelling <sup>□</sup>	46(8%) <sup>□</sup>	- <sup>□</sup>
Pyrexia <sup>□</sup>	43(7%) <sup>□</sup>	13(2%) <sup>□</sup>
Injection site pruritis <sup>□</sup>	23(4%) <sup>□</sup>	- <sup>□</sup>
Fatigue <sup>□</sup>	29(5%) <sup>□</sup>	14(2%) <sup>□</sup>
<b>Respiratory, thoracic and mediastinal disorders<sup>□</sup></b>		
Cough <sup>□</sup>	26(4%) <sup>□</sup>	26(4%) <sup>□</sup>
<b>Metabolism and nutrition<sup>□</sup></b>		
Vitamin D deficiency <sup>□</sup>	31(5%) <sup>□</sup>	25(4%) <sup>□</sup>

Adverse events leading to discontinuation and occurring in more than 1 subject were injection site reactions, hepatitis A, acute hepatitis B, headache, and diarrhea which occurred with an incidence of ≤1%. The incidence of serious adverse events was 5% in subjects receiving cabotegravir plus rilpivirine and 4% for subjects remaining on current antiretroviral therapy.

#### **Adverse drug reactions**

ADRs are adverse events that are considered to be reasonably associated with the use of a drug based on the comprehensive assessment of the available adverse event information. A causal relationship cannot be reliably established in individual cases.

Adverse drug reactions for cabotegravir plus rilpivirine were identified from pivotal Phase III clinical studies (FLAIR and ATLAS) based on an analysis of pooled data (N=591) and ATLAS-2M at Week 48.

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Cabotegravir plus rilpivirine were administered as a combination regimen (monthly and every 2 month dosing) and associated adverse reactions are listed in Table 3.

Adverse drug reactions listed include those attributable to both the oral and injectable formulations of cabotegravir and rilpivirine. When frequencies differed between phase III studies, the highest frequency category is quoted in Table 3.

The most frequently reported adverse drug reactions from monthly dosing studies were headache (up to 12%) and pyrexia<sup>3</sup> (10%).

The most frequently reported adverse drug reactions from ATLAS-2M every 2 month dosing were headache (7%) and pyrexia<sup>3</sup> (7%).

The adverse reactions considered at least possibly related to cabotegravir 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 ( $< 1/10,000$ ), including isolated reports.

**Table 3: Tabulated summary of adverse drug reactions**

MedDRA System Organ Class (SOC)	Frequency Category	Adverse drug reactions for cabotegravir + rilpivirine regimen
Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence
Gastrointestinal disorders	Common	Nausea Vomiting Abdominal pain <sup>1</sup> Flatulence Diarrhoea
Hepatobiliary Disorders	Uncommon	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash <sup>2</sup>
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Pyrexia <sup>3</sup>
	Common	Fatigue Asthenia Malaise

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MedDRA System Organ Class (SOC)	Frequency Category	Adverse drug reactions for cabotegravir + rilpivirine regimen
Investigations	Common	Weight increased
	Uncommon	Transaminase increased

<sup>1</sup> Abdominal pain includes the following grouped MedDRA preferred terms: abdominal pain, upper abdominal pain.

<sup>2</sup> Rash includes the following grouped MedDRA preferred terms: Rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash popular, rash pruritic.

<sup>3</sup> Pyrexia includes the following grouped MedDRA preferred terms: feeling hot, body temperature increased.

## Description of selected adverse reactions

### Weight increased

At the Week 48 time point, subjects in the FLAIR and ATLAS studies, who received cabotegravir plus rilpivirine gained a median of 1.5 kg in weight; those in the current antiretroviral therapy (CAR) group gained a median of 1.0 kg (pooled analysis). In the individual FLAIR and ATLAS studies, the median weight gains in the cabotegravir plus rilpivirine group were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR group. At the 48 week timepoint, in ATLAS-2M the median weight gain in both the monthly and 2-monthly cabotegravir plus rilpivirine dosing arms was 1.0 kg.

### Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 OVERDOSE

There is currently no experience with overdosage of VOCABRIA.

There is no specific treatment for overdose with VOCABRIA. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Cabotegravir is known to be highly protein bound in plasma; therefore, dialysis is unlikely to be helpful in removal of cabotegravir from the body. Management of overdose with cabotegravir injection should take into consideration the prolonged exposure to the medicine following an injection (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

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### **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 (EC<sub>50</sub>) values of 0.22 nM to 1.6 nM in peripheral blood mononuclear cells (PBMCs) and 293T 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 EC<sub>50</sub> values ranging from 0.02 nM to 1.06 nM for HIV-1. Cabotegravir EC<sub>50</sub> values against four HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM.

#### ***Antiviral Activity in combination with other medicinal products***

In *in vitro* combination studies, cabotegravir had weak synergistic antiviral effects with nucleoside reverse transcriptase inhibitors (lamivudine, tenofovir disoproxil fumarate, emtricitabine) and additive effects with the non-nucleoside reverse transcriptase inhibitor, rilpivirine.

#### ***Effect of Human Serum and Serum Proteins***

*In vitro* studies suggested a 660-fold shift in IC<sub>50</sub> of cabotegravir in the presence of 100% human serum (by method of extrapolation), and the protein adjusted IC<sub>50</sub> (PA-IC<sub>50</sub>) was estimated to be <1.1 µM .

#### ***Resistance in vitro***

Isolation from wild-type HIV-1 and activity against resistant strains: Viruses with >10-fold increase in cabotegravir EC<sub>50</sub> 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 range 1.3-4.6), S153Y (fold-change range 3.6-8.4), and I162M (fold-change = 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 known integrase resistant mutants tested, mild resistance (≥ 5-fold but <10-fold resistance) was seen with E92Q/N155H, G118R, G140S/Q148H, Y143H/N155H, Q148K, Q148R, T66K/L74M and G140S/Q148K. High resistance (≥10-fold resistance) was seen with E138K/Q148K, V72I/E138K/Q148K, E138K/Q148R, E138K/G140S/Q148R, L74M/V75A/G140S/Q148H, G140C/Q148R, Q148R/N155H and G140S/Q148R.

#### ***Resistance in vivo***

The number of subjects who met Confirmed Virologic Failure (CVF) criteria was low across the pooled FLAIR and ATLAS studies. 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 3 CVFs on cabotegravir plus rilpivirine in FLAIR with resistance data had Subtype A1 with IN substitution L74I (which by itself does not cause resistance to any INI)

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detected at baseline and suspected virologic failure (SVF). In addition, 2 of the 3 CVFs had treatment-emergent integrase inhibitor resistance associated substitution Q148R while 1 of the 3 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 2 of the 3 showed reduced phenotypic susceptibility to rilpivirine. The 3 CVFs in ATLAS had subtype A, A1 and AG. The 2 CVFs with subtype A and A1 both carried IN substitution L74I in baseline PBMC HIV-1 DNA and at SVF in HIV-1 RNA. In addition, 1 of the 3 CVFs carried the INI resistance-associated substitution N155H at SVF. All 3 CVFs had treatment-emergent rilpivirine resistance-associated substitution: E138A, E138E/K or E138K, and showed reduced phenotypic susceptibility to rilpivirine while 1 of the 3 also showed reduced phenotypic susceptibility to cabotegravir. In 2 of these 3 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 studies 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 every 2 month dose arm and 2 subjects (0.4%) in the monthly dose arm. Eight subjects met CVF criteria at or before the Week 24 timepoint.

At baseline in the every 2 month dose arm, 5 subjects had RPV 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 Y181Y/C + H221H/Y RPV resistance-associated mutation). At the SVF timepoint in the every 2 month dose 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 fold-change (FC) was above the clinical 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 (2); Q148R; Q148Q/R+N155N/H (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. Cabotegravir FCs for these subjects ranged from 1.8 to 9.1. All subjects remained sensitive to dolutegravir and bictegravir.

In the monthly dose arm, neither subject had any RPV 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 RPV. Both subjects also had INSTI resistance-associated mutations, either Q148R + E138E/K or N155N/H at SVF and 1 subject had reduced susceptibility to CAB. Neither subject had the INSTI substitution, L74I. All subjects remained sensitive to dolutegravir and bictegravir.

### ***Effects on Electrocardiogram***

In a randomised, placebo-controlled, three-period cross-over trial, 42 healthy subjects were



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randomised into 6 random sequences and received three doses of oral administration of placebo, cabotegravir 150 mg every 12 hours (mean steady state  $C_{max}$  was approximately 2.8-fold, 5.4-fold and 5.6 fold above the 30 mg once-daily dose, the 400 mg cabotegravir injection monthly dose and the 600 mg cabotegravir injection every 2 month dose, respectively, and single dose of moxifloxacin 400 mg (active control). After baseline and placebo adjustment, the maximum time-matched mean QTc change based on Fridericia's correction method (QTcF) for cabotegravir was 2.62 msec (1-side 90% upper CI:5.26 msec). Cabotegravir did not prolong the QTc interval over 24 hours post-dose.

## **Clinical trials**

### ***Monthly Dosing***

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

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 cabotegravir plus rilpivirine regimen or remain on the current antiretroviral (CAR) regimen. Subjects randomised to receive the cabotegravir plus rilpivirine regimen, initiated treatment with oral lead-in dosing with VOCABRIA 30 mg tablets plus rilpivirine 25 mg tablets, daily, for at least 4 weeks, followed by treatment with cabotegravir 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, 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 cabotegravir plus rilpivirine regimen or remained on the CAR regimen. Subjects randomised to receive the cabotegravir plus rilpivirine regimen, initiated treatment with oral lead-in dosing with VOCABRIA 30 mg tablets plus rilpivirine 25 mg tablets, daily, for at least 4 weeks, followed by treatment with cabotegravir injection (month 1: 600 mg, 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.

At baseline, in the pooled analysis, for the cabotegravir plus rilpivirine arm, the median age of subjects was 38 years, 27% were female, 27% were non-white, and 7% had CD4+ cell count less than 350 cells per mm<sup>3</sup>; these characteristics were similar between treatment arms.



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

In a pooled analysis of the two pivotal studies, cabotegravir plus rilpivirine was non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA  $\geq 50$  c/mL (1.9% and 1.7% respectively) at Week 48. The adjusted treatment difference between cabotegravir 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%). Furthermore, in the pooled analysis, cabotegravir plus rilpivirine was non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA  $< 50$  c/mL (93.1% and 94.4%, respectively) at Week 48. The adjusted treatment difference between cabotegravir plus rilpivirine and CAR (-1.4; 95% CI: -4.1, 1.4) for the pooled analysis met the non-inferiority criteria (lower bound of the 95% CI greater than -10%. [See Table 4]).

The non-inferiority result established in FLAIR and ATLAS demonstrated that the length of HIV-1 RNA virologic suppression prior to initiation of cabotegravir plus rilpivirine (i.e.  $< 6$  months or  $\geq 6$  months) did not impact overall response rates.

The primary endpoint and other week 48 outcomes, including outcomes by key baseline factors, for FLAIR and ATLAS are shown in Tables 6 and 7.

**Table 4: Virologic Outcomes of Randomised Treatment of FLAIR and ATLAS at 48 Weeks (Snapshot analysis)**

	FLAIR		ATLAS		Pooled Data	
	CAB + RPV N=283	CAR N=283	CAB + RPV N=308	CAR N=308	CAB +RPV N=591	CAR N=591
HIV-1 RNA $\geq 50$ copies/mL†	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)
<u>Reasons</u>						
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.

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

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

**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	
		CAB+RPV N=591 n/N (%)	CAR N=591 n/N (%)
Baseline CD4+ (cells/mm <sup>3</sup> )	<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 <sup>2</sup>	6/491 (1.2)	8/488 (1.6)
	$\geq$ 30 kg/m <sup>2</sup>	5/100 (5.0)	2/103 (1.9)
Age (years)	<50	9/492 (1.8)	8/466 (1.7)
	$\geq$ 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, age, race, BMI, baseline third agent treatment class) were comparable.

Subjects in both FLAIR and ATLAS were virologically suppressed prior to Day 1 or study entry, respectively, and a clinically relevant change from baseline in CD4+ cell counts was not observed.

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  $\geq$ 50 c/mL in cabotegravir plus rilpivirine (n=283) and CAR (n=283) was 3.2% and 3.2% respectively (adjusted treatment difference between cabotegravir 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 cabotegravir plus rilpivirine and CAR was 87% and 89%, respectively (adjusted treatment difference between cabotegravir plus rilpivirine and CAR [-2.8; 95% CI: -8.2, 2.5]).

### **Every 2 Month Dosing**

The efficacy and safety of cabotegravir injection given every 2 months, has been evaluated in one Phase IIIb randomised, multicentre, parallel-arm, open-label, non-inferiority study,

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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 cabotegravir plus rilpivirine injection regimen administered either every 2 months or monthly. Subjects initially on non-cabotegravir plus rilpivirine treatment received oral lead-in treatment comprising one cabotegravir 30 mg tablet plus one rilpivirine 25 mg tablet, daily, for at least 4 weeks. Subjects randomised to monthly cabotegravir 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 administered) received treatment for an additional 44 weeks. Subjects randomised to every 2 month cabotegravir 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) for an additional 44 weeks. Prior to randomisation, 63%, 13% and 24% of subjects received cabotegravir 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 and 6% had a CD4+ cell count less than 350 cells per mm<sup>3</sup>; 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  $\geq 50$  c/mL at Week 48 (snapshot algorithm for the ITT-E population).

In ATLAS-2M, cabotegravir + rilpivirine administered every 2 months was non-inferior to cabotegravir and rilpivirine administered every month on the proportion of subjects having plasma HIV-1 RNA  $\geq 50$  c/mL (1.7% and 1.0% respectively) at Week 48. The adjusted treatment difference between cabotegravir + 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%). Furthermore, cabotegravir + rilpivirine dosed every 2 months was non-inferior to cabotegravir plus rilpivirine dosed every month on the proportion of subjects having plasma HIV-1 RNA <50 c/mL (94% and 93%, respectively) at Week 48. The adjusted treatment difference between cabotegravir + rilpivirine dosed every 2 months and monthly (0.8; 95% CI: -2.1, 3.7) met the non-inferiority criteria (lower bound of the 95% CI greater than -10%). [See Table 6].

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

	2 month Dosing (Q8W)	Monthly Dosing (Q4W)
	N=522 (%)	N=523 (%)
HIV-1 RNA $\geq 50$ copies/mL <sup>†</sup>	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.

<sup>†</sup> 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.

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

		Number of HIV-1 RNA $\geq$ 50 c/mL/ Total Assessed (%)	
		2 Month Dosing (Q8W)	Monthly dosing (Q4W)
Baseline CD4+ cell count (cells/mm <sup>3</sup> )	<350	1/ 35 (2.9)	1/ 27 (3.7)
	350 to <500	1/ 96 (1.0)	0/ 89
	$\geq$ 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 <sup>2</sup>	3/409 (0.7)	3/425 (0.7)
	$\geq$ 30 kg/m <sup>2</sup>	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.

**Post-hoc analysis:**

Multivariable analyses of pooled phase 3 studies (ATLAS, FLAIR and ATLAS-2M), including data from 1039 HIV-infected adults with no prior exposure to cabotegravir plus rilpivirine, examined the influence of baseline viral and participant characteristics, dosing regimen, and post-baseline plasma drug concentrations on confirmed virologic failure (CVF) using

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regression modelling with a variable selection procedure. Through Week 48 in these studies, 13/1039 (1.25%) participants had CVF while receiving cabotegravir and rilpivirine. Four covariates were significantly associated ( $P < 0.05$  for each adjusted odds ratio) with increased risk of CVF: rilpivirine resistance mutations at baseline identified by proviral DNA genotypic assay, HIV-1 subtype A6/A1 (associated with integrase L74I polymorphism), rilpivirine trough concentration 4 weeks following initial injection dose, body mass index of at least 30 kg/m<sup>2</sup> (associated with cabotegravir pharmacokinetics). Other variables including Q4W or Q8W dosing, female gender, or other viral subtypes (non A6/A1) had no significant association with CVF. No baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI  $\geq 30$  mg/m<sup>2</sup> (see Table 8).

**Table 8 Week 48 outcomes by presence of key baseline factors of RPV RAM, Subtype A6/A1<sup>1</sup>, BMI  $\geq 30$  kg/m<sup>2</sup>**

Baseline Factors (number)	Virologic Successes (%) <sup>2</sup>	Confirmed Virologic Failure (%) <sup>3</sup>
0	694/732 (94.8)	3/732 (0.41)
1	261/272 (96.0)	1/272 (0.37) <sup>4</sup>
$\geq 2$	25/35 (71.4)	9/35 (25.7) <sup>5</sup>
<b>TOTAL</b>	980/1039 (94.3)	13/1039 (1.25)
(95% Confidence Interval)	(92.74%, 95.65%)	(0.67%, 2.13%)

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

<sup>2</sup> Based on the FDA Snapshot algorithm of RNA  $< 50$  copies/mL.

<sup>3</sup> Defined as two consecutive measurements of HIV RNA  $> 200$  copies/mL.

<sup>4</sup> Positive Predictive Value (PPV)  $< 1\%$ ; Negative Predictive Value (NPV) 98%; sensitivity 8%; specificity 74%

<sup>5</sup> PPV 26%; NPV 99.6%; sensitivity 69%; specificity 97.5%

RAM: resistance-associated mutations

### **Patient reported outcomes**

Patient reported outcomes were assessed by several distinct measures.

Treatment satisfaction significantly improved in the cabotegravir and rilpivirine injections group compared with daily oral antiretroviral therapy (CART) group (mean difference [95% CI] in HIV Treatment Satisfaction Questionnaire (HIVTSQs) at weeks 24 and 44 was 3.9 [3.0, 4.7] ( $p < 0.001$ ) and 3.3 [2.5, 4.2] ( $p < 0.001$ ) respectively, in the pooled ATLAS and FLAIR analysis). Key items driving this difference were "satisfaction to continue with treatment" as well as "flexibility" and "convenience".

Treatment acceptance also significantly improved in the cabotegravir and rilpivirine injections group compared with CART group (mean difference [95% CI] in ACCEPT General Dimension at weeks 24 and 44 was 4.9 [2.4, 7.5] ( $p < 0.01$ ) and 6.8 [4.3, 9.4] ( $p < 0.001$ ) respectively, in the pooled ATLAS and FLAIR analysis). Items were assessing acceptability based on advantages and disadvantages of treatment option.

Acceptability of injection site reactions (including pain) significantly improved from Week 5 (2.09 points) to weeks 24 (1.66 points;  $p < 0.001$ ) and 48 (1.61 points;  $p < 0.001$ ) in a pooled ATLAS and FLAIR analysis for participants in the cabotegravir and rilpivirine injections group according to "Acceptability of ISRs" dimension of Perception of Injection Questionnaire (PIN) (adapted from the Vaccinees' Perception of Injection (VAPI) Questionnaire) with 86% and

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84% of participants in ATLAS and FLAIR finding pain following injections as "totally" or "very acceptable" at week 48.

According to the three dimensions of the HIV/AIDS Targeted Quality of Life (HAT-QoL) included in the study, "medication concerns" significantly improved in the cabotegravir and rilpivirine injections group compared with CART (mean difference [95% CI] at weeks 24 and 48 was 3.4 [1.9, 4.9]( $p < 0.001$ ) and 3.5 [1.8, 5.2]( $p < 0.001$ ) respectively, in the pooled ATLAS and FLAIR analysis) mostly driven by the improvement in "treatment burden" scores. "Life satisfaction" and HIV "disclosure worries" showed no significant difference between treatment groups, indicating no impact of either treatment options on those concepts. SF-12 mental and physical component scores showed no significant difference in change from baseline between treatment groups at weeks 24 and 48, which indicates no improvement or worsening in mental or physical health status of participants in both groups.

## 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.

### Absorption

Cabotegravir is rapidly absorbed following oral administration, with median  $T_{max}$  at 3 hours post dose for the tablet formulation. The linearity of cabotegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, cabotegravir pharmacokinetics was dose-proportional to slightly less than proportional to dose from 5 mg to 60 mg. 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<sub>(0-∞)</sub> 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  $\leq 0.08$  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



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concentration ratio [median (range)] (n=16) was 0.003 (0.002 to 0.004), one week following a steady-state cabotegravir (monthly dose or every 2 month dose) 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.

### **Metabolism**

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).

### **Excretion**

Cabotegravir has a mean terminal half-life of 41 h and an apparent clearance (CL/F) of 0.21 L per hour observed following oral administration in healthy subjects.

### **Polymorphisms in drug metabolising enzymes**

In a meta-analysis of healthy and HIV-infected subject trials, HIV-infected subjects with UGT1A1 genotypes conferring poor cabotegravir metabolism had a 1.2-fold mean increase in steady-state cabotegravir AUC, C<sub>max</sub>, and C<sub>tau</sub> following injection administration compared with subjects with genotypes associated with normal metabolism via UGT1A1. 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

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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.

#### HBV/HCV Co-infected Patients

There are limited data for the use of cabotegravir in subjects with HBV co-infection. There are limited data for the use of cabotegravir in subjects with HCV co-infection.

### **5.3 PRECLINICAL SAFETY DATA**

#### **Genotoxicity**

Cabotegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

#### **Carcinogenicity**

Cabotegravir was not carcinogenic in long term oral studies in the mouse and rat at doses resulting in up to 7–8 and 26 times, respectively (75 mg/kg/day in male mice and rats and 35 mg/kg/day in female mice), the maximum AUC in patients.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

Lactose monohydrate  
Microcrystalline cellulose  
Hypromellose  
Sodium starch glycolate Type A  
Magnesium stearate  
Titanium dioxide  
Macrogol

### **6.2 INCOMPATIBILITIES**

In the absence of compatibility studies cabotegravir injection must not be mixed with other medicinal products

### **6.3 SHELF LIFE**



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## **9 DATE OF FIRST APPROVAL**

16 February 2021

## **10 DATE OF REVISION**

Not applicable

Version 1.0

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