swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Vocabria

International non-proprietary name:	cabotegravir
Pharmaceutical form:	prolonged-release suspension for injection
	film-coated tablets
Dosage strength(s):	prolonged-release suspension for injection: 200 mg/mL
	film-coated tablets: 30 mg
Route(s) of administration:	intramuscular use
	oral
Marketing authorisation holder:	ViiV Healthcare GmbH
Marketing authorisation no.:	67740
Decision and decision date:	extension of therapeutic indication approved on 14 October 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

3TC	Lamivudine
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC(0-τ)	Area under the plasma concentration-time curve over the dosing interval
AUC_{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
CAB	Cabotegravir
cART	Combination antiretroviral therapy
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
C_{τ}	Concentration at the end of a dosing interval
cp	copies
CPK	Creatine phosphokinase
CVF	Confirmed virological failure
CYP	Cytochrome P450
DDI	Drug-drug interaction
DGT	Dolutegravir
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HIV-1	Human Immunodeficiency Virus-1
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IM	Intramuscular
Ig	Immunoglobulin
INN	International non-proprietary name
INSTI	Integrase strand transfer inhibitor
ITT	Intention-to-treat
ISR	Injection site reaction (depending on context also: incurred sample reanalysis)
LoQ	List of Questions
LA	Long-acting
LSFU	Long-term safety and washout pharmacokinetic follow-up
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OLI	Oral lead-in

PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PI	Protease inhibitor
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
Q4W	Dosing every 4 weeks
Q8W	Dosing every 8 weeks
RMP	Risk management plan
RPV	Rilpivirine
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adolescents (from age of 12 and body weight ≥35 kg) who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen for at least 6 months before the switch to the cabotegravir-rilpivirine combination and who are without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class.

2.2.2 Approved indication

Vocabria injections are indicated in combination with rilpivirine injections for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adolescents aged 12 and over and with a body weight of at least 35 kg, who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral treatment for at least 6 months prior to the switch to the cabotegravir-rilpivirine combination and have no known or suspected resistance to, or no history of virological failure with agents of the NNRTI and INI class (see "Clinical efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The requested dosage for adolescents is the same as the dosage authorised for adults.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	2 September 2024
Formal objection	12 September 2024
Response to formal objection	25 September 2024
Formal control completed	2 October 2024
List of Questions (LoQ)	4 March 2025
Response to LoQ	30 April 2025
Preliminary decision	30 June 2025
Response to preliminary decision	25 August 2025
Final decision	14 October 2025

Decision	approval

3 Medical context

Human Immunodeficiency Virus-1 (HIV-1) infection is a life-threatening infection of major public health interest. If left untreated or treated sub-optimally, the course of HIV-1 infection is characterised by deterioration in immune function, with the subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death.

Worldwide there are around 40 million people living with HIV and it is estimated that in Switzerland, around 17,000 persons are living with HIV. In 2024, 318 new HIV diagnoses were made in Switzerland.

Generally, the initial antiretroviral treatment regimen for a treatment-naive patient consists of a three-drug regimen containing:

- two nucleoside reverse transcriptase inhibitors (NRTIs), also called an NRTI backbone, plus a third drug from one of the following three drug classes (anchor drug):
  - an integrase strand transfer inhibitor (INSTI),
  - a non-nucleoside reverse transcriptase inhibitor (NNRTI),
  - or a boosted protease inhibitor (PI).

Recently, two-drug regimens for the treatment of people with HIV have also been approved:
- DTG (dolutegravir) plus 3TC (lamivudine)
- DTG (dolutegravir) plus RPV (rilpivirine)

Furthermore, long-acting intramuscular injections have recently been approved for the treatment of HIV-1 infection in the adult population. Vocabria/Rekambys is a 2-drug antiretroviral (ARV) regimen. Vocabria contains the INSTI cabotegravir (CAB) and Rekambys contains the NNRTI rilpivirine.

4 Nonclinical aspects

4.1 Nonclinical conclusions

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable. Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

5 Clinical aspects

5.1 Clinical pharmacology

PK data was collected from virologically suppressed HIV-infected adolescents enrolled in the Phase 1/2 study 208580/MOCHA. The adolescent subjects received the approved doses of either CAB (Cohort 1C), RPV (Cohort 1R), or CAB in combination with RPV (Cohort 2). Rich and sparse PK samples were collected in the oral lead-in (OLI) and injection phases, respectively.

Target ranges for CAB concentrations were specified based on earlier studies. Following oral dosing, AUC(0-τ), Cτ, and Cmax for Cohort 1C met the pre-specified study targets. Whereas Week 16 Cτ was within the target range for both dosing regimens, Q4W and Q8W, following intramuscular (IM) injections in Cohort 1C, the 5th percentile Week 16 Cτ threshold was not met for the Q8W regimen. Higher concentrations of one active substance may compensate for low concentrations of the other with regard to efficacy. Overall, no association was observed between low CAB and/or low RPV trough concentrations and a loss of viral load suppression.
It appears that C0 values were generally higher in Cohort 2 subjects receiving CAB Q8W as compared to Cohort 1C subjects. However, both cohorts maintained CAB concentrations within the therapeutic range. Furthermore, this may be associated with outliers in Cohort 1C and the variability across cohorts.

The previously developed adult population PK model for CAB was updated using additional data from adolescents enrolled in the study 208580/MOCHA, as well the two supportive studies 213002 and 213003. The final analysis dataset included 1647 adult subjects and 209 adolescent subjects. The lowest body weight in the adult and adolescent populations was 41.2 kg and 35.2 kg, respectively. The adolescent body weight range covers the indication wording. Of note, the majority of the adolescent subjects were Black/African American (78.5%) and non-white (96.7%). In line with the previous analysis, the CAB PK was well described by a 2-compartment disposition model with first-order oral and LA IM absorption and first-order elimination. No additional covariates were identified as compared to the previous adult population PK model.

Based on CAB post hoc PK parameters, exposures in adolescents were slightly higher, but overall comparable to those in adults. Most likely, the increased CAB exposure in adolescents can be attributed to the lower body weight. No adapted DDI risk management is required for adolescents.

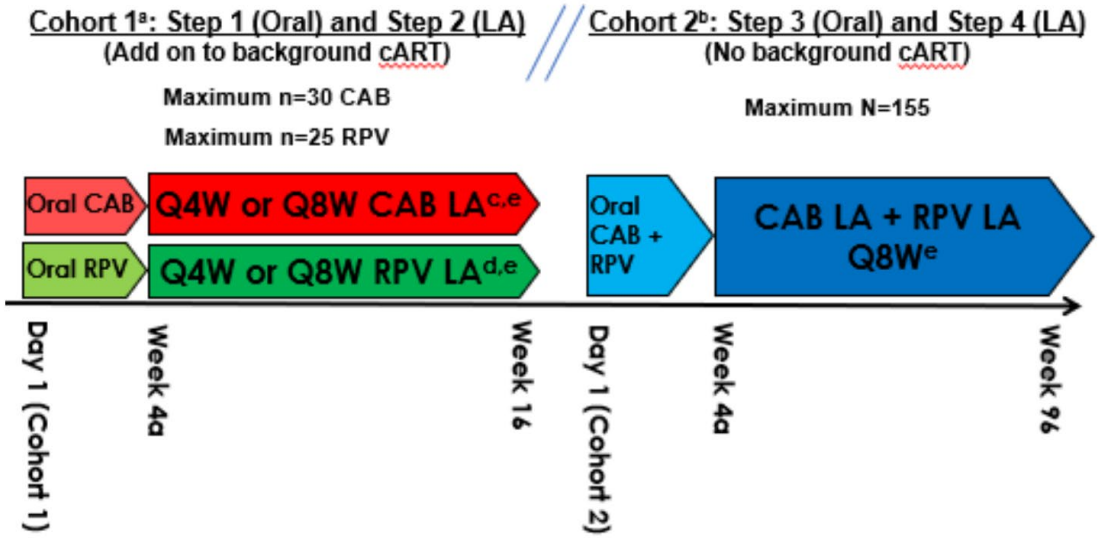
5.2 Dose finding and dose recommendation

No new information on dosing or dosing intervals is provided in this submission. The doses and dosing intervals recommended for adolescents are aligned with those for adults.

5.3 Efficacy

The application is supported by one study, Study 208580 (IMPAACT 2017 or MOCHA), an ongoing Phase 1/2, multicentre, open-label, non-comparative study of the safety, acceptability, tolerability, and PK of oral CAB and injectable CAB LA and injectable RPV LA in virologically suppressed adolescents (12 to <18 years of age) with HIV-1 and weighing at least 35 kg who are receiving stable cART consisting of 2 or more drugs from 2 or more classes of ARV drugs. A schematic of the study design for Study 208580 is presented in Figure 1.

Figure 1: Overview of study design for treatment period (CSR Study 208580, page 26)



a. Cohort 1 participants were assigned to Cohort 1C (participants received CAB + cART) or Cohort 1R (participants received RPV + cART) based on their pre-study cART regimen.
a. Cohort 2 was open to eligible participants who had completed Cohort 1 as well as eligible participants who had not been previously enrolled in the study.
b. PI/NNRTI-based cART
c. INSTI-based cART
d. Participants enrolled to Cohort 1 under Protocol Version 2.0 received Q4W LA injections during the injection phase. Participants enrolled in both Cohort 1 and Cohort 2 under Protocol Version 3.0 received Q8W LA injections during the injection phase.

Adolescent participants living with HIV were enrolled in **Cohort 1** and assigned to **Cohort 1C** (CAB+cART) or **Cohort 1R** (RPV+cART) based on their background cART regimen. Participants on PI-based or NNRTI-based cART were assigned to Cohort 1C, while participants on INSTI-based cART were assigned to Cohort 1R.

Following enrolment, participants received at least 4 weeks of oral lead-in (OLI) of CAB or RPV while continuing their background cART (Cohort 1 **Step 1**) to assess tolerability before starting the LA injections of the assigned drug. Specifically in Cohort 1C, participants received CAB 30 mg once daily orally for 4 to 6 weeks in addition to cART.

Participants were then administered Q4W for a total of 3 injections or Q8W for a total of 2 injections while continuing the background cART (Cohort 1 **Step 2**), similar to the two Q4W or Q8W adult-dosing schemes. Specifically in Cohort 1C this consisted of 3 IM injections of CAB LA each separated by 4 weeks (600 mg for first injection and 400 mg for second and third injections) in addition to cART or, after the protocol was amended, 2 IM injections of CAB LA 600 mg 4 weeks apart in addition to cART. Week 16 was considered the end of injection phase.

For **Cohort 2**, participants were either enrolled directly in Cohort 2, or adolescents who participated in Cohort 1 Step 2 could continue study participation in Cohort 2, if eligible. Cohort 2 participants discontinued their pre-study cART regimen and received both CAB and RPV at the doses established in Cohort 1. All Cohort 2 participants received both oral CAB 30 mg + oral RPV 25 mg once daily orally for 4 to 6 weeks (**Step 3**) followed by both CAB LA 600 mg + RPV LA 900 mg injections at Week 4 and Week 8, followed by injections Q8W through Week 96 (**Step 4**).

Participants who permanently discontinued injectable study product were to continue on-study for an additional 48 weeks after their last injection for long-term safety and washout pharmacokinetic follow-up (LSFU).

The primary study endpoints were related to safety and PK; **there were no primary efficacy endpoints as the number of patients was limited. The secondary efficacy endpoints included**:

Cohort 1:
- Participants with plasma HIV-1 RNA <50 cp/mL through Week 16
- Participants with protocol-defined confirmed virological failure

Cohort 2:
- Participants with plasma HIV-1 RNA <50 cp/mL through Week 24
- Participants with plasma HIV-1 RNA <50 cp/mL at Week 24 per snapshot algorithm
- Participants with plasma HIV-1 RNA <200 cp/mL through Week 24
- Participants with plasma HIV-1 RNA <200 cp/mL at Week 24 per snapshot algorithm
- Participants with protocol-defined confirmed virological failure

Efficacy data are presented for the All-Treated Population (that is participants who took at least 1 dose of any CAB product). **Results of Cohort 1R were not presented as they relate to the rilpivirine arm of the study.**

Cohort 1 was conducted in a total of 15 sites in 4 countries (Botswana, Thailand, US, and South Africa). Cohort 2 was conducted in a total of 18 sites in 5 countries (Botswana, Thailand, US, South Africa, and Uganda). For Cohort 1C, participants were enrolled at sites in the US (26.7%), Thailand (26.7%), and South Africa (46.7%). The majority of participants had a baseline CD4 cell count of at least 500 cells/mm^3; no participants had a baseline CD4 cell count less than 350 cells/mm^3. The majority of Cohort 2 participants were enrolled at sites in South Africa (29.9%) or Thailand (25.0%) and had a baseline CD4 cell count of at least 500 cells/mm^3; 4 (2.8%) participants had a baseline CD4 cell count less than 350 cells/mm^3. Most participants were therefore not deeply immunocompromised (with the limitation that the CD4 nadir values of the patients before any cART treatment are not known). Approximately half the participants were male and approximately half were female.

For Cohort 1C, the All-Treated Population included **30** participants (**8** Cohort 1C Q4W and **22** Cohort 1C Q8W participants). For Cohort 2, the All-Treated Population included **144** participants (including 44 participants who had previously participated in Cohort 1 and continued to Cohort 2). In consequence, most patients were on a Q8W regimen during the LA part of their treatment. Treatment compliance was excellent, at nearly 100% during both the oral lead-in and injection phases.

In Cohort 1C, 100% (n=28/28) of participants with a viral load assessment at **Week 16** were virologically suppressed (plasma HIV-1 RNA value <50 cp/mL). This was for both Q4W (n=7) and Q8W (n=21) dosing regimens. Two participants had no viral load evaluation at Week 16 in cohort 1C.

Through Week 16, 1 participant in Cohort 1C had quantifiable HIV-1 RNA values > 50 cp/mL (but under 200 cp/mL) at Week 8 and resuppressed at Week 12. Of note, while on LSFU the participant had a Confirmed Virological Failure (CVF) approximately 46 weeks past the last CAB injection (LSFU Week 48) while on cART. Genotypic testing at the CVF visit showed no CAB or RPV resistance-associated mutations. Nine months after the Cohort 1 LSFU Week 48 visit, the participant was enrolled in Cohort 2 and, after an elevated HIV-1 RNA at Cohort 2 entry (643 copies/mL), the participant was suppressed on study treatment through Week 64.

For Cohort 2, a total of 159 participants were screened in Cohort 2 and 144 participants were enrolled. As for Cohort 1C, treatment compliance was excellent, at nearly 100% during both the oral lead-in and injection phases.

In Cohort 2, 98.6% (n=139/141) of participants with a viral load assessment at **Week 24** were virologically suppressed. The 2 participants with HIV-1 RNA ≥50 cp/mL at Week 24 returned to HIV-1 RNA values <50 cp/mL at Week 32 or Week 40, and remained suppressed at subsequent visits. Per the snapshot algorithm analysis at Week 24 based on the HIV-1 RNA <50 cp/mL, 139 of 144 Cohort 2 participants (96.5%) had outcomes of virological success.

With the response to the LoQ, the applicant provided Week 48 data indicating that, in Cohort 2 participants (N=144), 97.2% achieved HIV-1 RNA <50 cp/mL per snapshot analysis, confirming the efficacy presented at Week 24 in the initial application.

Overall, study MOCHA showed with its secondary efficacy endpoints excellent anti-HIV-1 activity with nearly 100% virological control in both Cohort 1C and Cohort 2.

5.4 Safety

Overall safety database

Safety was assessed with the MOCHA study. The All-Treated Population (all participants who took at least 1 dose of any study intervention) was used for the safety analyses.

The safety analyses for Cohort 1C were conducted for the period from the start of study intervention administration (CAB) through Week 4 (oral lead-in) and through Week 16 (injection phase). Following Week 16, participants were followed (on cART, off study intervention) for up to an additional 48 weeks as part of LSFU. The safety analyses for Cohort 2 were conducted for the period from the start of study intervention administration (CAB + RPV) through Week 4 (oral lead-in) and continuing to the injection phase (CAB LA + RPV LA Q8W) for the Week 24 analysis. With the response to the LoQ, the applicant provided safety data up to Week 48 which was consistent with Week 24 data. As the study is ongoing and it is planned to continue injections until Week 96, longer-term safety data will become available.

30 participants were enrolled in Cohort 1C (CAB + cART) and 144 participants were enrolled in Cohort 2 (CAB + RPV). For the entire study, the median exposure to study intervention for Cohort 1C was 134 days (Q1, Q3: 133 - 136) and for Cohort 2, 371.5 days (range 15, 682). For Cohort 2, at the time of the Week 24 analysis, the largest percentage of participants (n= 74, 51.4%) have had 7 injection visits, with the next largest (n=24, 16.7%) having 6 injection visits. There have been 7 participants (4.9%) with 12 injection visits. In terms of number of weeks on treatment, the largest percentage of participants (n=113, 78.5%) have been on treatment for 48 to 71 weeks

Overall > 95% of participants completed the Week 16 and Week 24 visits.

Adverse events

For Cohort 1, data through Week 16 were presented because the Week 16 analysis is considered to capture the CAB or RPV injection phase for Cohort 1 (Figure 1). For Cohort 2, all available data (that is beyond Week 24) were presented.

Across the cohorts, the most commonly reported AE was injection site pain. Other than injection site pain in Cohort 1, common AEs (reported in ≥3 participants in total) were cough, oropharyngeal pain, and nasal congestion. Other than injection site pain in Cohort 2, the most commonly reported (by ≥10% of participants) AEs were cough, blood pressure increased, headache, nasal congestion, and upper respiratory tract infection.

Regarding adverse events related to the study drug in Cohort 1C through Week 16, 30.0% (n=9/30) of participants reported ISRs of injection site pain from the intramuscular administration.

Other than ISRs, AEs assessed as related to study intervention (Diarrhoea, Swelling, Scar, Decreased appetite, Headache, Insomnia) were reported by single participants and were ≤Grade 2 except for 1 participant with insomnia, which was Grade 3 in intensity.

Regarding adverse events related to the study drug in Cohort 2 (All available data), as for Cohort 1 the majority (34%, n=49/144) were ISRs. Of these, there was 1 participant with Grade 3 injection site pain and 2 participants with Grade 3 injection site abscess. Other than ISRs, AEs assessed as related to study intervention generally were reported by single participants. Non-ISR AEs assessed as related to study intervention and reported by >1 participant were headache, nausea, rash, and pruritic rash. All non-ISR AEs assessed as related to study intervention were ≤Grade 2.

The were no specific issues regarding adverse events during the oral lead-in phase.

For serious adverse events (SAEs), 1 participant in Cohort 1C and 2 participants in Cohort 2 had SAEs not related to study intervention. There were no **deaths** during the study.

Some adverse events of special interest **(AESIs)** were defined for the adult CAB + RPV - oral and LA -. For both Cohort 1C and Cohort 2 no AESIs relevant to hypersensitivity reactions; neuropsychiatric events of suicidal ideation/behaviour, bipolar disorder, psychosis, or mood disorders; hepatotoxicity; pancreatitis; or impact on creatinine were reported. All ISRs in Cohort 1C were ≤ Grade 2 in intensity, nonserious, and not treatment-limiting. For Cohort 2, one third of participants had an ISR, most had an ISR that was Grade 1 or 2. Two participants had Grade 3 ISRs (with injection site abscess). There were no Grade 4 or 5 ISRs. Most ISRs were injection site pain. In Cohort 1C, 2 participants developed a rash, all events were ≤ Grade 2, none were serious, and none led to discontinuation of study intervention. In Cohort 2, 4 participants reported having a rash or rash-like events. In 3 participants, the events occurred early on in Cohort 2 participation (during or shortly after OLI) and were considered related to study intervention. A fourth participant had an event of rash during the injection phase, which was considered unrelated to study intervention. All events were Grade 1 in intensity and non-serious. None led to discontinuation of study intervention. In Cohort 1C, no participant had an AE related to weight gain. In Cohort 2, 2 participants had AEs associated with weight increased that were Grade 1 in intensity and considered to be not related to study intervention in participants already overweight at baseline.

Clinically important changes in laboratory assessments for participants in study MOCHA were assessed as not related to the study intervention. Across the cohorts, the majority of participants had no changes in grade for all graded chemistry laboratory parameters. Grade 1 or 2 changes were observed in a few participants for alanin-aminotransferase (ALT), bilirubin, and lipase. Most participants did not have any grade shift from baseline in renal parameters Changes to Grade 3 were observed for serum creatinine (Cohort 1C only) and creatinine clearance (CrCl), and changes to Grade 4 were observed for creatine phosphokinase (CPK) (all CPK elevations were related to either exercise or a current medical condition). All were assessed as not related to study intervention. No participants in either cohort had an AESI relevant to hepatotoxicity. There were no clinically important changes in haematology parameters.

Regarding vital signs, no clinically important findings have been noted in the study and regarding electrocardiogram (ECG), there were no data indicative of a prolongation of the QTc interval.

Overall, with the limited number of participants in study MOCHA, which limits the interpretation of the safety results, it is considered that there were no new safety signal related to Vocabria in the adolescent population in comparison to the adult population.

5.5 Final clinical benefit risk assessment

Beneficial effects and respective uncertainties
CAB exposures in adolescents were slightly higher, but overall comparable to those in adults.

Clinical efficacy in the ongoing Phase 1/2 MOCHA study consisted of secondary efficacy endpoints assessing viral load suppression. In the all-treated population, these indicated that in Cohort 1C (CAB+cART) 100% (n=28/28) of participants with a viral load assessment at Week 16 and in Cohort 2 (CAB+RPV) 98.6% (n=139/141) of participants with a viral load assessment at Week 24 were virologically suppressed (i.e. HIV-1 RNA <50 cp/mL). These results are supported by Week 48 data.

Regarding participant experience outcomes, the majority of patients were not bothered by pain during and following injections, as assessed by a questionnaire.

The main uncertainty is that, although compliance (and therefore drug exposure) was excellent during the MOCHA study, it remains to be seen whether the same level of compliance can be achieved in a real-world setting. Indeed, in case of adherence problems with missing injections, patients will be exposed for long periods to sub-therapeutic concentrations of both drugs, which will promote the emergence of resistance mutations to the INSTI and NNRTI classes. Compliance requirements are clearly mentioned in the Information for healthcare professionals.

Unfavourable effects and respective uncertainties
There were no specific signals related to CAB use in the adolescent population in study MOCHA in comparison to adult data already discussed in the previous approval and mentioned in the Information for healthcare professionals. The majority of drug-related adverse events were injection site reactions, which is expected. These were all ≤Grade 2 and resolved in a few days.

The limited number of participants (n=174) in study MOCHA limits AE detection and interpretation. As the study is ongoing and it is planned to continue injections through Week 96, further safety data will be gathered by the applicant.

Benefit-risk balance
In HIV-1 infected adolescents 12 years of age and older and weighing at least 35 kg who are virologically suppressed, CAB + RPV long-acting injections showed high clinical efficacy up to Week 24 with > 95% of patients achieving viral suppression. There were no specific safety issues in the studied population. The benefit-risk of Vocabria for the requested indication is considered positive.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Vocabria was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Vocabria prolonged-release suspension for injection

Composition

Active substances

Cabotegravir.

Excipients

Mannitol (E421), polysorbate 20, macrogol 3350, water for injection ad solutionem per 1 mL.

Pharmaceutical form and active substance quantity per unit

Prolonged-release suspension for injection for intramuscular administration:
Each 2 mL vial contains 400 mg cabotegravir (200 mg/mL) as free acid.
Each 3 mL vial contains 600 mg cabotegravir (200 mg/mL) as free acid.

Indications/Uses

Vocabria injections are indicated in combination with rilpivirine injections for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents aged 12 and over and with a body weight of at least 35 kg, who have been virologically suppressed (HIV-1 RNA <50 copies/mL*)* on a stable antiretroviral treatment for at least 6 months prior to the switch to the cabotegravir-rilpivirine combination and have no known or suspected resistance to or no history of virological failure with agents of the NNRTI and INI class (see *"Clinical efficacy"*).

Dosage/Administration

Usual dosage
Adults and adolescents (aged 12 and over and with a body weight of at least 35 kg)
Treatment must be managed by a physician experienced in the treatment of HIV infection.

Vocabria injections must be administered by a healthcare professional.
Vocabria injections should always be given in combination with rilpivirine injections for the treatment of HIV-1 infection. Therefore, people should also always refer to the prescribing information for rilpivirine injections.
Vocabria injections may be initiated with an oral lead-in or without (starting directly with injections). The physician and patient can decide either to use cabotegravir tablets as part of an oral lead-in before starting with Vocabria injections, with a view to assessing the tolerability of cabotegravir (see Table 1), or to start therapy with Vocabria injections directly.
Vocabria injections may be administered on a monthly basis or every 2 months (see Table 2 for the monthly dosage recommendations and Table 3 for the dosage recommendations for every 2 months). The physician and patient should discuss both dosing options prior to starting Vocabria injections and select the most suitable dosing frequency for the patient.
Prior to starting Vocabria injection, the treating physician should have carefully selected patients who agree to the required injection schedule and advise 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.
After stopping Vocabria and rilpivirine injection therapy, it is essential to initiate an alternative fully suppressive antiretroviral regimen within a month following the last injection of Vocabria in the case of a monthly dose and within 2 months of the last Vocabria injection in the case of dosing every 2 months.

Oral lead-in

In the case of oral lead-in, the oral administration of cabotegravir tablets is recommended for approximately one month (at least 28 days, up to a maximum of 2 months) in virologically suppressed patients prior to the initiation of treatment with cabotegravir injections in order to assess tolerability to cabotegravir. One Vocabria tablet (30 mg) should be taken with one rilpivirine tablet (25 mg) once daily. When administered with rilpivirine, Vocabria tablets should be taken with a meal (see prescribing information for Vocabria tablets).

Table 1: Dosing schedule for oral lead-in

	ORAL LEAD-IN
Medicinal product	*During Month 1 (at least 28 days, maximum of 2 months) followed by first injection*[a]
Vocabria	30 mg once daily
Rilpivirine	25 mg once daily

[a.] *See dosing schedule for monthly injections in Table 2 and for injections every 2 months in Table 3.*

Monthly dosing (suspension for injection)

Initial injection (600 mg corresponding to a dose of 3 mL)

On the final day of current antiretroviral therapy or oral lead-in, an initial injection of 3 mL (600 mg) Vocabria (intramuscularly) is recommended (see “Mode of administration”).

Subsequent injections (400 mg corresponding to a dose of 2 mL)

After the initial injection of Vocabria, the recommended dose for subsequent injections is a single 2 mL (400 mg) intramuscular injection, administered once a month (see “Mode of administration”). Patients may be given injections up to 7 days before or after the date of the planned administration of the monthly 2 mL dose.

Table 2: Dosing schedule for monthly intramuscular administration

	INITIAL INJECTION *i.m.*	*SUBSEQUENT INJECTIONS* *i.m.*
Medicinal product	*Therapy started directly with injection: Month 1* *or* *following oral lead-in: one-time*	*One month after initial injection and monthly thereafter*
Vocabria	3 mL (600 mg)	2 mL (400 mg)
Rilpivirine	3 mL (900 mg)	2 mL (600 mg)

Dosing every 2 months (suspension for injection)

Initial injections (600 mg corresponding to a dose of 3 mL)

On the final day of current antiretroviral therapy or oral lead-in, the recommended initial intramuscular Vocabria injection is 3 mL (600 mg). One month later, a second intramuscular Vocabria injection of 3 mL (600 mg) should be administered. Patients may be given this second initial injection up to 7 days before or after the scheduled administration date.

Subsequent injections (600 mg corresponding to a dose of 3 mL)

After the second initial injection, the subsequent intramuscular Vocabria injections of 3 mL (600 mg) should be administered every 2 months. Patients may be given subsequent injections up to 7 days before or after the scheduled administration date.

Table 3: Dosing schedule for intramuscular administration every 2 months

	INITIAL INJECTIONS *i.m.*	*SUBSEQUENT INJECTIONS* *i.m.*
Medicinal product	*Therapy started directly with injection: Month 1 + 2 or following oral lead-in and 1 month thereafter*	*Two months after final initial injection and every 2 months thereafter*
Vocabria	3 mL (600 mg)	3 mL (600 mg)
Rilpivirine	3 mL (900 mg)	3 mL (900 mg)

Change in dosing frequency:

Dosage recommendations when switching from monthly administration to injections every 2 months

Patients switching from a schedule with subsequent injections every month to a dosing schedule with subsequent injections every 2 months should receive a single intramuscular injection of 3 mL (600 mg) Vocabria one month after the last 2 mL (400 mg) subsequent injection and then 3 mL (600 mg) every 2 months thereafter.

Dosage recommendations when switching from injections every 2 months to monthly injections

Patients switching from a dosing schedule with administration every 2 months to a monthly dosing schedule in the maintenance phase should receive a single intramuscular injection of 2

mL (400 mg) of Vocabria two months after the last 3 mL (600 mg) Vocabria injection and 2 mL (400 mg) monthly thereafter.

Missed injections

Adherence to the injection dosing schedule is strongly recommended. Patients who miss an injection appointment should be clinically reassessed to ensure resumption of therapy remains appropriate (see Table 4 and 5).

Missed monthly injection

Oral bridging treatment and resumption of monthly injections:

If a delay of more than 7 days from an injection appointment cannot be avoided, Vocabria tablets (30 mg once daily) may be used in combination with rilpivirine tablets (25 mg once daily) for up to 2 consecutive months.

Alternatively, another fully suppressive oral antiretroviral therapy may be used until injection therapy is resumed. The current HIV treatment guidelines should be taken into account when choosing the regimen. See *"Clinical efficacy"* for data on oral bridging treatment with other fully suppressive antiretroviral therapies.

The first dose of oral therapy must be taken one month (+/-7 days) after the last cabotegravir or rilpivirine injection, and injection therapy should be resumed on the last day of oral therapy (see Table 4). If more than two consecutive monthly injections are missed and need to be replaced, an alternative oral treatment should be started one month after the last injection of Vocabria.

Table 4: Recommended dosing schedule for the resumption of monthly injections after missed injection or after oral bridging treatment

Time since last injection	*Recommendation*
≤ 2 months:	Continue with the dosing schedule with 2 mL (400 mg) injection once a month as soon as possible
> 2 months:	Resume single injection of 3 mL (600 mg), and then continue the dosing schedule with 2 mL (400 mg) injections once a month

Missed 2-monthly injection:

Oral bridging treatment and resumption of injections every 2 months:

If a delay of more than 7 days from a scheduled injection appointment cannot be avoided, Vocabria tablets (30 mg) may be used in combination with rilpivirine tablets (25 mg) once daily for up to two consecutive months.

Alternatively, another fully suppressive oral antiretroviral therapy may be used until resumption of injection therapy. The current HIV treatment guidelines should be taken into account when choosing the regimen. See *"Clinical efficacy"* for data on oral bridging treatment with other fully suppressive antiretroviral therapies.

The first dose of oral therapy must be taken two months (+/-7 days) after the last Vocabria or rilpivirine injection, and injection therapy should be resumed on the last day of oral therapy (see Table 5).

Table 5: Recommended dosing schedule for the resumption of injections every 2 months after missed injections or after oral bridging treatment

Missed injection appointment	*Time since last injection*	*Recommendation*
Injection 2	*≤ 2 months:*	Resume 3 mL (600 mg) injection as soon as possible and continue with the dosing schedule with injections every 2 months.
	> 2 months:	Re-initiate with 3 mL (600 mg) dose, followed by a second 3 mL (600 mg) initial injection one month later and then continue with the dosing schedule with injections every 2 months.
Injection 3 or later	*≤ 3 months:*	Resume 3 mL (600 mg) injection as soon as possible and continue with dosing schedule with injections every 2 months.
	> 3 months:	Re-initiate with 3 mL (600 mg) dose, followed by a second 3 mL initial injection one month later and then continue with the dosing schedule with injections every 2 months.

Special dosage instructions

Hepatic impairment

No dosage adjustment is required in patients with mild to 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 *"Pharmacokinetics – Kinetics in specific patient groups"*).

Renal impairment

No dosage adjustment is required in patients with mild (creatinine clearance of ≥ 60 to < 90 mL/min), moderate (creatinine clearance of ≥ 30 to < 60 mL/min) or severe (creatinine clearance of ≥ 15 to < 30 mL/min) renal impairment who are not on dialysis (see *"Pharmacokinetics – Kinetics in specific patient groups"*).

Elderly patients

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 *"Pharmacokinetics – Kinetics in specific patient groups"*).

Children and adolescents

The safety and efficacy of cabotegravir in children under 12 years of age or adolescents with a body weight of less than 35 kg has not been established.

Mode of administration

For gluteal intramuscular (i.m.) injection use only. Do not inject intravenously.
It is important to take into consideration the BMI of the patient to ensure that the needle length is sufficient to reach the gluteus muscle.
The cabotegravir and rilpivirine injections should be administered at separate gluteal injection sites (on opposite sides) during the same visit. If opposite sides are not possible, the injections should be given at least 2 cm apart. A 2 cm space should also be kept from previous injection sites or any reactions at previous injection sites.
Please follow the detailed step-by-step instructions for injection in the instructions for use in the package. Follow these instructions carefully when preparing the suspension for injection to prevent the liquid from leaking.
Vocabria injections must be administered by a healthcare professional.

Contraindications

Cabotegravir is contraindicated in patients:

- with known hypersensitivity to cabotegravir or to any of the other components of the injection formulation
- receiving strong UGT1A1 inducers e.g. rifampicin, rifapentine, phenytoin, phenobarbital, carbamazepine and oxcarbazepine as they are expected to decrease cabotegravir plasma concentrations and may result in loss of virological response.

Vocabria injections are only indicated for treatment of HIV-1 infection in combination with rilpivirine injections; therefore, the prescribing information for rilpivirine injections should also be consulted.

Warnings and precautions

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. In order to identify patients at risk of a hypersensitivity reaction, oral lead-in with cabotegravir was performed in clinical trials. Discontinue cabotegravir and other suspected active substances immediately if signs or symptoms of a hypersensitivity reaction develop (including severe skin rash, or skin rash accompanied by fever, general malaise, fatigue, muscle or joint pain, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). In this case, the patient's clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated if necessary (see *"Dosage/Administration", "Contraindications", "Long-acting properties of cabotegravir injection", "Undesirable effects", "Clinical efficacy"*).

Long-acting properties of cabotegravir injection

Residual concentrations of cabotegravir injection may remain in the patients' circulation for prolonged periods (up to 12 months or longer). Therefore, the prolonged release of cabotegravir beyond the active dosing period has to be taken into consideration in the individual benefit/risk assessment and when the medicinal product is discontinued (see *"Warnings and precautions (Hypersensitivity reactions, Hepatoxicity)", "Interactions with other agents", "Pregnancy, lactation", "Undesirable effects", "Pharmacokinetics" and "Overdose").*

There is no mechanism by which the release of cabotegravir after intramuscular injection can be stopped or neutralised or removed from the muscle (e.g. by aspiration) or the blood (e.g. by haemodialysis) due to strong protein binding.

Hepatotoxicity

Hepatotoxicity has been reported in a limited number of patients receiving cabotegravir with or without known pre-existing hepatic disease (see *"Undesirable effects"*).

Monitoring of liver function values is recommended. Cabotegravir should be discontinued if hepatotoxicity is suspected (see *"Long-acting properties of cabotegravir injection")*.

Risk of resistance following treatment discontinuation

To minimise the risk of developing viral resistance, it is essential to initiate an alternative, fully suppressive antiretroviral therapy 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 virological failure is suspected, an alternative therapy should be adopted as soon as possible.

Opportunistic infections

Patients receiving cabotegravir or any other antiretroviral treatment may still be at risk of developing opportunistic infections or other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these HIV comorbidities.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome has been reported in patients receiving combination antiretroviral therapy. In the initial phase of combination antiretroviral therapy, patients whose immune systems respond to treatment may develop an inflammatory reaction to indolent or residual opportunistic infections (e.g. with *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jirovecii* pneumonia and tuberculosis), which may require further evaluation and treatment. There have also been reports of autoimmune diseases (such as Graves' disease and autoimmune hepatitis) occurring as part of an immune reconstitution inflammatory syndrome. However, the timing of onset is more variable, and these events may occur many months after the start of treatment.

Transmission of infection

The results of observational studies have shown there is no risk of sexual transmission of HIV if viral suppression is achieved and maintained. However, the risk of sexual transmission of HIV cannot be ruled out if the prescribed ART is not taken on a regular basis and/or viral suppression is not achieved and maintained.

Concomitant treatment with rilpivirine

Vocabria injections are indicated for the treatment of HIV-1 infection in combination with rilpivirine; therefore, the prescribing information for rilpivirine injections should also be consulted.

Interactions with medicinal products

Caution should be exercised when prescribing Vocabria together with other medicinal products that may reduce cabotegravir exposure (see *"Interactions"*).

Concomitant use of Vocabria injections with rifabutin is to be avoided (see *"Interactions"*).

Patients with hepatitis B and hepatitis C virus co-infection

Patients with hepatitis B co-infection were excluded from participating in the studies with Vocabria. It is not recommended that patients with hepatitis B co-infection start treatment with Vocabria. The current treatment guidelines for the treatment of HIV infection in patients with hepatitis B virus co-infection must be followed, as well as the "*Interactions*" (see below).

Very limited data are available on the use of Vocabria in patients with hepatitis C virus co-infection. If hepatitis C infection occurs during treatment with Vocabria, the current treatment guidelines for HIV infection in patients with hepatitis C virus co-infection must be followed, as well as the *"Interactions"* (see below).

Interactions

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

Effect of Vocabria on other medicinal products

In vivo, cabotegravir did not have an effect on the CYP3A4 substrate midazolam. 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, breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic cation transporter (OCT)1, OCT2, OATP1B1, OATP1B3, multidrug and toxin extrusion (MATE) transporter 1, MATE 2-K, multidrug resistance protein (MRP) 2 or MRP4.

In vitro, cabotegravir inhibited the organic anion transporters (OAT) 1 (IC_{50}=0.81 µM) and OAT3 (IC_{50}=0.41 µM). However, based on physiologically based pharmacokinetic (PBPK) modelling, no interactions with OAT substrates are 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.

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

Effect of other medicinal products on Vocabria
Cabotegravir is primarily metabolised by UGT1A1, 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 decreased efficacy (see *"Contraindications"*).
Simulations using physiologically based pharmacokinetic (PBPK) modelling show that no clinically significant interactions are expected in relation to the concomitant administration of cabotegravir with other medicinal products that inhibit UGT enzymes.
In vitro, cabotegravir was not a substrate of OATP1B1, OATP1B3, OATP2B1 or OCT1.
Cabotegravir is a substrate of P-gp and BCRP; however, because of its high permeability, no alteration in absorption is expected when administered concomitantly with either P-gp or BCRP inhibitors.

No drug interaction studies have been performed with cabotegravir as an injection. The drug interaction data provided in Table 6 are obtained from studies with oral cabotegravir.

Table 6: Interactions with other medicinal products

Effect of concomitantly administered medicinal products on the pharmacokinetics of cabotegravir[1]				
Concomitantly administered drug class + drug and dose	*Effects on drug concentration GMR (90% CI) No effect = 1.00*			*Recommendation for concomitant use*
	C_{max}	*AUC*	C_{τ} *or* C_{24}	
HIV-1 antiviral agents				
NNRTI Etravirine 200 mg twice daily	1.04 (0.99, 1.09)	1.01 (0.96, 1.06)	1.00 (0.94, 1.06)	Etravirine did not significantly affect the cabotegravir plasma concentration. No dose adjustment is necessary.
NNRTI Rilpivirine 25 mg once daily	1.05 (0.96, 1.15)	1.12 (1.05, 1.19)	1.14 (1.04, 1.24)	Rilpivirine did not significantly affect the cabotegravir plasma concentration. No dose adjustment is necessary.
Other agents				
Rifabutin 300 mg once daily	0.83 (0.76, 0.90)	0.77 (0.74, 0.83)	0.74 (0.70, 0.78)	As rifabutin can significantly reduce the plasma concentration of cabotegravir, concomitant administration should be avoided.
Rifampicin 600 mg once daily	0.94 (0.87, 1.02)	0.41 (0.36, 0.46)	0.50 (0.44, 0.57)	Rifampicin significantly decreased cabotegravir plasma concentrations due to induction of UGT metabolism, which is likely to result in loss of therapeutic effect. Dosage recommendations for the concomitant administration of Vocabria with rifampicin have not been established and the concomitant administration of Vocabria with rifampicin is contraindicated.

[1] Cabotegravir 30 mg administered orally once daily for all studies except for rifampicin, where cabotegravir 30 mg was administered as single dose

GMR = geometric mean ratio

Effect of cabotegravir[1] on the pharmacokinetics of concomitantly administered medicinal products				
Concomitantly administered drug class + drug and dose	*Effects on drug concentration GMR (90% CI) No effect = 1.00*			*Recommendation for concomitant use*
	C_{max}	*AUC*	*C_τ or C_{24}*	
HIV-1 antiviral agents				
Rilpivirine 25 mg once daily	0.96 (0.85, 1.09)	0.99 (0.89, 1.09)	0.92 (0.79, 1.07)	Cabotegravir did not significantly change rilpivirine plasma concentrations. No dose adjustment of rilpivirine is necessary when administered concomitantly with Vocabria.
Other agents				
Ethinylestradiol 0.03 mg once daily	0.92 (0.83, 1.03)	1.02 (0.97, 1.08)	1.00 (0.92, 1.10)	Cabotegravir did not significantly change ethinylestradiol/levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when administered concomitantly with Vocabria.
Levonorgestrel 0.15 mg once daily	1.05 (0.96, 1.15)	1.12 (1.07, 1.18)	1.07 (1.01, 1.15)	Cabotegravir did not significantly change levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when administered concomitantly with Vocabria.
Midazolam 3 mg	1.09 (0.94, 1.26)	1.10 (0.95, 1.26)	Not Available	Cabotegravir did not significantly change midazolam plasma concentrations to a clinically relevant extent. No dose adjustment of CYP3A substrates is necessary when administered concomitantly with Vocabria.
[1] Cabotegravir 30 mg administered orally once daily for all studies except for rifampicin, where cabotegravir 30 mg was administered as single dose *GMR = geometric mean ratio*				

Other agents expected to decrease cabotegravir concentrations without clinical data		
Concomitant agent	*Medicinal product*	*Recommendation for concomitant use*
Antimycobacterials	Rifapentine	Rifapentine, a metabolic inducer, may significantly decrease cabotegravir plasma concentrations; concomitant use is contraindicated.
Anticonvulsants	Carbamazepine, oxcarbazepine, phenytoin, phenobarbital	Metabolic inducers may significantly decrease cabotegravir plasma concentrations; concomitant use is contraindicated.

Pregnancy, lactation

Pregnancy

There are no studies of cabotegravir in pregnant women. The effect of cabotegravir on human pregnancy is unknown.
Animal studies have shown reproductive toxicity at exposures significantly above the maximum exposure for humans, indicating little relevance for clinical use (see *"Preclinical data"*).
The significance of these findings for human pregnancy is not known. Vocabria should not be used during pregnancy or in women who are planning to become pregnant or who do not use a reliable contraceptive method, unless the expected benefits justify the possible risks to the foetus or unborn child.
Women should be advised on the use of effective contraception. Cabotegravir and oestrogen- and/or progesterone-based contraceptives can be used concomitantly without dose adjustment (*see "Interactions"*).
After cabotegravir injection, residual concentrations have been detected in the body of patients for up to 12 months or longer, which should be considered for the duration of effective contraception (see *"Warnings and precautions"*).

Lactation

Based on animal studies, it can be assumed that cabotegravir passes into breast milk, although this has not been confirmed for humans.
After cabotegravir therapy, residual concentrations may still be present in breast milk for up to 12 months or longer after the last injection.
It is recommended that HIV-positive women do not breastfeed their babies to avoid HIV transmission and the possibility of undesirable effects in the breastfed infant.

Fertility

No data are available on the effects of cabotegravir on human fertility in men or women. Animal studies indicate no effects of cabotegravir on male or female fertility (*see "Preclinical data"*).

Effects on ability to drive and use machines

There have been no studies to investigate the effect of cabotegravir on the ability to drive and use machines. Vocabria can cause dizziness, headaches and nausea. 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 use machines.

Undesirable effects

Clinical trial data

Adverse drug reactions (ADRs) associated with cabotegravir alone or combination therapy of cabotegravir plus rilpivirine (monthly dosing or dosing every 2 months) are listed in Table 7.
The table shows all undesirable effects attributable to both the oral and injectable formulations of cabotegravir and rilpivirine.

Frequencies were calculated from Phase III clinical studies, and where they differed between the monthly schedule and the treatment schedule every 2 months, the highest frequency category is quoted in Table 7.
The most frequently reported ADRs from monthly dosing studies were injection site reactions (up to 84% of patients), headache (up to 12% of patients) and pyrexia[3] (10% of patients).
The most frequently reported ADRs from the ATLAS-2M study with dosing every 2 months were injection site reactions (76% of patients), headache (7% of patients) and pyrexia[3] (7% of patients).

The clinical ADRs are listed below by MedDRA system organ class and by frequency.
Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) and very rare (<1/10,000, including isolated reports).

Table 7: Undesirable effects

MedDRA system organ class	*Frequency**	*ADRs for combination therapy cabotegravir plus rilpivirine*
Immune system disorders	Uncommon	Hypersensitivity[5] (including angioedema[5], urticaria[5])
Metabolic and nutritional disorders	Common	Weight increased

Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
	Uncommon	Suicidal ideation or suicide attempts (in particular among patients with a history of depression or psychiatric disorders)
Nervous system disorders	Very common	Headache (12%)
	Common	Dizziness
	Uncommon	Somnolence Vasovagal reactions (in response to injections)
Gastrointestinal disorders	Common	Nausea Vomiting Abdominal pain[1] Flatulence Diarrhoea Lipase increased (grades 3-4)
Hepatobiliary disorders	Uncommon	Hepatotoxicity Transaminases increased (AST/ALT)
Skin and subcutaneous tissue disorders	Common	Rash[2]
	Very rare	Stevens-Johnson syndrome[5], toxic epidermal necrolysis[5]
Musculoskeletal and connective tissue disorders	Common	Myalgia Creatine phosphokinase increased (grades 3-4)
General disorders	Very common	Pyrexia[3] (10%)
	Common	Fatigue Asthenia Malaise

Administration site conditions: reactions at the injection site[4] (84%)	Very common	Pain (79%) Nodules (17%) Induration (12%)
	Common	Discomfort Swelling Erythema Pruritus Bruising Warmth Haematoma
	Uncommon	Cellulitis Abscess Anaesthesia Haemorrhage Discolouration

*The frequency of the identified undesirable effects is based on all reported events and is not restricted to those regarded by the investigator as, at least potentially, having some connection.

[1] Abdominal pain includes the following grouped MedDRA preferred terms: abdominal pain, upper abdominal pain.

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

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

[4] Injection site reactions listed in the table have been reported in 2 or more patients.

[5] Post-marketing experience

The general safety profile in Week 96 and Week 124 of the FLAIR study corresponded to the profile observed in Week 48, with no new safety findings identified. In the extension phase of the FLAIR study in Week 124, there were no new safety concerns as a result of dispensing with the oral lead-in in the case of direct introduction of rilpivirine plus cabotegravir injections without any oral lead-in.

The general safety profile in Week 152 of the ATLAS-2M study corresponded to the profile observed in Week 48 and Week 96, with no new safety findings identified.

Description of selected adverse reactions and additional information

Frequent adverse drug reactions with Vocabria/Rekambys once a month compared to standard daily oral therapy (CAR)

Table 8: Systemic undesirable effects reported in ≥1% of virologically suppressed subjects with HIV-1 infection in the pooled FLAIR and ATLAS studies (Week 48)

Undesirable effects	CAB+RPV (N=591)	CAR (N=591)
Headache	12%	6%
Pyrexia[3]	10%	2%
Diarrhoea	9%	7%
Creatine phosphokinase increased (grades 3-4)	8%	4%
Lipase increased (grades 3-4)	6%	3%
Nausea	5%	3%
Fatigue	5%	2%
Rash[2]	5%	3%
Dizziness	4%	1%
Myalgia	4%	1%
Abdominal pain[1]	4%	2%
Insomnia	4%	1%
Anxiety	4%	2%
Asthenia	3%	<1%
Vomiting	2%	1%
Depression	2%	2%
Malaise	2%	<1%
Abnormal dreams	1%	<1%

Flatulence	1%	<1%

[1] Abdominal pain includes the following grouped MedDRA preferred terms: abdominal pain, upper abdominal pain.

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

[3] Pyrexia includes the following grouped MedDRA preferred terms: pyrexia, feeling hot, body temperature increased.

CAR = current antiretroviral regimen

It should be noted that FLAIR and ATLAS were open-label switch studies (see also details in *"Clinical efficacy"*). Higher frequencies of undesirable effects have been reported in the cabotegravir and rilpivirine arm, which may either be attributed to the treatment regimen or due to bias caused by the study design.

Local injection site reactions (ISRs)

Monthly dosing

In Phase III studies (ATLAS, FLAIR and ATLAS-2M studies with monthly administration), up to 1% of patients discontinued treatment with Vocabria plus rilpivirine because of ISRs. Out of 30,393 injections, 6,815 ISRs were reported and the severity of the reactions was generally mild (Grade 1, 75% of patients) or moderate (Grade 2, 36% of patients). 4% of patients experienced severe (Grade 3) ISRs, and no patients experienced Grade 4 ISRs.

The median duration of overall ISR events was 3 days (1 day to 341 days), with up to 11% of patients reporting unresolved ISRs at the time of their next injection. The percentage of patients reporting ISRs decreased over time from 70% at Week 4 to 19% at Week 48.

Dosing every 2 months

In the ATLAS-2M study, less than 1% of patients discontinued treatment with Vocabria plus rilpivirine because of ISRs. Out of 8,470 injections, 2,507 ISRs were reported and the severity of the reactions was generally mild (Grade 1, 71% of patients) or moderate (Grade 2, 27% of patients). 3% of patients experienced severe (Grade 3) ISRs, and no patients experienced Grade 4 ISRs.

The median duration of overall ISR events was 3 days (1 day to 424 days), with 5% of patients reporting unresolved ISRs at the time of their next injection.

The percentage of patients reporting ISRs decreased over time from 70% at Week 4 to 20% at Week 48.

Weight gain

According to a pooled analysis of the FLAIR and ATLAS studies, at Week 48, patients who received cabotegravir plus rilpivirine gained a median of 1.5 kg in weight, while those in the CAR group (CAR = current antiretroviral regimen) gained a median of 1.0 kg. In the individual FLAIR and ATLAS studies, the median weight gain in the cabotegravir plus rilpivirine arm was 1.3 kg and 1.8 kg, respectively, compared to 1.5 kg and 0.3 kg in the CAR arms. At Week 48, in the ATLAS-2M study, the median weight gain in both the monthly and 2-monthly CAB+RPV dosing arms was 1.0 kg.

Laboratory abnormalities

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).

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

Elevated lipase values were identified in clinical studies with cabotegravir plus rilpivirine. Compared with the CAR group, there was a grade 3-4 increase in lipase values with cabotegravir plus rilpivirine. Increases in lipase values were generally asymptomatic and did not result in treatment being discontinued.

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

Paediatric population

Based on data from the analyses of Week 16 (cohort 1C, n=30) and Week 24 (cohort 2, n=144) of the MOCHA study, in adolescents (aged 12 and over and with a body weight of 35 kg or more), no new safety concerns were identified compared to the safety profile in adults (see *"Clinical efficacy"*).

Additional information on specific patient groups

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

For other adverse reactions associated with rilpivirine, the prescribing information for rilpivirine should be consulted.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

There is currently no experience of overdose with Vocabria.

Treatment

There is no specific treatment in the event of cabotegravir overdose. If overdose occurs, the patient must be treated with appropriate supportive treatment and be monitored accordingly.

Further management should be as clinically indicated or as recommended by the relevant toxicological information centre, if available.
Due to the high plasma protein binding of cabotegravir, dialysis is unlikely to be helpful in removing the medicinal product from the body.
Management of overdose with cabotegravir injection should take into consideration the prolonged exposure following an injection (see *"Warnings and precautions"*).

Properties/Effects

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.

Pharmacodynamics

Antiviral activity in cell culture

Cabotegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentrations (EC_{50}) necessary to reduce viral replication by 50% 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 a cell culture test against a panel of 24 clinical HIV-1 isolates (three in each group of M-subtypes A, B, C, D, E, F and G, and 3 in group O), with EC_{50} values ranging from 0.02 nM to 1.06 nM. The EC_{50} values against three HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM. There are no clinical data for patients with HIV-2.

Antiviral activity in combination with other antiviral agents

No medicinal products with inherent anti-HIV activity were antagonistic to cabotegravir (in vitro tests were conducted for cabotegravir in combination with rilpivirine, lamivudine, tenofovir and emtricitabine).

Effect of human serum and serum proteins

In vitro tests in MT4 cells suggested a 408-fold shift in the IC_{50} of cabotegravir in the presence of 100% human serum (by method of extrapolation), and the protein-adjusted IC_{50} (PA-IC_{50}) was estimated to be 102 nM in PBMC.

Resistance in vitro

Isolation from wild-type HIV-1 and activity against resistant strains: viruses with a >10-fold increase in cabotegravir EC_{50} 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 2.8-8.4) and I162M (fold change = 2.8). As noted above, the detection of T124A corresponds to the 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 strain NL-432 in the presence of 6.4 nM of cabotegravir through Day 56.

Among the multiple mutants, the highest fold change was observed with the mutants containing Q148K or Q148R. E138K/Q148H resulted in a 0.92-fold decrease in susceptibility to cabotegravir, but E138K/Q148K resulted in an 81-fold decrease in susceptibility to cabotegravir. G140C/Q148R,

G140S/Q148R and N155H/Q148R resulted in a 22-, 12- and 61-fold decrease in susceptibility to cabotegravir, respectively. N155H did not alter susceptibility to cabotegravir more than 6-fold for other N155H double mutants.

Resistance in vivo

Only a few people met the criteria (two consecutive plasma HIV-1 RNA levels ≥200 copies/mL after prior suppression to <200 copies/mL) for confirmed virological failure (CVF) in the pooled FLAIR and ATLAS Phase III trials (see also *"Clinical efficacy"*). In the pooled analysis, there were 7 cases of CVF on cabotegravir plus rilpivirine (n=591, 1.2%) and 7 cases of CVF with continuation of current standard antiretroviral therapy (CAR).

The three cases of CVF on cabotegravir plus rilpivirine in study 201684 (FLAIR) with resistance data had Subtype A1 with IN substitution L74I, which by itself does not cause resistance to any INI. This substitution was detected at baseline and associated with suspected virological failure (SVF). In addition, two-thirds of the cases of CVF had treatment-emergent INI resistance-associated substitution Q148R, while one-third had G140R with reduced phenotypic susceptibility to cabotegravir. All three cases of CVF carried one rilpivirine resistance-associated substitution (K101E, E138E/A/K/T or E138K) and two-thirds showed reduced phenotypic susceptibility to rilpivirine.

The three cases of CVF in study 201585 (ATLAS) had subtype A, A1 and AG. The two cases of CVF with subtype A and A1 both carried IN substitution L74I. This was in PBMC HIV-1 DNA at baseline and in HIV-1 RNA at the time of SVF. In addition, one-third of cases of CVF carried the INI resistance-associated substitution N155H at the time of SVF. All three cases of CVF had treatment-emergent rilpivirine resistance-associated substitutions (E138A, E138E/K or E138K) and showed reduced phenotypic susceptibility to rilpivirine, while one-third also showed phenotypic susceptibility to cabotegravir. In two-thirds of cases of CVF, the rilpivirine resistance-associated substitutions observed during SVF were also observed at baseline in PBMC HIV-1 DNA. In the seventh case of CVF (FLAIR), the patient concerned never received an injection and had no resistance mutations.

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 Phase IIIb ATLAS-2M study (see also *"Clinical efficacy"*), 10 patients met CVF criteria through Week 48: 8 patients (1.5%) in the Q8W arm and 2 patients (0.4%) in the Q4W arm. 8 participants met CVF criteria at or before the Week 24 timepoint. At the SVF timepoint, the 10 cases of CVF showed HIV-1 subtype A (n=2), A1 (n=2), B (n=4), C (n=1) or complex (n=1).

At baseline, 5 patients in the Q8W arm had RPV resistance-associated mutations of Y181Y/C + H221H/Y, Y188Y/F/H/L, Y188L, E138A or E138E/A, and 1 patient had cabotegravir resistance mutation G140G/R (in addition to the above Y188Y/F/H/L RPV resistance-associated mutation). At the SVF timepoint, 6 patients in the Q8W arm had rilpivirine resistance-associated mutations, with 2 patients having an addition of K101E and 1 patient having an addition of E138E/K from baseline to the SVF timepoint. The RPV fold change (FC) was above the biological cut-off for 7 patients and ranged from 2.4 to 15. Five of the 6 patients 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 out of 7 patients. The integrase genotype and phenotype assay failed for one patient and the cabotegravir phenotype was unavailable for another. The fold changes for the Q8W patients 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 patient with CVF had any RPV or INSTI resistance-associated substitutions at baseline. One patient had the NNRTI substitution G190Q in combination with the NNRTI polymorphism V189I. At the SVF timepoint, one patient had the rilpivirine resistance-associated mutations K101E + M230L during treatment and the other retained the G190Q + V189I NNRTI substitutions with the addition of V179V/I. Both patients showed reduced susceptibility to RPV. Both patients also had INSTI resistance-associated mutations, either Q148R + E138E/K or N155N/H at the time of SVF, 1 patient had reduced susceptibility to CAB. Neither patient had the INSTI substitution L74I. The fold changes for the Q4W patients were 1.8 and 4.6 for cabotegravir, 1.0 and 1.4 for dolutegravir and 1.1 and 1.5 bictegravir.

By Week 152, 13 patients met the CVF criteria during the maintenance and extension phase; 2 patients (Q8W arm) met the CVF criteria following the analysis in Week 96 (see Table 9). In ten patients, CVF occurred before Week 48 (8 patients in the Q8W arm and 2 patients in the Q4W arm) and 1 patient (Q8W arm) met the CVF criteria between Week 48 and Week 96.

Table 9: Cumulative proportion of patients meeting the CVF criteria by visit up to Week 152 of the maintenance phase + extension phase (ITT-E population): Study 207966 Week 152 analysis

SVF timepoint[a]	Q8W (N=522) n (%)	Q4W (N=523) n (%)
Week 8	1 (0.2)	0
Week 16	4 (0.8)	1 (0.2)
Week 24	7 (1.3)	1 (0.2)
Week 32	7 (1.3)	2 (0.4)
Week 48	8 (1.5)	2 (0.4)
Week 88	9 (1.7)	2 (0.4)
Week 112	10 (1.9)	2 (0.4)
Week 120	11 (2.1)	2 (0.4)

a. First of the 2 consecutive HIV-1 RNA values ≥200 c/mL.
Comment: in this context, this relates to the cumulative proportion of CVFs up to the examination visit.
Note: the only visits shown are those where at least one new CVF occurred.

In addition to the 9 patients with CVF in the Q8W group, 2 patients met CVF criteria between Week 96 and Week 152 (see Table 9). One patient, who switched from study 201585 after he had received CAB + RPV LA for 1 to 24 weeks, met the CVF criteria in Week 112. At baseline, this patient showed the L74I IN polymorphism. At the SVF timepoint, 3 NNRTI mutations were observed, K103N and RPV-resistance-associated mutations E138A and Y181Y/C. The INI-resistance-associated mutation Q148R was found together with the L74I polymorphism. A reduced phenotypic propensity for RPV (FC=3.4) and CAB (FC=9.5) was observed. The HIV-1 virus subtype at the SVF timepoint was A. The other patient met the CVF criteria in Week 120 and did not show any resistance-associated mutations at the baseline timepoint. At the SVF timepoint, the RPV resistance mutations E138A and M230M/L were identified, as well as the INI-resistance mutation Q148R. The phenotype analysis showed a reduced RPV (FC=16) and CAB sensitivity (FC=3.3). The patient was a carrier of the HIV-1 subtype B/C at the SVF timepoint. There were no other CVF patients in the Q4W group.

Effects on electrocardiogram

In a randomised, placebo-controlled, three-period crossover study, 42 healthy subjects were randomised into 6 random sequences and received three oral doses of placebo, three oral doses of 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 oral dose, the 400 mg dose for the monthly cabotegravir injection and the 600 mg dose for the cabotegravir injection every 2 months, respectively) or a 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) was 2.62 ms (one-sided upper 90% CI: 5.26 ms). Cabotegravir did not prolong the QTc interval within 24 hours of administration.

Clinical efficacy

Adults

Monthly dosing

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

In the FLAIR study, 629 HIV-1-infected, antiretroviral treatment (ART)-naive patients received a dolutegravir integrase strand transfer inhibitor (INSTI)-containing treatment regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 2 other nucleoside reverse transcriptase inhibitors if subjects were HLA-B*5701-positive). Patients who were virologically suppressed (HIV-1 RNA <50 copies per mL, n=566) were then randomised 1:1 to receive either cabotegravir plus rilpivirine or to remain on the current antiretroviral (CAR) regimen. Subjects randomised to receive cabotegravir plus rilpivirine initiated oral lead-in treatment with a cabotegravir 30 mg tablet plus a rilpivirine 25 mg tablet daily for about one month (at least 28 days, maximum 77 days), followed by cabotegravir injections (month 1: 600 mg injection, from month 2 onwards: 400 mg injection) plus rilpivirine injections (month 1: 900 mg injection, from month 2 onwards: 600 mg injection) every month for up to 96 weeks.

In the ATLAS study, 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 cabotegravir plus rilpivirine or remained on their current antiretroviral (CAR) regimen. Subjects randomised to receive cabotegravir plus rilpivirine initiated oral lead-in treatment with a cabotegravir 30 mg tablet plus a rilpivirine 25 mg tablet daily for about one month (at least 28 days, maximum 73 days) followed by cabotegravir injections (month 1: 600 mg injection, from month 2 onwards: 400 mg

injection) plus rilpivirine injections (month 1: 900 mg injection, from month 2 onwards: 600 mg injection) for an additional 44 weeks. In the ATLAS study, 50%, 17% and 33% of patients received an NNRTI, PI or INI, respectively, as their baseline third drug class prior to randomisation. This distribution remained similar after randomisation in the control arm (CAR).

In the pooled analysis of the FLAIR and ATLAS studies, in the cabotegravir plus rilpivirine treatment arm, the median age of subjects at baseline was 38 years, 27% were female, 27% were non-white and 7% had less than 350 CD4+ cells per mm^3. These characteristics were similar between treatment arms.

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

In a pooled analysis of the FLAIR and ATLAS studies, cabotegravir plus rilpivirine was non-inferior to CAR with regard to the proportion of patients having plasma HIV-1 RNA ≥50 copies/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 limit of the 95% CI below 4%).
The non-inferiority results established in FLAIR and ATLAS demonstrated that the length of virological suppression prior to initiation of treatment with cabotegravir plus rilpivirine (5 months or ≥6 months) did not impact overall response rates.
The primary endpoint and other Week 48 outcomes, including outcomes by key baseline factors for patients, for FLAIR and ATLAS are shown in Tables 10 and 11.

Table 10: Virological outcomes of randomised treatment in FLAIR and ATLAS after 48 weeks (snapshot analysis)

	FLAIR		*ATLAS*		*Pooled data*	
	CAB + RPV N=283 N (%)	*CAR N=283 N (%)*	*CAB + RPV N=308 N (%)*	*CAR N=308 N (%)*	*CAB+RPV N=591 N (%)*	*CAR N=591 N (%)*
HIV-1 RNA ≥50 copies/mL†	6 (2.1)	7 (2.5)	5 (1.6)	3 (1.0)	11 (1.9)	10 (1.7)
*Treatment difference in % (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)
No virological data at the Week 48 window	12 (4.2)	12 (4.2)	18 (5.8)	11 (3.6)	30 (5.1)	23 (3.9)
Reasons						
Discontinued study/treatment due to adverse events or death	8 (2.8)	2 (0.7)	11 (3.6)	5 (1.6)	19 (3.2)	7 (1.2)
Discontinued study/treatment for other reasons	4 (1.4)	10 (3.5)	7 (2.3)	6 (1.9)	11 (1.9)	16 (2.7)
No data during time window but continued study participation	0	0	0	0	0	0

* adjusted for baseline stratification factors.

† Includes subjects who discontinued the study due to lack of efficacy or suppression.

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

Table 11: Proportion of patients with plasma HIV-1 RNA ≥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^3)	<350	0/42	2/54 (3.7)
	≥350 to <500	5/120 (4.2)	0/117
	≥500	6/429 (1.4)	8/420 (1.9)
Sex	Male	6/429 (1.4)	9/423 (2.1)
	Female	5/162 (3.1)	1/168 (0.6)
Ethnicity	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 (third drug class)	PI	1/51 (2.0)	0/54
	INI	6/385 (1.6)	9/382 (2.4)
	NNRTI	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 patient baseline characteristics (CD4+ count, sex, age, ethnicity, BMI, baseline third agent class) were not clinically meaningful.

Participants in both studies were virologically suppressed prior to Day 1 or randomisation, respectively, and a clinically relevant change from baseline in CD4+ cell counts was not observed.

Week 96 FLAIR
In the FLAIR study, after 96 weeks, the results remained consistent with the results after 48 weeks. The proportion of patients having plasma HIV-1 RNA ≥50 copies/mL for 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).

Week 124 FLAIR – start of therapy with direct to injection (DTI)
In the FLAIR study, safety and efficacy were assessed at Week 124 in patients who had decided in the extension phase (at Week 100) to switch from abacavir/dolutegravir/lamivudine to Vocabria plus rilpivirine. Patients were given the opportunity to switch, with or without oral lead-in, with one group forming with oral lead-in (“oral lead-in” (OLI) group) (n = 121) and one group forming which started directly with injections (“direct to injection” (DTI) group (n = 111).
At Week 124, the proportion of patients with HIV-1 RNA ≥ 50 copies/mL was 0.8% for the group with oral lead-in and 0.9% for the group which started directly with injections.
Also in Week 124, comparable virus suppression rates (HIV-1 RNA <50 copies/mL) were recorded in the DTI group (110/111 [99.1%]) and the OLI group (113/121 [93.4%]).

Dosing every 2 months
The efficacy and safety of the cabotegravir injection administered every 2 months has been evaluated in a Phase IIIb randomised, multicentre, parallel-arm, open-label, non-inferiority study, ATLAS-2M

(207966). The primary analysis was conducted after all patients completed their Week 48 visit or discontinued the study prematurely.

In the ATLAS-2M study, 1,045 HIV-1-infected, ART-experienced, virologically suppressed patients were randomised (1:1) and received a cabotegravir plus rilpivirine injection regimen administered either every 2 months or monthly.
Study participants not initially treated with cabotegravir/rilpivirine received oral lead-in treatment comprising one cabotegravir 30 mg tablet plus one rilpivirine 25 mg tablet daily for about one month (at least 4 weeks, maximum 85 days). Patients randomised to monthly cabotegravir injections (month 1: 600 mg injection, from month 2 onwards: 400 mg injection) and rilpivirine injections (month 1: 900 mg injection, from month 2 onwards: 600 mg injection) received treatment for an additional 44 weeks. Patients randomised to every-2-month cabotegravir injections (600 mg injections at months 1, 2, 4 and every 2 months thereafter) and rilpivirine injections (900 mg injections 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 patients received cabotegravir/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 mm3; these characteristics were similar between the treatment arms.

The primary endpoint in ATLAS-2M was the proportion of patients with a plasma HIV-1 RNA ≥50 copies/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 + rilpivirine administered every month with regard to the proportion of patients having plasma HIV-1 RNA ≥50 copies/mL (1.7% and 1.0%, respectively) at Week 48. The adjusted treatment difference between cabotegravir plus rilpivirine administered every 2 months and cabotegravir plus rilpivirine administered every month (0.8; 95% CI: -0.6, 2.2) met the non-inferiority criterion (upper limit of the 95% CI below 4%). The efficacy results in Week 96 and Week 152 are consistent with the results for the primary endpoint in Week 48 (see Table 12).

Table 12: Virological outcomes of randomised treatment in ATLAS-2M after 48, 96 and 152 weeks (snapshot analysis)

	Dosing every 2 months (Q8W) N=522 (%)	*Monthly dosing (Q4W) N=523 (%)*
Week 48		
HIV-1 RNA ≥50 copies/mL†, n (%)	9 (1.7)	5 (1.0)
*Treatment difference in % (95% CI)**	0.8 (-0.6, 2.2)	
HIV-1 RNA <50 copies/mL, n (%)	492 (94.3)	489 (93.5)
No virological data at the Week 48 window, n (%)	21 (4.0)	29 (5.5)
Reasons		
Discontinued study/treatment due to adverse events or death, n (%)	9 (1.7)	13 (2.5)
Discontinued study/treatment for other reasons, n (%)	12 (2.3)	16 (3.1)
No data during time window but continued study participation, n (%)	0	0
Week 96		
HIV-1 RNA ≥50 copies/mL†, n (%)	11 (2.1)	6 (1.1)
HIV-1 RNA <50 copies/mL, n (%)	475 (91.0)	472 (90.2)
No virological data at the Week 96 window, n (%)	36 (6.9)	45 (8.6)
Reasons		
Discontinued study/treatment due to adverse events or death, n (%)	17 (3.3)	17 (3.3)
Discontinued study/treatment for other reasons, n (%)	16 (3.1)	27 (5.2)
No data during time window but continued study participation, n (%)	3 (0.6)	1 (0.2)

Week 152		
HIV-1 RNA ≥50 copies/mL[†]*,* n (%)	14 (2.7)	5 (1.0)
HIV-1 RNA <50 copies/mL, n (%)	456 (87.4)	449 (85.9)
No virological data at the Week 152 window, n (%)	52 (10.0)	69 (13.2)
Reasons		
Discontinued study/treatment due to adverse events or death, n (%)	23 (4.4)	24 (4.6)
Discontinued study/treatment for other reasons, n (%)	28 (5.4)	44 (8.4)
No data during the time window but continued study participation, n (%)	1 (0.2)	1 (0.2)

***** adjusted for baseline stratification factors.
† Includes subjects who discontinued the study due to lack of efficacy or suppression.
N = Number of patients in each treatment group, CI = confidence interval

Table 13: Proportion of patients with plasma HIV-1 RNA ≥50 copies/mL at Week 48 for key baseline factors of patients (snapshot outcomes)

Baseline factors of patients		*Number of patients with HIV-1 RNA ≥50 copies/mL/ total assessed (%)*	
		Dosing every 2 months (Q8W) n/N (%)	*Monthly dosing (Q4W) n/N (%)*
Baseline CD4+ (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)
Sex	Male	4/385 (1.0)	5/380 (1.3)
	Female	5/137 (3.5)	0/143

Baseline factors of patients		*Number of patients with HIV-1 RNA ≥50 copies/mL/ total assessed (%)*	
		Dosing every 2 months (Q8W) n/N (%)	*Monthly dosing (Q4W) n/N (%)*
Ethnicity	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/Non-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 CAB/RPV exposure	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, CAB = cabotegravir, RPV = rilpivirine

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

Post-hoc analysis – factors that are associated with virological failure

In multivariable analyses (MVA) of pooled Phase 3 studies (ATLAS up to Week 96, FLAIR up to Week 124 and ATLAS-2M up to Week 152), the influence of various factors on the risk of confirmed virological failure (CVF) was examined. The baseline factor analysis (BFA) examined baseline viral and patient characteristics, as well as the dosing regimen (Q4W or Q8W). The MVA incorporated the baseline factors and included the post-baseline predicted plasma drug concentrations for CVF using regression modelling with a variable selection procedure. After a total of 4,291 person-years, the

unadjusted CVF incidence rate was 0.54 per 100 person-years; 23 cases of CVF were reported (1.4% of 1,651 persons in these studies).

The BFA showed that rilpivirine resistance mutations (incidence rate ratio IRR=21.65, p<0.0001), the 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/m^2, p=0.01) were associated with CVF. Other variables, including Q4W or Q8W dosing, female sex or CAB/INSTI-resistant mutations, had no significant association with CVF. A combination of at least two of the following key baseline factors were associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1 or BMI ≥30 kg/m^2 (see Table 14).

Table 14: Virological outcomes by presence of key baseline factors of rilpivirine resistance-associated mutations, subtype A6/A1[1] and BMI ≥30 kg/m^2

Baseline factors (number)	Virological success (%)[2]	Confirmed virological failure (%)[3]
0	884/970 (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)	1,231/1,431 (86.0) (84.1%, 87.8%)	23/1,431 (1.6)[6] (1.0%, 2.4%) 18/1,224 (1.47)[7]

[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, Week 124 for FLAIR and 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 data set with all non-missing covariates for the baseline factors (for a total of 1,651 subjects).
[7] Analysis data set with all non-missing covariates for the multivariable modelling, including the drug concentrations.

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 only one risk factor, with CVF identified in 6/24 patients [25.0%,

95% CI (9.8%, 46.7%)] treated with the every-2-month dosing regimen and 5/33 patients [15.2%, 95% CI (5.1%, 31.9%)] treated with the monthly dosing regimen.

Adolescents

MOCHA

The safety, tolerability and pharmacokinetics of oral and injectable cabotegravir and injectable rilpivirine were investigated in a multicentre, open-label, non-comparative phase I/II study, MOCHA (IMPAACT 2017, study 208580).

Week 16 MOCHA cohort 1

55 HIV-1-infected and virologically suppressed adolescents aged 12 to <18 years and with a body weight of at least 35 kg were admitted to one of four subgroups: 1C monthly dosing, 1C every 2 months, 1R monthly dosing or 1R every 2 months.

In cohort 1C, the participants (n=30) received one 30 mg cabotegravir tablet every day for at least four weeks, followed by monthly cabotegravir injections over the course of three months (month 1: 600 mg injection, months 2 and 3: 400 mg injection), or cabotegravir injections every two months over the course of two months (months 1 and 2: 600 mg injection), while continuing to receive cART. In cohort 1R, participants (n=25) received one 25 mg rilpivirine tablet every day for at least four weeks, followed by monthly rilpivirine injections over the course of three months (month 1: 900 mg injection, months 2 and 3: 600 mg injection) or rilpivirine injections every two months over the course of two months (months 1 and 2: 900 mg injection), while continuing to receive the standard cART.

At baseline, the average age of the participants in cohort 1 was 15.0 years, the average weight was 50.0 kg (range: 37.4 to 98.5), 47.3% were female, 92.7% were non-white, the median CD4+ cell count was 725 cells per mm^3 (range: 397 to 1,808) and no participant had a CD4+ cell count of less than 350 cells per mm^3.

The primary objectives in Week 16, which consisted of using the adult dose by evaluating the safety and confirming the PK in HIV-infected, virologically suppressed adolescents, were achieved, meaning that the participants could pass forward into cohort 2 (see *“Undesirable effects”, “Pharmacokinetics”, “Specific patient groups”*).

Week 24 MOCHA cohort 2

Cohort 2 included suitable participants who had previously completed cohort 1 as well as suitable participants who had not yet taken part in the study. The participants from cohort 2 (n=144)

discontinued their cART regimen prior to the study and received one 30 mg cabotegravir tablet plus one 25 mg rilpivirine tablet daily for at least four weeks, followed by every-2-month cabotegravir injections (month 1 and 2: 600 mg injection, then 600 mg injection every 2 months) and rilpivirine injections (month 1 and 2: 900 mg injection, then 900 mg injection every 2 months).
At baseline, the average age of the participants in cohort 2 was 15.0 years, the average weight was 48.5 kg (range: 35.2 to 100.9), 51.4% were female, 98.6% were non-white, the median CD4+ cell count was 739.5 cells per mm^3 (range: 81 to 1,925) and 4 participants had a CD4+ cell count of less than 350 cells per mm^3.
The primary objective in Week 24 of confirming the safety of injectable cabotegravir plus injectable rilpivirine in HIV-infected, virologically suppressed adolescents was achieved (see *"Undesirable effects"*). Antiviral activity was evaluated as a secondary objective, demonstrating that 139 out of 141 participants (98.6%) were still virologically suppressed (HIV-1 RNA plasma level <50 c/mL) based on available data in Week 24.

Oral bridging therapy with other ART
In a retrospective analysis of pooled data from 3 clinical studies (FLAIR, ATLAS-2M and LATTE-2/study 200056), 29 patients were included who received an oral bridging therapy for an average duration of 59 days (25th and 75th percentile 53-135) with an ART other than Vocabria plus rilpivirine (alternative oral bridging therapy) during treatment with intramuscular (i.m.) long-acting (LA) Vocabria plus rilpivirine injections. The median age of the patients was 32 years, 14% were female, 31% were non-Caucasian, 97% received an integrase inhibitor (INI)-based regimen as an alternative oral bridging therapy, 41% received an NNRTI as part of their alternative oral bridging therapy (including rilpivirine in 11 out of 12 cases) and 62% received an NRTI. Three patients stopped their treatment during or shortly after the oral bridging phase for non-safety-related reasons. In the majority (≥ 96%) of patients, viral suppression (plasma HIV-1 RNA < 50 copies/mL) could be maintained. During bridging with an alternative oral bridging therapy and during the phase after the alternative oral bridging therapy (up to 2 injections with Vocabria plus rilpivirine after oral bridging), no cases of CVF (plasma HIV-1 RNA ≥ 200 copies/mL) were observed.

Pharmacokinetics

Cabotegravir pharmacokinetics are similar between healthy and HIV-infected subjects. The pharmacokinetic variability of cabotegravir is moderate to high. In HIV-infected subjects participating in Phase III studies, between-subject CVb% for C_{tau} ranged from 39% to 48%. Higher between-subject

variability ranging from 41% to 89% was observed with single-dose administration of a long-acting cabotegravir injection.

Table 15: Pharmacokinetic parameters following once-daily oral use of cabotegravir and initial monthly intramuscular injections followed by injections every 2 months in adult participants

Administration phase	*Dosing schedule*	*Geometric mean (5th/95th percentiles)*[a]		
		$AUC_{(0\text{-}tau)}$[b] *(µg•h/mL)*	*C_{max} (µg/mL)*	*C_{tau}*[b] *(µg/mL)*
Oral lead-in[c]	once daily 30 mg	145 (93.5; 224)	8.0 (5.3; 11.9)	4.6 (2.8; 7.5)
Initial injection[d]	600 mg i.m. initial dose	1,591 (714; 3,245)	8.0 (5.3; 11.9)	1.5 (0.65; 2.9)
Monthly injection[e]	400 mg i.m. monthly	2,415 (1,494; 3,645)	4.2 (2.5; 6.5)	2.8 (1.7; 4.6)
Injection every 2 months[e]	600 mg i.m. every 2 months	3,764 (2,431; 5,857)	4.0 (2.3; 6.8)	1.6 (0.8; 3.0)

[a] The values for the pharmacokinetic (PK) parameters are based on individual post hoc estimates from population PK models for the oral regimen as well as the initial monthly regimen (in FLAIR and ATLAS) or the regimen with doses every 2 months (in ATLAS-2M).

[b] tau refers to the following administration intervals: 24 hours for oral use as well as 1 month for monthly (or 2 months for every 2 months) i.m. injection of a prolonged-release suspension.

[c] The values for the pharmacokinetic parameters for oral lead-in represent steady state.

[d] The C_{max} values for initial injection are primarily attributable to the oral lead-in (as the initial injection took place on the same day as the last oral dose), while the $AUC_{(0\text{-}tau)}$ and C_{tau} values are attributable to the initial injection. In the case of administration without OLI (DTI n=110), the geometric mean (5th/95th percentiles) for CAB C_{max} (1 week after the initial injection) was 1.89 µg/mL (0.438; 5.69), while the geometric mean for CAB C_{tau} was 1.43 µg/mL (0.403; 3.90).

[e] The values for the pharmacokinetic parameters for monthly injections and injections every 2 months are based on the data from Week 48.

Absorption

Cabotegravir exhibits absorption-limited pharmacokinetics because it is slowly absorbed into the circulation from the gluteal muscle resulting in sustained plasma concentrations. Following a single intramuscular dose, plasma cabotegravir concentrations are detectable on the first day and gradually rise to reach a maximum plasma concentration with a median T_{max} of 7 days. Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection. Pharmacokinetic steady state is achieved by 44 weeks.

The plasma concentrations of cabotegravir increase in proportion to or slightly less than in proportion to the administered dose following single and repeat intramuscular injections of doses ranging from 100 mg to 800 mg.

Distribution

In vitro data shows that cabotegravir is highly bound (approximately >99%) to human plasma proteins. Following oral administration of cabotegravir tablets, the mean apparent volume of distribution (Vz/F) of cabotegravir in plasma was 12.3 L. In humans, the Vc/F in the plasma was estimated at 5.27L and Vp/F at 2.43 L. These volume estimates, along with the assumption of high F, suggest some distribution of cabotegravir to the extracellular space. Cabotegravir is detectable in the female and male genital tract. Median cervical and vaginal tissue:plasma ratios ranged from 0.16 to 0.28 and the median rectal tissue:plasma ratio was ≤0.08 following a single intramuscular injection of 400 mg at 4, 8 and 12 weeks after administration. Cabotegravir is detectable in cerebrospinal fluid (CSF). In HIV-infected patients receiving cabotegravir plus rilpivirine injections, the cabotegravir CSF:plasma concentration ratio [median range] (n=16) was 0.003 (0.002 to 0.004) one week following a steady-state cabotegravir injection (Q4W or Q8W). Consistent with therapeutic cabotegravir concentrations in the CSF, CSF HIV-1 RNA (n=16) was <50 copies/mL in 16 subjects (100%) and <2 copies/mL in 15 subjects (94%). At the same time point, plasma HIV-1 RNA (n=18) was <50 copies/mL in 18 subjects (100%) and <2 copies/mL in 12 subjects (66.7%).

Metabolism

Cabotegravir is primarily metabolised by UGT1A1 with a minor UGT1A9 component. Cabotegravir is the predominant circulating compound in plasma, representing >90% of total radiocarbon in plasma. Following oral administration in humans, cabotegravir is primarily eliminated through metabolism; renal elimination of the unchanged active substance is low (<1% of the dose). 47% of the total oral dose is excreted as the unchanged active substance in the faeces. It is unknown if all or part of this is due to unabsorbed active substance 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 samples. 27% of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (75% of urine radioactivity, 20% of the total dose).

Elimination

Cabotegravir mean apparent terminal half-life is limited by the absorption rate and is estimated to be 5.6 to 11.5 weeks after a single dose i.m. injection. The significantly longer apparent half-life compared to oral administration reflects absorption from the injection site into the systemic circulation. The apparent CL/F was 0.151 L/h based on population pharmacokinetic analyses.

Kinetics in specific patient groups

Sex

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

Ethnicity

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

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 (see "*Clinical efficacy*").

Patients with HBV and HCV co-infection

There are very limited data on the use of cabotegravir in subjects with HCV co-infection. There are no data on the use of cabotegravir in subjects with HBV co-infection.

Hepatic impairment

No clinically relevant pharmacokinetic differences between patients with moderate hepatic impairment and healthy subjects were observed. No dose adjustment is therefore 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.

Renal impairment

No clinically relevant pharmacokinetic differences between patients with severe renal impairment (creatinine clearance of ≥15 to <30 mL/min and not on dialysis) and healthy subjects were observed.

No dose adjustment is therefore necessary for patients with mild, moderate or severe renal impairment. Cabotegravir has not been studied in patients on dialysis.

Elderly patients

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

Children and adolescents

Population pharmacokinetic analyses showed no clinically relevant differences in exposure between adolescents (aged 12 or over and with a minimum body weight of 35 kg) and HIV-1-infected and non-infected adult participants of the cabotegravir development programme, meaning that no dose adjustment is required for adolescents with a body weight of ≥35 kg.

Table 16: Pharmacokinetic parameters following once-daily oral use of cabotegravir and initial monthly intramuscular injections followed by injections every 2 months in adolescent participants aged 12 to <18 years (≥35 kg)

Administration phase	*Dosing schedule*	*Geometric mean (5th/95th percentiles)*[a]		
		$AUC_{(0\text{-}tau)}$[b] *(µg•h/mL)*	*C_{max} (µg/mL)*	*C_{tau}*[b] *(µg/mL)*
Oral lead-in[c]	once daily 30 mg	203 (136; 320)	11 (7.4; 16.6)	6.4 (4.2; 10.5)
Initial injection[d]	600 mg i.m. initial dose	2,085 (1,056; 4,259)	11 (7.4; 16.6)	1.9 (0.80; 3.7)
Monthly injection[e]	400 mg i.m. monthly	3,416 (2,303; 5,109)	5.7 (3.8; 8.9)	4.2 (2.7; 6.5)
Injection every 2 months[e]	600 mg i.m. every 2 months	5,184 (3,511; 7,677)	5.1 (3.1; 8.2)	2.5 (1.3; 4.2)

[a] The values for the pharmacokinetic (PK) parameters are based on individual post hoc estimates from population PK models in an HIV-1-infected adolescent population (n=147) with a body weight of 35.2-98.5 kg as well as a non-HIV-1-infected adolescent population (n=62) with a body weight of 39.9-167 kg.

[b] tau refers to the following administration intervals: 24 hours for oral use as well as 1 month for monthly (or 2 months for every 2 months) i.m. injection of a prolonged-release suspension.

[c] The values for the pharmacokinetic parameters for oral lead-in represent steady state.

[d] The C_{max} values for initial injection are primarily attributable to the oral lead-in (as the initial injection took place on the same day as the last oral dose), while the $AUC_{(0\text{-}tau)}$ and C_{tau} values are attributable to the initial injection.
[e] The values for the pharmacokinetic parameters represent steady state.

Genetic polymorphisms

In a meta-analysis of healthy and HIV-infected subjects, HIV-infected subjects with UGT1A1 genotypes conferring slow cabotegravir metabolism had an average 1.2-fold increase in steady-state cabotegravir AUC, C_{max} and C_{tau} following cabotegravir injection vs. an average 1.38-fold increase following administration of the oral formulation. This is similar to the average 1.3- to 1.5-fold increase in steady-state cabotegravir AUC, C_{max} and C_{tau} observed following administration of the oral formulation in healthy and HIV-infected subjects combined. These differences are not considered clinically relevant. Polymorphisms in UGT1A9 were not associated with differences in the pharmacokinetics of cabotegravir. Therefore, no dose adjustment is required in subjects with either UGT1A1 or UGT1A9 polymorphisms.

Preclinical data

Long-term toxicity (or repeat dose toxicity)

The effect of long-term treatment with high doses of cabotegravir has been evaluated in toxicity studies with repeated oral administration in rats (26 weeks) and 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 at 27 times the maximum recommended human dose [MHRD] of 30 mg orally or 500 mg/kg/day at 3.7 times the MHRD of 30 mg orally, respectively.
In the 14-day oral toxicity study in monkeys, a dose of 1,000 mg/kg/day was not tolerated and resulted in gastrointestinal-associated disorders (weight loss, vomiting, loose/watery stools and moderate to severe dehydration).
In the 28-day oral toxicity study in monkeys, end-of-study cabotegravir exposure at a dose of 500 mg/kg/day was similar to that achieved in the 14-day study at a dose of 1,000 mg/kg/day. This suggests that the gastrointestinal intolerance observed in the 14-day study was the result of oral administration and not systemic toxicity.

In a 3-month study in rats, cabotegravir was administered as a once-monthly subcutaneous injection (up to 100 mg/kg/dose), once-monthly intramuscular injection (up to 75 mg/kg/dose) or once-weekly subcutaneous injection (100 mg/kg/dose) (at exposures >30 times the exposure in humans at the

MRHD of 400 mg i.m.). No systemic adverse effects or target organ toxicities were identified. Local inflammatory reactions (erythema and oedema graded very slight to severe) were noted in animals given 75 mg/kg/dose (monthly i.m. injections, >30 times the exposure in humans at the MRHD of 400 mg i.m.). Treatment-related histology findings were limited to granulomatous inflammation and mixed inflammatory cell infiltration at the corresponding injection sites, with correlating macroscopic changes.

Mutagenicity and carcinogenicity

Cabotegravir did not prove to be 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 at ~7 times and the rat at ~26 times the MHRD of 30 mg orally.

Reproductive toxicity

When administered orally at 1,000 mg/kg/day cabotegravir (>25 times the exposure in humans at the MHRD of 30 mg orally) for up to 26 weeks, no adverse effects on male or female reproductive organs or spermatogenesis were identified, and cabotegravir had no functional effects on the mating habits or fertility of male or female rats.

In embryo-foetal development studies, there was no teratogenicity following oral administration of cabotegravir to pregnant rats and rabbits at doses up to 1,000 or 2,000mg/kg/day (30-fold or 0.66 times the exposure in humans at the MRHD of 30 mg orally).A reduction in foetal body weight occurred in caesarean-delivered rats at 1,000 mg/kg/day; however, as there was no reproducible effect at this dose on the birth weights or postnatal growth and development of naturally delivered pups, the foetal finding was not considered adverse. Cabotegravir was shown to cross the placenta of rats and was detected in foetal tissue. In pre- and postnatal studies in rats (PPN), cabotegravir at 1,000 mg/kg/day reproducibly delayed the onset of delivery and was associated with an increase in stillbirths and neonatal mortalities. There was no effect on survival when foetuses were delivered by caesarean section. A lower dose of 5 mg/kg/day (approximately 14 times the MRHD at 30 mg orally) was not associated with delayed delivery or neonatal mortality.

Other information

Incompatibilities

As no compatibility studies have been carried out, the cabotegravir injection must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date marked as “EXP” on the pack.

Special precautions for storage

Do not store above 30°C. Do not freeze. Store in the original packaging and keep out of the reach of children.

Shelf life in the syringe

Chemical and physical in-use stability has been demonstrated for 2 hours at 25°C.
Once the suspension has been drawn into the syringe, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Instructions for handling
Complete, illustrated instructions for administration can be found in the instructions for use included in the pack.

Authorisation number

67740 (Swissmedic)

Packs

Vocabria 400 mg prolonged-release suspension for injection: 2 mL (A)
Vocabria 600 mg prolonged-release suspension for injection: 3 mL (A)
Each pack contains a syringe, a vial adapter and an injection needle.

Marketing authorisation holder

ViiV Healthcare GmbH, 6340 Baar

Date of revision of the text

June 2025

Instructions for use for Vocabria 2 mL prolonged-release suspension for injection

Overview

A complete dose comprises two injections: 2 mL cabotegravir and 2 mL rilpivirine.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution. The preparation steps for both medicinal products are identical. Follow these instructions carefully when preparing the suspension for injection to prevent the liquid from leaking.

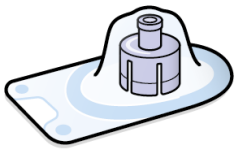
Cabotegravir and rilpivirine suspensions are intended for intramuscular use only.

Both injections must be administered into the gluteal muscle. The ventrogluteal muscle is recommended. The order of injections is not important.

Cabotegravir vial

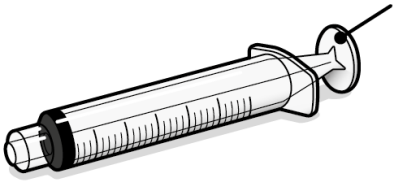
Closure (with rubber stopper under the cap)

Vial adapter



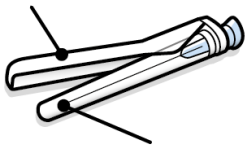
Syringe

Plunger



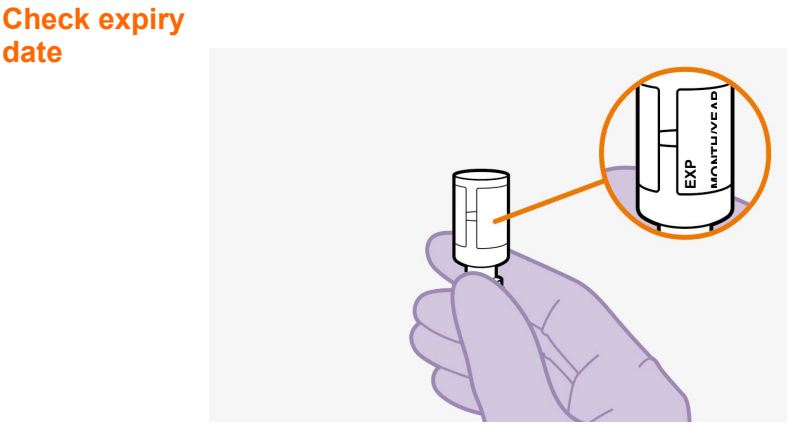
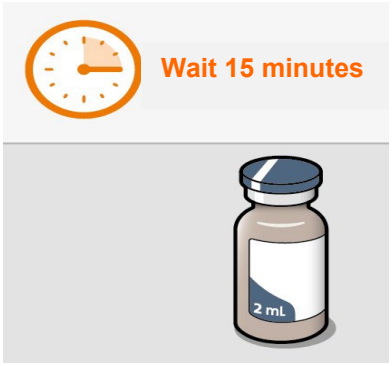
Injection needle

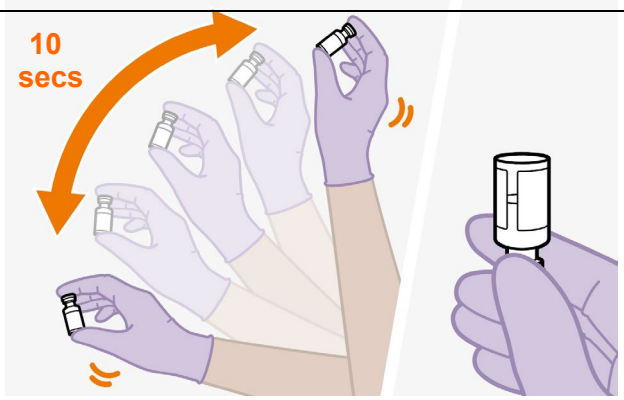
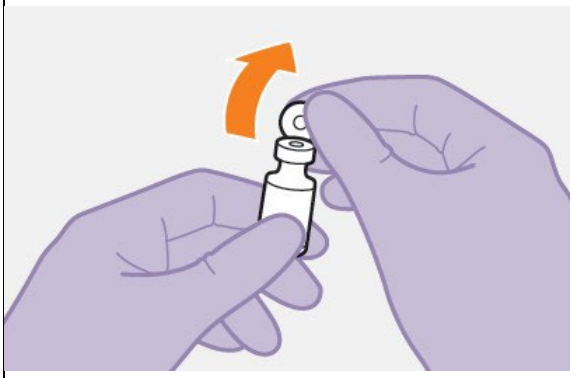
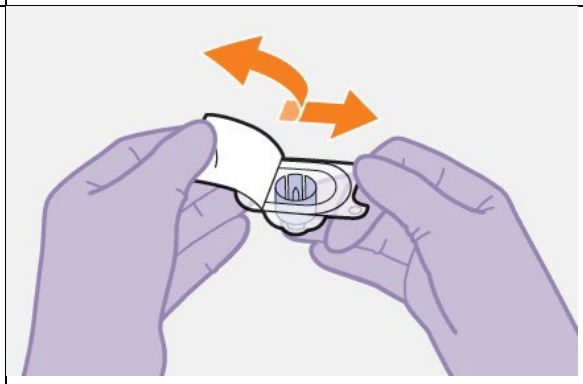
Needle guard

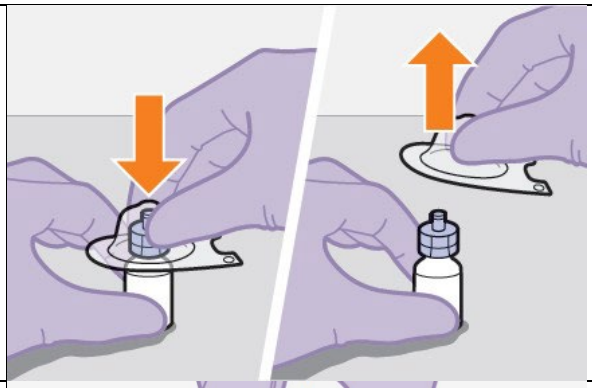
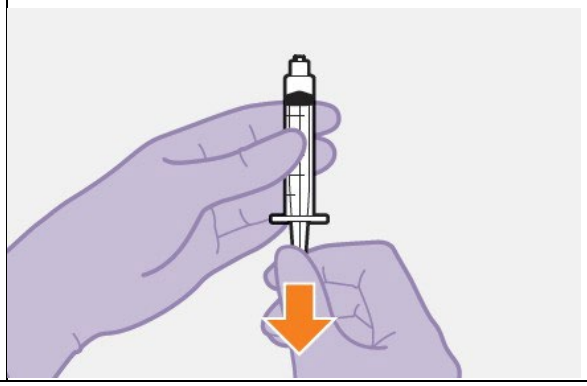


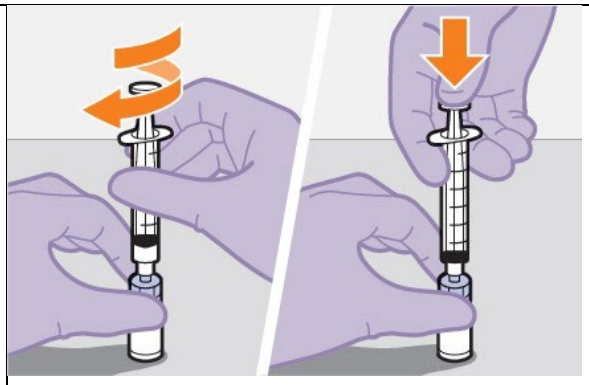
Needle cap

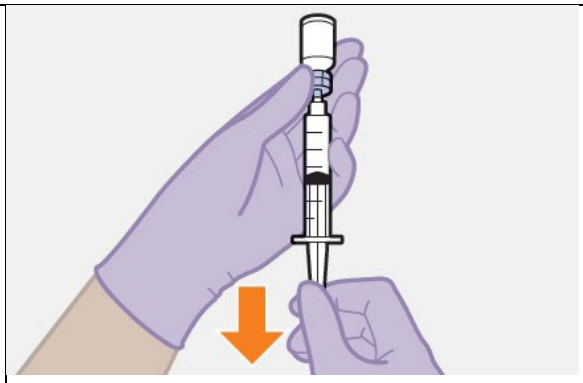
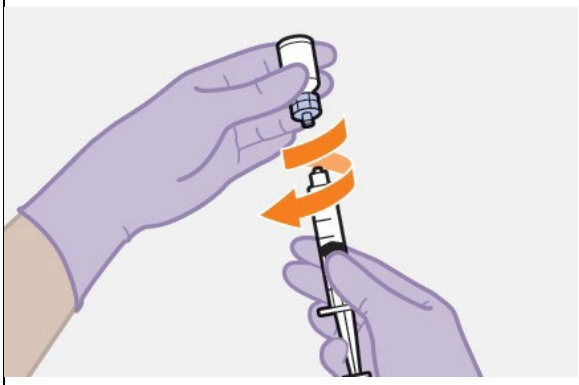
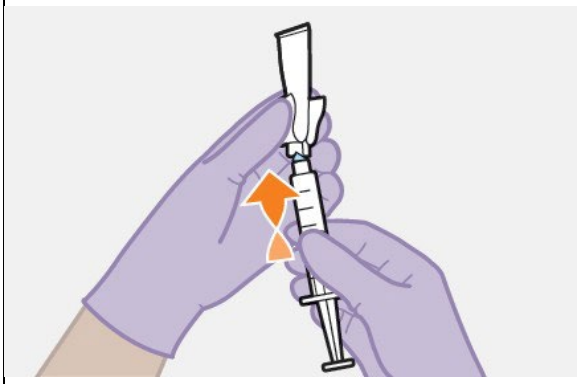
Your pack contains
1 vial of cabotegravir 1 vial adapter 1 syringe 1 injection needle (0.65 mm, 38 mm [23G, approx. 3.8 cm]) Consider the patient's build and use medical judgement to select an appropriate injection needle length.
You will also need
Non-sterile gloves 2 alcohol wipes 2 gauze pads A suitable sharps container 1 pack of rilpivirine 2 mL prolonged-release suspension for injection
Preparation

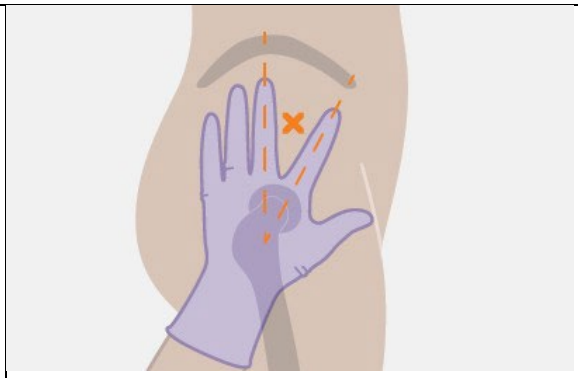
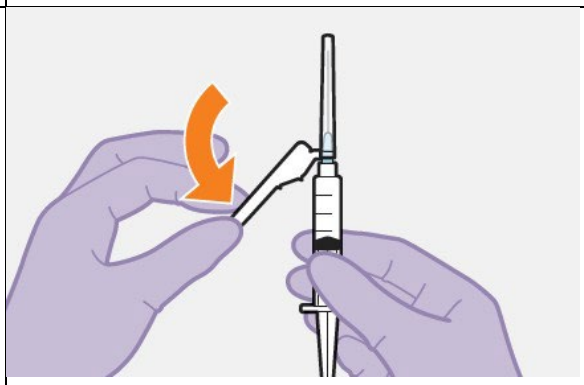
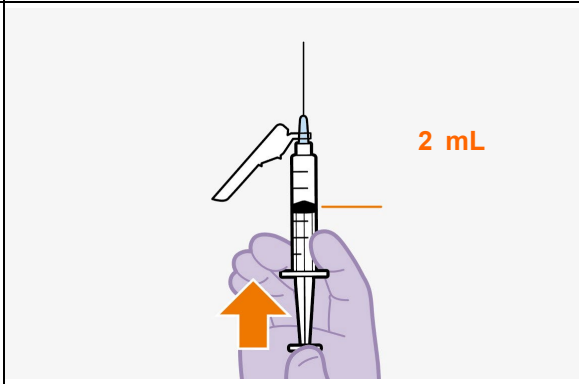
1. Inspect vial • Check the expiry date. • Inspect the vial yourself. If you can see foreign matter, do not use the product. Note: the Cabotegravir vial has a brown tint to the glass. Do not use if the expiry date has passed.	
2. Wait 15 minutes • If the pack has been stored in the fridge, wait at least 15 minutes before injecting to allow the liquid to come to room temperature.	

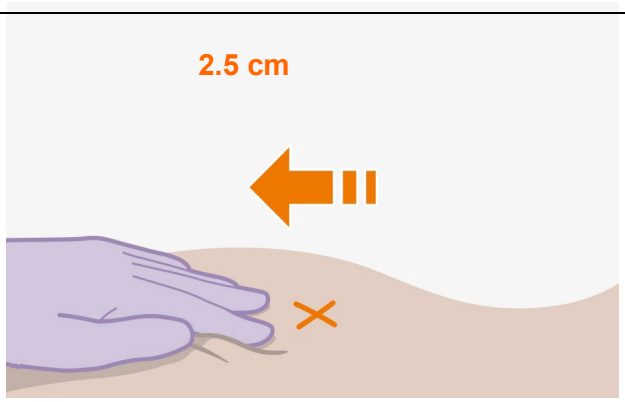
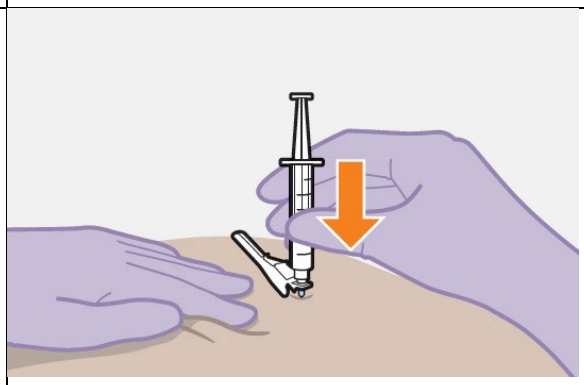
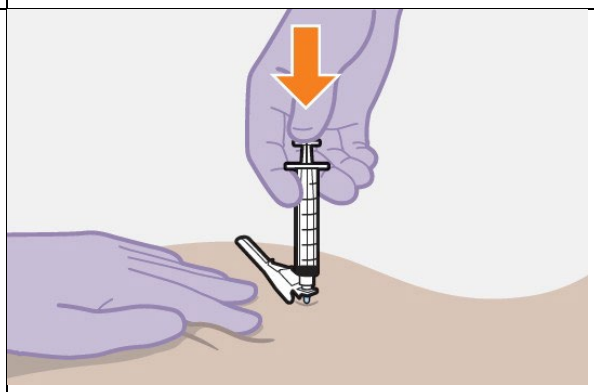
3. Shake vigorously • Hold the vial firmly and shake vigorously for a full 10 seconds. • Invert the vial and check if the suspension looks uniform. If the suspension is not uniform, shake the vial again. • It is normal to see small air bubbles. Note**:** the order in which the vials are prepared is not important.	
4. Remove closure • Remove the closure from the vial. • Wipe the rubber stopper with an alcohol wipe. Do not allow anything to touch the rubber stopper after wiping it.	
5. Peel open vial adapter packaging • Peel off the paper backing from the vial adapter packaging. Note: do not remove the adapter from its packaging for the next step. The adapter will not fall out if the packaging is turned upside down.	

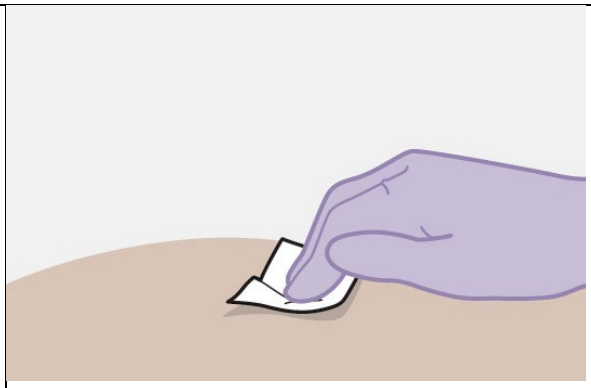
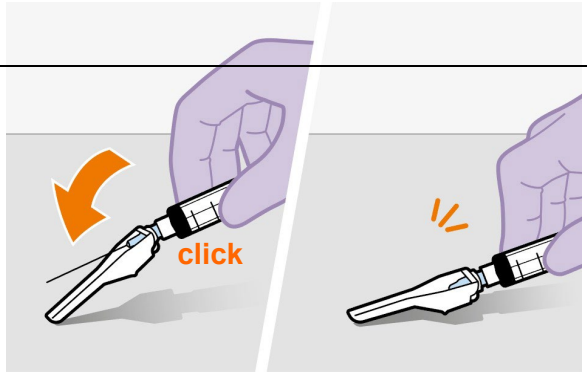
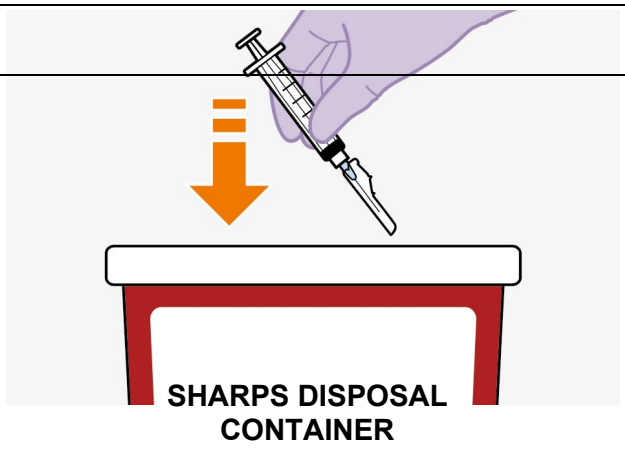
6. Attach vial adapter • Put the vial on a level surface. • Press the adapter straight down onto the vial, as shown. The adapter must snap securely into place.	
7. Remove packaging Then remove the packaging as shown.	
8. Prepare syringe • Remove the syringe from its packaging. • Draw 1 mL of air into the syringe. This will make it easier to draw up the suspension later.	

9. Attach syringe • Hold the adapter and vial as shown. • Screw the syringe firmly onto the vial adapter. • Press the plunger all the way down to push the air into the vial.	

10. Slowly draw up dose • Invert the syringe and vial and withdraw as much of the liquid as possible into the syringe. There may be more liquid than the dose amount in the vial. Note: keep the syringe upright to avoid leakage.	
11. Unscrew syringe • Hold the syringe plunger as shown to prevent liquid from leaking. It is normal to notice a certain amount of counterpressure. • Screw the syringe off the adapter as shown. Note: check that the suspension looks uniform and white to light pink.	
12. Attach injection needle • Peel open the needle packaging part way to expose the needle attachment. • Keeping the syringe upright, firmly twist the syringe onto the needle. • Completely remove the packaging.	
Injection	

13. Prepare injection site Injections must be administered into the gluteal muscle. Choose one of the following injection sites: Ventrogluteal (as shown; recommended) Dorsogluteal (upper outer quadrant) Note: for intramuscular use only. Do not administer injection intravenously.	
14. Remove needle cap • Fold the needle guard away from the needle. • Pull off the needle cap.	
15. Remove excess dose amount • Hold the syringe upright with the needle pointing up. Press the plunger to the correct dose amount to remove excess liquid and any air bubbles. Note: clean the injection site with an alcohol wipe. Allow the skin to air dry before continuing.	

16. Stretch skin Use the z-track technique to minimise leakage from the injection site. • Drag the skin covering the injection site, displacing it by about 2.5 cm. • Keep it held in this position during the injection.	
17. Insert needle • Insert the needle to its full depth, or deep enough to reach the muscle tissue.	
18. Inject dose • Still holding the skin stretched – slowly press the plunger all the way down. • Ensure the syringe is completely empty. • Withdraw the needle and release the stretched skin immediately.	

19. Assess the injection site • Apply pressure to the injection site using a gauze pad. • A small plaster may be used if bleeding occurs. Do not massage the injection site.	
20. Make needle safe • Fold the needle guard back over the needle. • Gently apply pressure to the needle using a hard surface to lock the needle guard in place. • It will make a click when it locks.	
After injection	
21. Safe disposal Dispose of used needles, syringes, vials and adapters according to local health and safety regulations.	

Repeat the process for the second medicinal product If you have only injected one of the two medicinal products, repeat all preparation steps and the injection again for the second medicinal product.	

Instructions for use for Vocabria 3 mL prolonged-release suspension for injection

Overview

A complete dose comprises two injections: 3 mL cabotegravir and 3 mL rilpivirine.

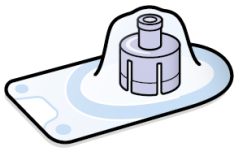
Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution. The preparation steps for both medicinal products are identical. Follow these instructions carefully when preparing the suspension for injection to prevent the liquid from leaking.

Cabotegravir and rilpivirine suspensions are intended for intramuscular use only.
Both injections must be administered into the gluteal muscle. The ventrogluteal muscle is recommended. The order of injections is not important.

Cabotegravir vial

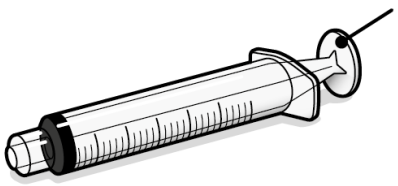
Closure
(with rubber stopper under the cap)

Vial adapter

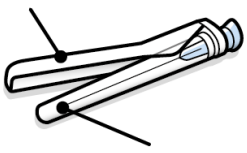


Syringe

Plunger



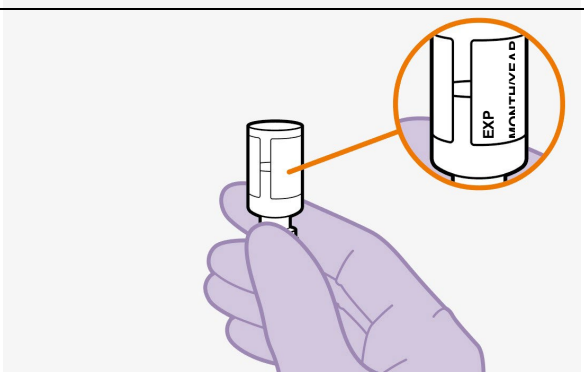
Needle guard



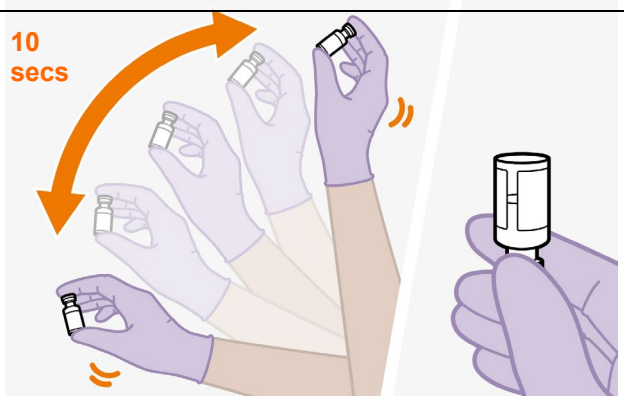
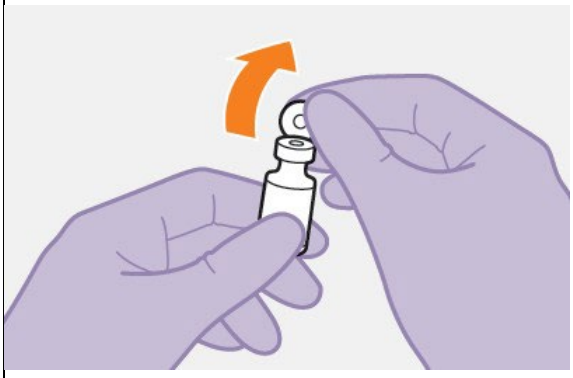
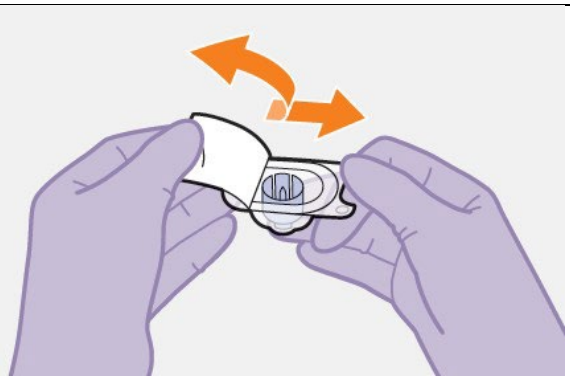
Injection needle

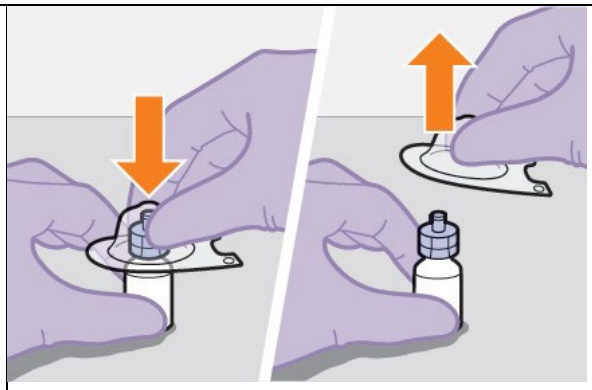
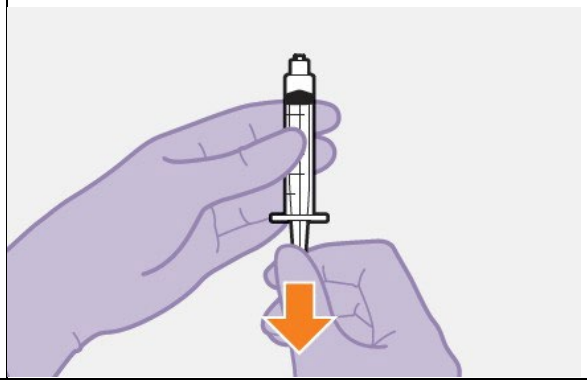
Needle cap

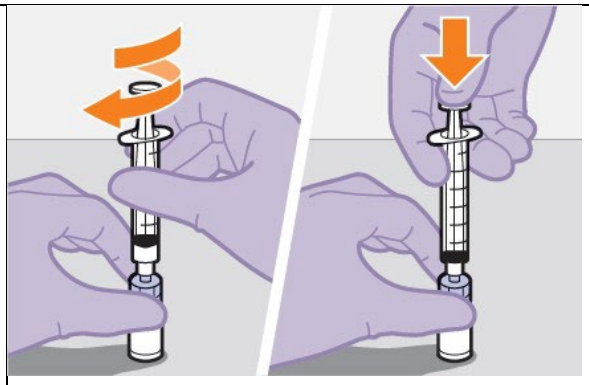
Your pack contains
1 vial of cabotegravir 1 vial adapter 1 syringe 1 injection needle (0.65 mm, 38 mm [23G, approx. 3.8 cm]) Consider the patient's build and use medical judgement to select an appropriate injection needle length.
You will also need
Non-sterile gloves 2 alcohol wipes 2 gauze pads A suitable sharps container 1 pack of rilpivirine 3 mL prolonged-release suspension for injection
Preparation

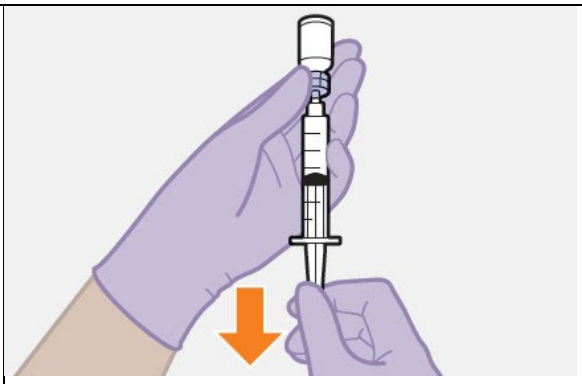
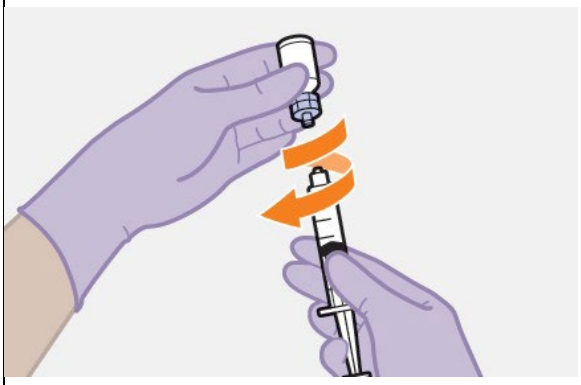
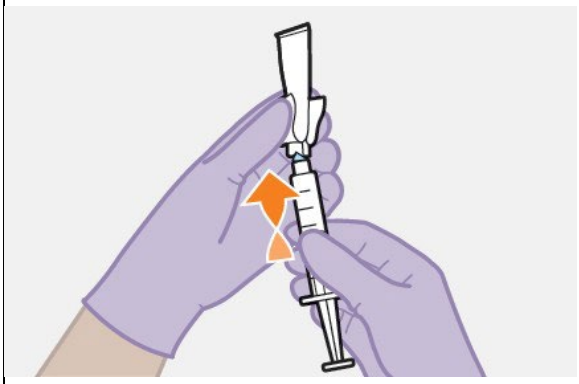
1. Inspect vial • Check the expiry date. • Inspect the vial yourself. If you can see foreign matter, do not use the product. Note: the Cabotegravir vial has a brown tint to the glass. Do not use if the expiry date has passed.	**Check expiry date** 

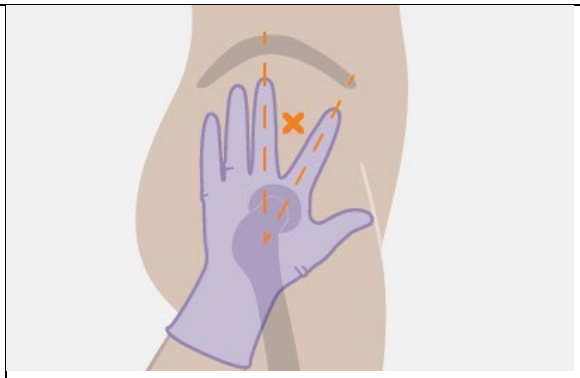
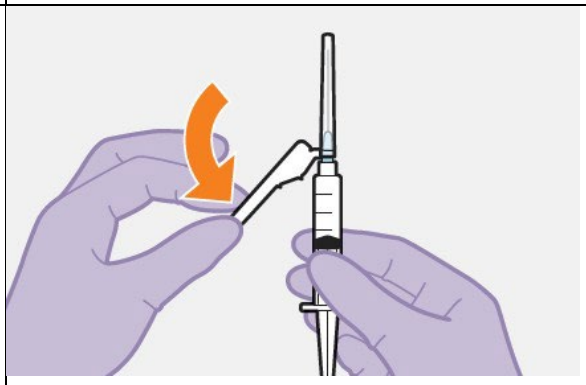
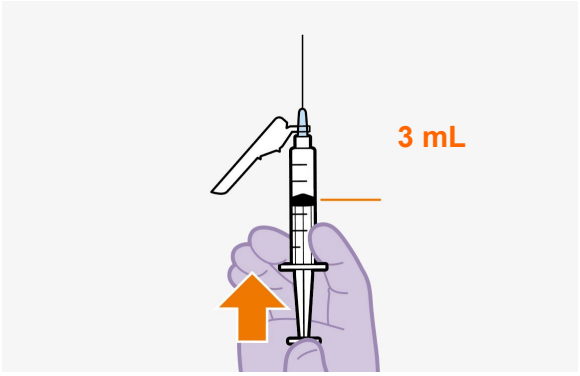
2. Wait 15 minutes • If the pack has been stored in the fridge, wait at least 15 minutes before injecting to allow the liquid to come to room temperature.		•

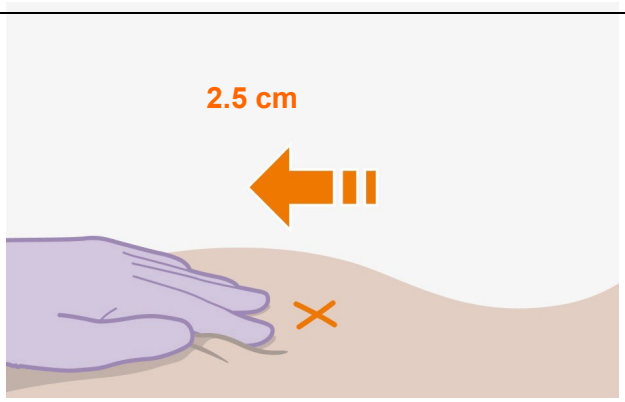
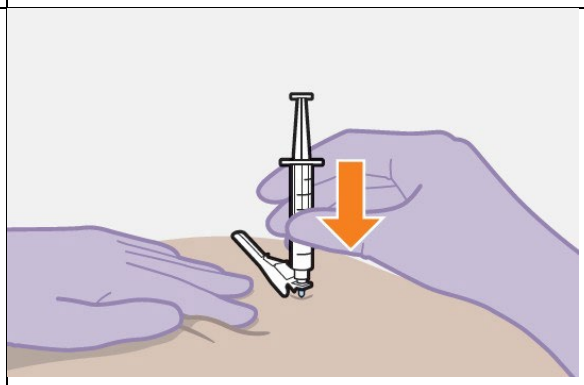
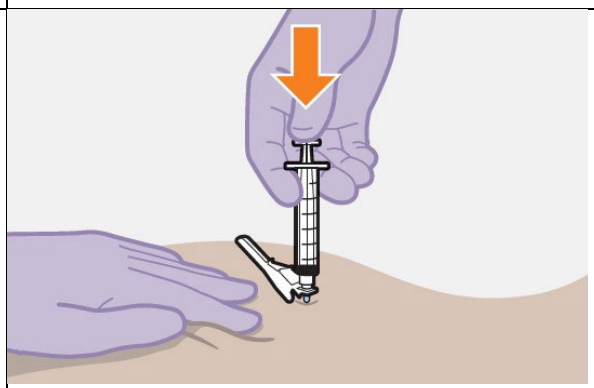
3. Shake vigorously • Hold the vial firmly and shake vigorously for a full 10 seconds. • Invert the vial and check if the suspension looks uniform. If the suspension is not uniform, shake the vial again. • It is normal to see small air bubbles. Note: the order in which the vials are prepared is not important.	
4. Remove closure • Remove the closure from the vial. • Wipe the rubber stopper with an alcohol wipe. Do not allow anything to touch the rubber stopper after wiping it.	
5. Peel open vial adapter packaging • Peel off the paper backing from the vial adapter packaging. Note: do not remove the adapter from its packaging for the next step. The adapter will not fall out if the packaging is turned upside down.	

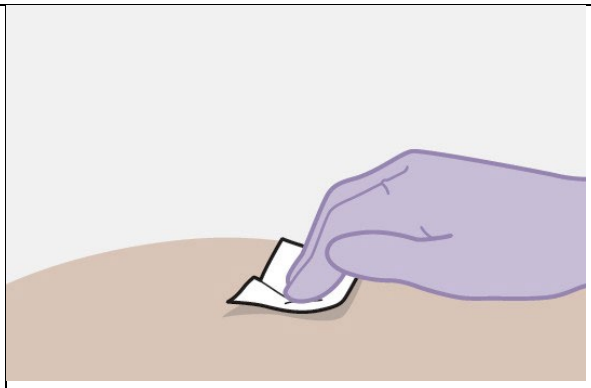
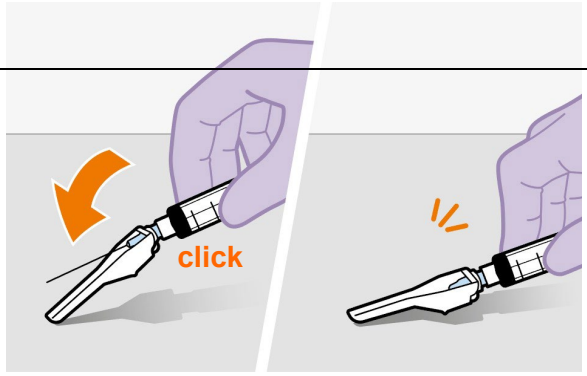
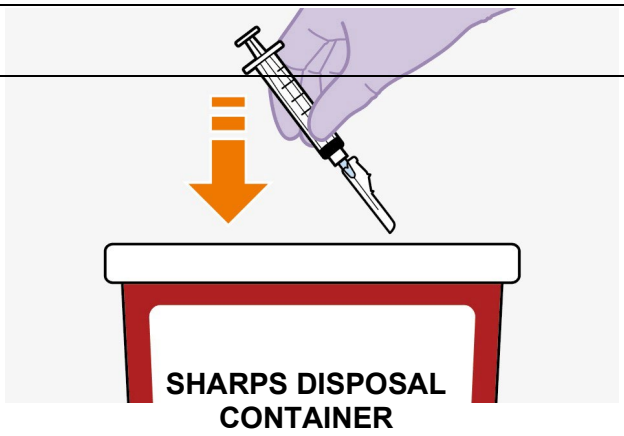
6. Attach vial adapter • Put the vial on a level surface. • Press the adapter straight down onto the vial, as shown. The adapter must snap securely into place.	
7. Remove packaging • Then remove the packaging as shown.	
8. Prepare syringe • Remove the syringe from its packaging. • Draw 1 mL of air into the syringe. This will make it easier to draw up the suspension later.	

9. Attach syringe • Hold the adapter and vial as shown. • Screw the syringe firmly onto the vial adapter. • Press the plunger all the way down to push the air into the vial.	

10. Slowly draw up dose • Invert the syringe and vial and withdraw as much of the liquid as possible into the syringe. There may be more liquid than the dose amount in the vial. Note: keep the syringe upright to avoid leakage.	
11. Unscrew syringe • Hold the syringe plunger as shown to prevent liquid from leaking. It is normal to notice a certain amount of counterpressure. • Screw the syringe off the adapter as shown. Note: check that the suspension looks uniform and white to light pink.	
12. Attach injection needle • Peel open the needle packaging part way to expose the needle attachment. • Keeping the syringe upright, firmly twist the syringe onto the needle. • Completely remove the packaging.	
Injection	

13. Prepare injection site Injections must be administered into the gluteal muscle. Choose one of the following injection sites: Ventrogluteal (as shown; recommended) Dorsogluteal (upper outer quadrant) Note: for intramuscular use only. Do not administer the injection intravenously.	
14. Remove needle cap • Fold the needle guard away from the needle. • Pull off the needle cap.	
15. Remove excess dose amount • Hold the syringe upright with the needle pointing up. Press the plunger to the correct dose amount to remove excess liquid and any air bubbles. Note: clean the injection site with an alcohol wipe. Allow the skin to air dry before continuing.	

16. Stretch skin Use the z-track technique to minimise leakage from the injection site. • Drag the skin covering the injection site, displacing it by about 2.5 cm. • Keep it held in this position during the injection.	
17. Insert needle • Insert the needle to its full depth, or deep enough to reach the muscle tissue.	
18. Inject dose • Still holding the skin stretched – slowly press the plunger all the way down. • Ensure the syringe is completely empty. • Withdraw the needle and release the stretched skin immediately.	

19. Assess the injection site • Apply pressure to the injection site using a gauze pad. • A small plaster may be used if bleeding occurs. Do not massage the injection site.	
20. Make needle safe • Fold the needle guard back over the needle. • Gently apply pressure to the needle using a hard surface to lock the needle guard in place. • It will make a click when it locks.	
After injection	
21. Safe disposal Dispose of used needles, syringes, vials and adapters according to local health and safety regulations.	

Repeat the process for the second medicinal product If you have only injected one of the two medicinal products, repeat all preparation steps and the injection again for the second medicinal product.	

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Vocabria, film-coated tablets

Composition

Active substances

Cabotegravir (as cabotegravir sodium, equivalent to 1.52 – 1.87 mg sodium per tablet).

Excipients

Tablet core: lactose monohydrate 163.59 mg, microcrystalline cellulose, hypromellose, sodium starch glycolate type A (equivalent to 1.15 – 1.72 mg sodium per tablet), magnesium stearate.

Film coating: hypromellose, titanium dioxide (E171), macrogol 400.

The total sodium content is 2.67 – 3.59 mg sodium per tablet.

Pharmaceutical form and active substance quantity per unit

One film-coated tablet contains 30 mg cabotegravir (as cabotegravir sodium).

Indications/Uses

Vocabria tablets are indicated in combination with rilpivirine tablets for the short-term (see *"Dosage/Administration")* treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents aged 12 and over and with a body weight of at least 35 kg who have been virologically suppressed (HIV-1 RNA <50 copies/mL) for at least 6 months on a stable antiretroviral therapy regimen and have no known or suspected resistance to and no history of virological failure with agents of the NNRTI and INI class.
The treatment is used as

- oral lead-in to test the tolerability of cabotegravir in combination with rilpivirine tablets prior to starting therapy with long-acting Vocabria injections or
- oral bridging treatment for adults and adolescents who will miss planned Vocabria injections.

Dosage/Administration

Treatment must be initiated by a physician experienced in the treatment of HIV infection.
Vocabria tablets should always be given in combination with rilpivirine tablets for the short-term treatment of HIV-1 infection. The recommended dose of rilpivirine is specified in the prescribing information for rilpivirine tablets.
Before starting treatment with Vocabria, the treating physician should carefully select patients who agree with the injection schedule required (see prescribing information for Vocabria prolonged-release suspension for injection) and advise them of the importance of complying with the scheduled dosing intervals in order to maintain viral suppression and reduce the risk of any viral “rebound” or potential development of resistance if doses are missed.
Vocabria tablets may be used before starting cabotegravir injections as oral lead-in to test the tolerability of cabotegravir (see Table 1).
Alternatively, physicians and patients may start directly with long-acting injection therapy (see prescribing information for Vocabria prolonged-release suspension for injection).

Dosage

Adults and adolescents (aged 12 and over and with a body weight of at least 35 kg)
Oral lead-in
In the case of oral lead-in, the oral administration of Vocabria tablets is recommended for approximately one month (at least 28 days, up to a maximum of 2 months) in virologically suppressed patients prior to the initiation of treatment with Vocabria injections in order to test the tolerability of cabotegravir. One Vocabria tablet (30 mg) must be taken with one rilpivirine tablet (25 mg). When administered with rilpivirine, Vocabria tablets should be taken with food.

Table 1: Recommended dosage schedule

	ORAL LEAD-IN
Medicinal product	*During month 1* *(at least 28 days, maximum of 2 months)*
Vocabria	30 mg once daily
Rilpivirine	25 mg once daily

Oral dose after missed monthly and every-two-month injections of Vocabria
Oral bridging treatment and resumption of injections:
If a delay of more than 7 days from a scheduled injection appointment cannot be avoided, Vocabria tablets (30 mg once daily) may be used in combination with rilpivirine tablets (25

mg once daily) to replace up to two consecutive monthly injections or one every-two-month injection. When administered with rilpivirine, Vocabria tablets should be taken with food. The first dose of oral therapy must be taken one month (+/- 7 days) after the last cabotegravir and/or rilpivirine injection for the monthly dosage schedule. For the every-two-month dosage schedule, the first dose of oral therapy must be taken two months (+/- 7 days) after the last cabotegravir and/or rilpivirine injection. Injection therapy should be resumed on the last day of oral therapy (see also prescribing information for Vocabria prolonged-release suspension for injection).

Missed dose

If the patient misses a dose of oral cabotegravir, the patient should take the missed dose as soon as possible, provided 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 dosage schedule.

Special dosage instructions

Hepatic impairment

No dose adjustment is required in patients with mild to 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 *"Pharmacokinetics – Kinetics in specific patient groups"*).

Renal impairment

No dose adjustment is required in patients with mild (creatinine clearance of ≥60 to <90 mL/min), moderate (creatinine clearance of ≥30 to <60 mL/min) or severe (creatinine clearance of ≥15 to <30 mL/min) renal impairment who are not on dialysis (see *"Pharmacokinetics – Kinetics in specific patient groups"*).

Elderly patients

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 *"Pharmacokinetics – Kinetics in specific patient groups"*).

Children and adolescents

The safety and efficacy of cabotegravir in children under 12 years of age or adolescents with a body weight of less than 35 kg has not been established.

Mode of administration
When taken at the same time as rilpivirine, cabotegravir must be taken with food.

Contraindications

Cabotegravir is contraindicated in patients:

- with known hypersensitivity to cabotegravir or to any of the other components of the tablets
- receiving strong UGT1A1 inducers, e.g. rifampicin, rifapentine, phenytoin, phenobarbital, carbamazepine and oxcarbazepine, as they are expected to decrease cabotegravir plasma concentrations and may result in loss of virological response.

Vocabria tablets are only indicated for treatment of HIV-1 infection in combination with rilpivirine tablets; therefore, the prescribing information for rilpivirine tablets should also be consulted.

Warnings and precautions

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. In order to identify patients at risk of a hypersensitivity reaction, oral lead-in with cabotegravir was performed in clinical trials. Discontinue cabotegravir and other suspected active substances immediately if signs or symptoms of a hypersensitivity reaction develop (including severe skin rash, or skin rash accompanied by fever, general malaise, fatigue, muscle or joint pain, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). In this case, the patient's clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated if necessary (see *"Dosage/Administration", "Contraindications", "Undesirable effects", "Clinical efficacy"*).

Hepatotoxicity
Hepatotoxicity has been reported in a limited number of patients receiving cabotegravir with or without known pre-existing hepatic disease (see *"Undesirable effects"*).
Monitoring of liver function values is recommended. Cabotegravir should be discontinued if hepatotoxicity is suspected.

Lactose
Vocabria tablets contain lactose. Patients with rare hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

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

Opportunistic infections

Patients receiving cabotegravir or any other antiretroviral treatment may still be at risk of developing opportunistic infections or other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these HIV comorbidities.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome has been reported in patients receiving combination antiretroviral therapy. In the initial phase of combination antiretroviral therapy, patients whose immune systems respond to treatment may develop an inflammatory reaction to indolent or residual opportunistic infections (e.g. with *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jirovecii* pneumonia and tuberculosis), which may require further evaluation and treatment. There have also been reports of autoimmune diseases (such as Graves' disease and autoimmune hepatitis) occurring as part of an immune reconstitution inflammatory syndrome. However, the timing of onset is more variable, and these events may occur many months after the start of treatment.

Transmission of infection

The results of observational studies have shown there is no risk of sexual transmission of HIV if viral suppression is achieved and maintained. However, the risk of sexual transmission of HIV cannot be ruled out if the prescribed ART is not taken on a regular basis and/or viral suppression is not achieved and maintained.

Concomitant treatment with rilpivirine

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

Interactions with other medicinal products

Caution should be exercised when prescribing Vocabria together with other medicinal products that may reduce cabotegravir exposure (see *"Interactions"*).

Polyvalent cation-containing antacids should be taken at least 2 hours before or 4 hours after taking Vocabria tablets (see *"Interactions"*).

It is recommended to take Vocabria at least 2 hours before or 4 hours after taking calcium and iron supplements.

Patients with hepatitis B and hepatitis C virus co-infection

Patients with hepatitis B co-infection were excluded from participating in the studies with Vocabria. It is not recommended that patients with hepatitis B co-infection start treatment with Vocabria. The current treatment guidelines for the treatment of HIV infection in patients with hepatitis B virus co-infection must be followed, as well as the *"Interactions"* (see below).

Very limited data are available on the use of Vocabria in patients with hepatitis C virus co-infection. If hepatitis C infection occurs during treatment with Vocabria, the current treatment guidelines for HIV infection in patients with hepatitis C virus co-infection must be followed, as well as the "*Interactions"* (see below).

Interactions

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

Effect of Vocabria on other medicinal products

In vivo, cabotegravir did not have an effect on the CYP3A4 substrate midazolam. 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, breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic cation transporter (OCT)1, OCT2, OATP1B1, OATP1B3, multidrug and toxin extrusion (MATE) transporter 1, MATE 2-K, multidrug resistance protein (MRP) 2 or MRP4.

In vitro, cabotegravir inhibited the organic anion transporters (OAT) 1 (IC_{50}=0.81 µM) and OAT3 (IC_{50}=0.41 µM). However, based on physiologically based pharmacokinetic (PBPK) modelling, no interactions with OAT substrates are 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.

Based on the in vitro and clinical interaction profile, cabotegravir is not expected to alter

concentrations of other antiretroviral medicinal products, including protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, entry inhibitors and ibalizumab.

Effect of other medicinal products on Vocabria

Cabotegravir is primarily metabolised by UGT1A1, 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 decreased efficacy (see *"Contraindications"*).

Simulations using physiologically based pharmacokinetic (PBPK) modelling show that no clinically significant interactions are expected in relation to concomitant administration of cabotegravir with other medicinal products that inhibit UGT enzymes. In vitro, cabotegravir was not a substrate of OATP1B1, OATP1B3, OATP2B1 or OCT1.

Cabotegravir is a substrate of P-gp and BCRP; however, because of its high permeability, no alteration in absorption is expected when administered concomitantly with either P-gp or BCRP inhibitors.

Table 2: Interactions with other medicinal products

Effect of concomitantly administered medicinal products on the pharmacokinetics of cabotegravir[1]				
Concomitantly administered drug class + drug and dose	*Effects on drug concentration GMR (90% CI) No effect = 1.00*			*Recommendation for concomitant use*
	C_{max}	*AUC*	C_{τ} *or* C_{24}	
HIV-1 antiviral agents				
NNRTI Etravirine 200 mg twice daily	1.04 (0.99, 1.09)	1.01 (0.96, 1.06)	1.00 (0.94, 1.06)	Etravirine did not significantly affect the cabotegravir plasma concentration. No dose adjustment of Vocabria tablets is necessary.
NNRTI Rilpivirine 25 mg once daily	1.05 (0.96, 1.15)	1.12 (1.05, 1.19)	1.14 (1.04, 1.24)	Rilpivirine did not significantly affect the cabotegravir plasma concentration. No dose adjustment of Vocabria tablets is necessary.
Other agents				
Rifabutin 300 mg once daily	0.83 (0.76, 0.90)	0.77 (0.74, 0.83)	0.74 (0.70, 0.78)	Rifabutin did not significantly affect the cabotegravir plasma concentration. No dose adjustment is required. Prior to initiation of oral cabotegravir therapy, the prescribing information for Vocabria injection should be consulted regarding concomitant use with rifabutin.
Rifampicin 600 mg once daily	0.94 (0.87, 1.02)	0.41 (0.36, 0.46)	0.50 (0.44, 0.57)	Rifampicin significantly decreased cabotegravir plasma concentrations due to induction of UGT metabolism, which is likely to result in loss of therapeutic effect. Dosage recommendations for the concomitant administration of Vocabria with rifampicin have not been established and the concomitant administration of Vocabria with rifampicin is contraindicated.

[1] Cabotegravir 30 mg administered orally once daily for all studies except for rifampicin, where cabotegravir 30 mg was administered as single dose

GMR = geometric mean ratio

Effect of cabotegravir[1] on the pharmacokinetics of concomitantly administered medicinal products				
Concomitantly administered drug class + drug and dose	*Effects on drug concentration GMR (90% CI) No effect = 1.00*			*Recommendation for concomitant use*
	C_{max}	*AUC*	C_{τ} *or* C_{24}	
HIV-1 antiviral agents				
Rilpivirine 25 mg once daily	0.96 (0.85, 1.09)	0.99 (0.89, 1.09)	0.92 (0.79, 1.07)	Cabotegravir did not significantly change rilpivirine plasma concentrations. No dose adjustment of rilpivirine is necessary when administered concomitantly with Vocabria tablets.
Other agents				
Ethinylestradiol 0.03 mg once daily	0.92 (0.83, 1.03)	1.02 (0.97, 1.08)	1.00 (0.92, 1.10)	Cabotegravir did not significantly change ethinylestradiol/levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when administered concomitantly with Vocabria tablets.
Levonorgestrel 0.15 mg once daily	1.05 (0.96, 1.15)	1.12 (1.07, 1.18)	1.07 (1.01, 1.15)	Cabotegravir did not significantly change levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when administered concomitantly with Vocabria tablets.
Midazolam 3 mg	1.09 (0.94, 1.26)	1.10 (0.95, 1.26)	Not available	Cabotegravir did not significantly change midazolam plasma concentrations to a clinically relevant extent. No dose adjustment of CYP3A substrates is necessary when administered concomitantly with Vocabria tablets.

[1] Cabotegravir 30 mg administered orally once daily for all studies except for rifampicin, where cabotegravir 30 mg was administered as single dose
GMR = geometric mean ratio

Other agents expected to decrease cabotegravir concentrations without clinical data		
Concomitant agent	*Medicinal product*	*Recommendation for concomitant use*
Antimycobacterials	Rifapentine	Rifapentine, a metabolic inducer, may significantly decrease cabotegravir plasma concentrations; concomitant use is contraindicated.
Anticonvulsants	Carbamazepine, oxcarbazepine, phenytoin, phenobarbital	Metabolic inducers may significantly decrease cabotegravir plasma concentrations; concomitant use is contraindicated.
Antacids	Magnesium, aluminium, calcium	The concomitant administration of antacids 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 the oral administration of Vocabria.

Pregnancy, lactation

Pregnancy

There are no studies of cabotegravir in pregnant women. The effect of cabotegravir on human pregnancy is unknown.
Animal studies have shown reproductive toxicity at exposures significantly above the maximum exposure for humans, indicating little relevance for clinical use (*see "Preclinical data"*). The significance of these findings for human pregnancy is not known. Vocabria should not be used during pregnancy or in women who are planning to become pregnant or who do not use a reliable contraceptive method, unless the expected benefits justify the possible risks to the foetus or unborn child.
Women should be advised on the use of effective contraception. Cabotegravir and oestrogen- and/or progesterone-based contraceptives can be used concomitantly without dose adjustment (*see "Interactions"*).

Lactation

Based on animal studies, it can be assumed that cabotegravir passes into breast milk, although this has not been confirmed for humans.
It is recommended that HIV-positive women do not breastfeed their babies to avoid HIV transmission and the possibility of undesirable effects in the breastfed infant.

Fertility

No data are available on the effects of cabotegravir on human fertility in men or women. Animal studies indicate no effects of cabotegravir on male or female fertility (*see "Preclinical data"*).

Effects on ability to drive and use machines

There have been no studies to investigate the effect of cabotegravir on the ability to drive and use machines. Vocabria can cause dizziness, headaches and nausea. 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 use machines.

Undesirable effects

Clinical trial data

Adverse drug reactions (ADRs) associated with cabotegravir alone or combination therapy of cabotegravir plus rilpivirine (monthly dosing or dosing every 2 months) are listed in Table 3.
The table shows all undesirable effects attributable to both the oral and injectable formulations of cabotegravir and rilpivirine.
Frequencies were calculated from Phase III clinical studies, and where they differed between the monthly schedule and the treatment schedule every 2 months, the highest frequency category is quoted in Table 3.
The most frequently reported ADRs from monthly dosing studies were injection site reactions (up to 84% of patients), headache (up to 12% of patients) and pyrexia[3] (10% of patients).
The most frequently reported ADRs from the ATLAS-2M study with dosing every 2 months were injection site reactions (76% of patients), headache (7% of patients) and pyrexia[3] (7% of patients).

The clinical ADRs are listed below by MedDRA system organ class and by frequency.
Frequencies are defined as: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) and very rare (<1/10,000; including isolated reports).

Table 3: Undesirable effects

MedDRA system organ class	*Frequency**	*ADRs for combination therapy cabotegravir plus rilpivirine*
Immune system disorders	Uncommon	Hypersensitivity[4] (including angioedema[4], urticaria[4])

Metabolic and nutritional disorders	Common	Weight increased
Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
	Uncommon	Suicidal ideation or suicide attempts (in particular among patients with a history of depression or psychiatric disorders)
Nervous system disorders	Very common	Headache (12%)
	Common	Dizziness
	Uncommon	Somnolence
Gastrointestinal disorders	Common	Nausea Vomiting Abdominal pain[1] Flatulence Diarrhoea Lipase increased (grades 3-4)
Hepatobiliary disorders	Uncommon	Hepatotoxicity Transaminases increased (AST/ALT)
Skin and subcutaneous tissue disorders	Common	Rash[2]
	Very rare	Stevens-Johnson syndrome[4], toxic epidermal necrolysis[4]
Musculoskeletal and connective tissue disorders	Common	Myalgia Creatine phosphokinase increased (grades 3-4)
General disorders and administration site conditions	Very common	Pyrexia[3] (10%)
	Common	Fatigue Asthenia Malaise

*The frequency of the identified undesirable effects is based on all reported events and is not restricted to those regarded by the investigator as, at least potentially, having some connection.

[1] Abdominal pain includes the following grouped MedDRA preferred terms: abdominal pain, upper abdominal pain.

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

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

[4] Post-marketing experience

The general safety profile in Week 96 and Week 124 of the FLAIR study corresponded to the profile observed in Week 48, with no new safety findings identified. In the extension phase of the FLAIR study in Week 124, there were no new safety concerns as a result of dispensing with the oral lead-in in the case of direct introduction of rilpivirine plus cabotegravir injections without any oral lead-in.

The general safety profile in Week 152 of the ATLAS-2M study corresponded to the profile observed in Week 48 and Week 96, with no new safety findings identified.

Description of selected adverse reactions and additional information

Frequent adverse drug reactions with Vocabria/Rekambys once a month compared to standard daily oral therapy (CAR)

Table 4: Systemic undesirable effects reported in ≥1% of virologically suppressed subjects with HIV-1 infection in the pooled FLAIR and ATLAS studies (Week 48)

Undesirable effects	CAB+RPV (N=591)	CAR (N=591)
Headache	12%	6%
Pyrexia[3]	10%	2%
Diarrhoea	9%	7%
Creatine phosphokinase increased (grades 3-4)	8%	4%
Lipase increased (grades 3-4)	6%	3%
Nausea	5%	3%
Fatigue	5%	2%
Rash[2]	5%	3%
Dizziness	4%	1%
Myalgia	4%	1%
Abdominal pain[1]	4%	2%

Insomnia	4%	1%
Anxiety	4%	2%
Asthenia	3%	<1%
Vomiting	2%	1%
Depression	2%	2%
Malaise	2%	<1%
Abnormal dreams	1%	<1%
Flatulence	1%	<1%

[1] Abdominal pain includes the following grouped MedDRA preferred terms: abdominal pain, upper abdominal pain.

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

[3] Pyrexia includes the following grouped MedDRA preferred terms: pyrexia, feeling hot, body temperature increased.

CAR = current antiretroviral regimen

It should be noted that FLAIR and ATLAS were open-label switch studies (see details also in *"Clinical efficacy"*). Higher frequencies of undesirable effects have been reported in the cabotegravir and rilpivirine arm, which may either be attributed to the treatment regimen or due to bias caused by the study design.

Weight gain

According to a pooled analysis of the FLAIR and ATLAS studies, at Week 48, patients who received cabotegravir plus rilpivirine gained a median of 1.5 kg in weight, while those in the CAR group (CAR = current antiretroviral regimen) gained a median of 1.0 kg. In the individual FLAIR and ATLAS studies, the median weight gain in the cabotegravir plus rilpivirine arm was 1.3 kg and 1.8 kg, respectively, compared to 1.5 kg and 0.3 kg in the CAR arm. At Week 48, in the ATLAS-2M study, the median weight gain in both the monthly and 2-monthly CAB+RPV dosing arms was 1.0 kg.

Laboratory abnormalities

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).

Elevated transaminases (ALT/AST) were observed in subjects receiving cabotegravir plus rilpivirine during the clinical trials. These elevations were primarily attributed to acute viral hepatitis. A few

patients had transaminase elevations attributed to suspected drug-related hepatotoxicity (see "*Warnings and precautions"*).
Elevated lipase values were identified in clinical studies with cabotegravir plus rilpivirine. Compared with the CAR group, there was a grade 3-4 increase in lipase values with cabotegravir plus rilpivirine. Increases in lipase values were generally asymptomatic and did not result in treatment being discontinued.
Asymptomatic creatine phosphokinase (CPK) elevations, mainly in association with physical exercise, have also been reported with cabotegravir plus rilpivirine.

Paediatric population
Based on data from the analyses of Week 16 (cohort 1C, n=30) and Week 24 (cohort 2, n=144) of the MOCHA study, in adolescents (aged 12 and over and with a body weight of 35 kg or more), no new safety concerns were identified compared to the safety profile in adults (see *"Clinical efficacy"*).

Additional information on specific patient groups
The safety and efficacy of cabotegravir in children and adolescents aged under 18 years have not been established.
For other adverse reactions associated with rilpivirine, the prescribing information for rilpivirine should be consulted.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

There is currently no experience of overdose with Vocabria.

Treatment

There is no specific treatment in the event of cabotegravir overdose. If overdose occurs, the patient must be treated with appropriate supportive treatment and be monitored accordingly.
Further management should be as clinically indicated or as recommended by the relevant toxicological information centre, if available.
Due to the high plasma binding of cabotegravir, dialysis is unlikely to be helpful in removing the medicinal product from the body.

Properties/Effects

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.

Pharmacodynamics

Antiviral activity in cell culture
Cabotegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentrations (EC_{50}) necessary to reduce viral replication by 50% 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 a cell culture test against a panel of 24 clinical HIV-1 isolates (three in each group of M-subtypes A, B, C, D, E, F and G, and 3 in group O), with EC_{50} values ranging from 0.02 nM to 1.06 nM. The EC_{50} values against three HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM. There are no clinical data for patients with HIV-2.

Antiviral activity in combination with other antiviral agents
No medicinal products with inherent anti-HIV activity were antagonistic to cabotegravir (in vitro tests were conducted for cabotegravir in combination with rilpivirine, lamivudine, tenofovir and emtricitabine).

Effect of human serum and serum proteins
In vitro tests in MT4 cells suggested a 408-fold shift in the IC_{50} of cabotegravir in the presence of 100% human serum (by method of extrapolation), and the protein-adjusted IC_{50} (PA-IC_{50}) was estimated to be 102 nM in PBMC.

Resistance in vitro
Isolation from wild-type HIV-1 and activity against resistant strains: viruses with a >10-fold increase in cabotegravir EC_{50} 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 2.8-8.4) and I162M (fold change = 2.8). As noted above, the detection of T124A corresponds to the 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 strain NL-432 in the presence of 6.4 nM of cabotegravir through Day 56.
Among the multiple mutants, the highest fold change was observed with the mutants containing Q148K or Q148R. E138K/Q148H resulted in a 0.92-fold decrease in susceptibility to cabotegravir, but E138K/Q148K resulted in an 81-fold decrease in susceptibility to cabotegravir. G140C/Q148R, G140S/Q148R and N155H/Q148R resulted in a 22-, 12- and 61-fold decrease in susceptibility to cabotegravir, respectively. N155H did not alter susceptibility to cabotegravir more than 6-fold for other N155H double mutants.

Resistance in vivo
Only a few people met the criteria (two consecutive plasma HIV-1 RNA levels ≥200 copies/mL after prior suppression to <200 copies/mL) for confirmed virological failure (CVF) in the pooled FLAIR and ATLAS Phase III trials (see also *"Clinical efficacy"*). In the pooled analysis, there were 7 cases of CVF on cabotegravir plus rilpivirine (n=591, 1.2%) and 7 cases of CVF with continuation of current standard antiretroviral therapy (CAR).
The three cases of CVF on cabotegravir plus rilpivirine in study 201684 (FLAIR) with resistance data had Subtype A1 with IN substitution L74I, which by itself does not cause resistance to any INI. This substitution was detected at baseline and associated with suspected virological failure (SVF). In addition, two-thirds of the cases of CVF had treatment-emergent INI resistance-associated substitution Q148R, while one-third had G140R with reduced phenotypic susceptibility to cabotegravir. All three cases of CVF carried one rilpivirine resistance-associated substitution (K101E, E138E/A/K/T or E138K) and two-thirds showed reduced phenotypic susceptibility to rilpivirine.
The three cases of CVF in study 201585 (ATLAS) had subtype A, A1 and AG. The two cases of CVF with subtype A and A1 both carried IN substitution L74I. This was in PBMC HIV-1 DNA at baseline and in HIV-1 RNA at the time of SVF. In addition, one-third of cases of CVF carried the INI resistance-associated substitution N155H at the time of SVF. All three cases of CVF had treatment-emergent rilpivirine resistance-associated substitutions (E138A, E138E/K or E138K) and showed reduced phenotypic susceptibility to rilpivirine, while one-third also showed phenotypic susceptibility to cabotegravir. In two-thirds of cases of CVF, the rilpivirine resistance-associated substitutions observed during SVF were also observed at baseline in PBMC HIV-1 DNA.
In the seventh case of CVF (FLAIR), the patient concerned never received an injection and had no resistance mutations.
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 Phase IIIb ATLAS-2M study (see also “Clinical efficacy”), 10 patients met CVF criteria through Week 48: 8 patients (1.5%) in the Q8W arm and 2 patients (0.4%) in the Q4W arm. 8 participants met CVF criteria at or before the Week 24 timepoint. At the SVF timepoint, the 10 cases of CVF showed HIV-1 subtype A (n=2), A1 (n=2), B (n=4), C (n=1) or complex (n=1).
At baseline, 5 patients in the Q8W arm had RPV resistance-associated mutations of Y181Y/C + H221H/Y, Y188Y/F/H/L, Y188L, E138A or E138E/A, and 1 patient had cabotegravir resistance mutation G140G/R (in addition to the above Y188Y/F/H/L RPV resistance-associated mutation). At the SVF timepoint, 6 patients in the Q8W arm had rilpivirine resistance-associated mutations, with 2 patients having an addition of K101E and 1 patient having an addition of E138E/K from baseline to the SVF timepoint. The RPV fold change (FC) was above the biological cut-off for 7 patients and ranged from 2.4 to 15. Five of the 6 patients 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 out of 7 patients. The integrase genotype and phenotype assay failed for one patient and the cabotegravir phenotype was unavailable for another. The fold changes for the Q8W patients 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 patient with CVF had any RPV or INSTI resistance-associated substitutions at baseline. One patient had the NNRTI substitution G190Q in combination with the NNRTI polymorphism V189I. At the SVF timepoint, one patient had the rilpivirine resistance-associated mutations K101E + M230L during treatment and the other retained the G190Q + V189I NNRTI substitutions with the addition of V179V/I. Both patients showed reduced susceptibility to RPV. Both patients also had INSTI resistance-associated mutations, either Q148R + E138E/K or N155N/H at the time of SVF, 1 patient had reduced susceptibility to CAB. Neither patient had the INSTI substitution L74I. The fold changes for the Q4W patients were 1.8 and 4.6 for cabotegravir, 1.0 and 1.4 for dolutegravir and 1.1 and 1.5 bictegravir.
By Week 152, 13 patients met the CVF criteria during the maintenance and extension phase; 2 patients (Q8W arm) met the CVF criteria following the analysis in Week 96 (see Table 5). In ten patients, CVF occurred before Week 48 (8 patients in the Q8W arm and 2 patients in the Q4W arm) and 1 patient (Q8W arm) met the CVF criteria between Week 48 and Week 96.

Table 5: Cumulative proportion of patients meeting the CVF criteria by visit up to Week 152 of the maintenance phase + extension phase (ITT-E population): Study 207966 Week 152 analysis

SVF timepoint[a]	Q8W (N=522) n (%)	Q4W (N=523) n (%)
Week 8	1 (0.2)	0
Week 16	4 (0.8)	1 (0.2)
Week 24	7 (1.3)	1 (0.2)
Week 32	7 (1.3)	2 (0.4)
Week 48	8 (1.5)	2 (0.4)
Week 88	9 (1.7)	2 (0.4)
Week 112	10 (1.9)	2 (0.4)
Week 120	11 (2.1)	2 (0.4)

a. First of the 2 consecutive HIV-1 RNA values ≥200 c/mL.
Comment: this summary relates to the cumulative proportion of CVFs up to the examination visit.
Note: the only visits shown are those where at least one new CVF occurred.

In addition to the 9 patients with CVF in the Q8W group, 2 patients met CVF criteria between Week 96 and Week 152 (see Table 5). One patient, who switched from study 201585 after he had received CAB + RPV LA for 1 to 24 weeks, met the CVF criteria in Week 112. At baseline, this patient showed the L74I IN polymorphism. At the SVF timepoint, 3 NNRTI mutations were observed, K103N and RPV-resistance-associated mutations, E138A and Y181Y/C. The INI-resistance-associated mutation Q148R was found together with the L74I polymorphism. A reduced phenotypic propensity for RPV (FC=3.4) and CAB (FC=9.5) was observed. The HIV-1 virus subtype at the SVF timepoint was A. The other patient met the CVF criteria in Week 120 and did not show any resistance-associated mutations at the baseline timepoint. At the SVF timepoint, the RPV resistance mutations E138A and M230M/L were identified, as well as the INI-resistance mutation Q148R. The phenotype analysis showed a reduced RPV (FC=16) and CAB sensitivity (FC=3.3). The patient was a carrier of the HIV-1 subtype B/C at the SVF timepoint. There were no other CVF patients in the Q4W group.

Effects on electrocardiogram

In a randomised, placebo-controlled, three-period crossover study, 42 healthy subjects were randomised into 6 random sequences and received three oral doses of placebo, three oral doses of 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 oral dose, the 400 mg dose for the monthly cabotegravir injection and the 600 mg dose for the cabotegravir injection every 2 months, respectively), or a 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) was 2.62 ms (one-sided upper 90% CI: 5.26 ms). Cabotegravir did not prolong the QTc interval within 24 hours of administration.

Clinical efficacy

Adults

Monthly dosing

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

In the FLAIR study, 629 HIV-1-infected, antiretroviral treatment (ART)-naive patients 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). Patients who were virologically suppressed (HIV-1 RNA <50 copies per mL, n=566) were then randomised 1:1 to receive either cabotegravir plus rilpivirine or to remain on the current antiretroviral (CAR) regimen. Subjects randomised to receive cabotegravir plus rilpivirine initiated oral lead-in treatment with a cabotegravir 30 mg tablet plus a rilpivirine 25 mg tablet daily for about one month (at least 28 days, maximum 77 days), followed by cabotegravir injections (month 1: 600 mg injection, from month 2 onwards: 400 mg injection) plus rilpivirine injections (month 1: 900 mg injection, from month 2 onwards: 600 mg injection) every month for up to 96 weeks.

In the ATLAS study, 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 cabotegravir plus rilpivirine or remained on their current antiretroviral (CAR) regimen. Subjects randomised to receive cabotegravir plus rilpivirine initiated oral lead-in treatment with a cabotegravir 30 mg tablet plus a rilpivirine 25 mg tablet daily for about one month (at least 28 days, maximum 73 days) followed by cabotegravir injections (month 1: 600 mg injection, from month 2 onwards: 400 mg injection) plus rilpivirine injections (month 1: 900 mg injection, from month 2 onwards: 600 mg injection) for an additional 44 weeks. In the ATLAS study, 50%, 17% and 33% of patients received an NNRTI, PI or INI, respectively, as their baseline third drug agent class prior to randomisation. This distribution remained similar after randomisation in the control arm (CAR).

In the pooled analysis of the FLAIR and ATLAS studies, in the cabotegravir plus rilpivirine treatment arm, the median age of subjects at baseline was 38 years, 27% were female, 27% were non-white and 7% had less than 350 CD4+ cells per mm^3. These characteristics were similar between treatment arms.

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

In a pooled analysis of FLAIR and ATLAS, cabotegravir plus rilpivirine was non-inferior to CAR with regard to the proportion of patients having plasma HIV-1 RNA ≥50 copies/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 limit of the 95% CI below 4%).
The non-inferiority results established in FLAIR and ATLAS demonstrated that the length of virological suppression prior to initiation of treatment with cabotegravir plus rilpivirine (5 months or ≥6 months) did not impact overall response rates.
The primary endpoint and other Week 48 outcomes, including outcomes by key baseline factors for patients, for FLAIR and ATLAS are shown in Tables 6 and 7.

Table 6: Virological outcomes of randomised treatment in FLAIR and ATLAS after 48 weeks (snapshot analysis)

	FLAIR		*ATLAS*		*Pooled data*	
	CAB + RPV N=283 N (%)	*CAR N=283 N (%)*	*CAB + RPV N=308 N (%)*	*CAR N=308 N (%)*	*CAB+RPV N=591 N (%)*	*CAR N=591 N (%)*
HIV-1 RNA ≥50 copies/mL†	6 (2.1)	7 (2.5)	5 (1.6)	3 (1.0)	11 (1.9)	10 (1.7)
*Treatment difference in % (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)
No virological data at the Week 48 window	12 (4.2)	12 (4.2)	18 (5.8)	11 (3.6)	30 (5.1)	23 (3.9)
Reasons						
Discontinued study/treatment due to adverse events or death	8 (2.8)	2 (0.7)	11 (3.6)	5 (1.6)	19 (3.2)	7 (1.2)

Discontinued study/treatment for other reasons	4 (1.4)	10 (3.5)	7 (2.3)	6 (1.9)	11 (1.9)	16 (2.7)
No data during time window but continued study participation	0	0	0	0	0	0

* adjusted for baseline stratification factors.
† Includes subjects who discontinued the study due to lack of efficacy or suppression.
N = Number of patients in each treatment group, CI = confidence interval, CAB = cabotegravir, RPV = rilpivirine, CAR = current antiviral regimen.

Table 7: Proportion of patients with plasma HIV-1 RNA ≥50 copies/mL at Week 48 for key baseline factors of patients (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^3)	<350	0/42	2/54 (3.7)
	≥350 to <500	5/120 (4.2)	0/117
	≥500	6/429 (1.4)	8/420 (1.9)
Sex	Male	6/429 (1.4)	9/423 (2.1)
	Female	5/162 (3.1)	1/168 (0.6)
Ethnicity	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 (third drug class)	PI	1/51 (2.0)	0/54
	INI	6/385 (1.6)	9/382 (2.4)
	NNRTI	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 patient characteristics (CD4+ count, sex, age, ethnicity, BMI, baseline third agent class) were not clinically meaningful.

Participants in both studies were virologically suppressed prior to Day 1 or randomisation, respectively, and a clinically relevant change from baseline in CD4+ cell counts was not observed.

Week 96 FLAIR

In the FLAIR study, after 96 weeks, the results remained consistent with the results after 48 weeks. The proportion of patients having plasma HIV-1 RNA ≥50 copies/mL for 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).

Week 124 FLAIR – start of therapy with direct to injection (DTI)

In the FLAIR study, safety and efficacy were assessed at Week 124 in patients who had decided in the extension phase (at Week 100) to switch from abacavir/dolutegravir/lamivudine to Vocabria plus rilpivirine. Patients were given the opportunity to switch, with or without oral lead-in, with one group forming with an oral lead-in phase ("oral lead-in" (OLI) group) (n = 121) and one group forming which started directly with injections ("direct to injection" (DTI) group (n = 111).

At Week 124, the proportion of patients with HIV-1 RNA ≥ 50 copies/mL was 0.8% for the group with oral lead-in and 0.9% for the group which started directly with injections.

Also in Week 124, comparable virus suppression rates (HIV-1 RNA <50 c/mL) were recorded in the DTI group (110/111 [99.1%]) and the OLI group (113/121 [93.4%]).

<u>Dosing every 2 months</u>

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

In the ATLAS-2M study, 1,045 HIV-1-infected, ART-experienced, virologically suppressed patients were randomised (1:1) and received a cabotegravir plus rilpivirine injection regimen administered either every 2 months or monthly.

Patients not initially treated with cabotegravir/rilpivirine received oral lead-in treatment comprising one cabotegravir 30 mg tablet plus one rilpivirine 25 mg tablet daily for about one month (at least 4 weeks, maximum 85 days). Patients randomised to monthly cabotegravir injections (month 1: 600 mg injection, from month 2 onwards: 400 mg injection) and rilpivirine injections (month 1: 900 mg injection, from month 2 onwards: 600 mg injection) received treatment for an additional 44 weeks. Patients randomised to every-2-month cabotegravir injections (600 mg injections at months 1, 2, 4 and every 2 months thereafter) and rilpivirine injections (900 mg injections 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 patients received cabotegravir/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^3; these characteristics were similar between the treatment arms.

The primary endpoint in ATLAS-2M was the proportion of patients with a plasma HIV-1 RNA ≥50 copies/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 + rilpivirine administered every month with regard to the proportion of patients having plasma HIV-1 RNA ≥50 copies/mL (1.7% and 1.0%, respectively) at Week 48. The adjusted treatment difference between cabotegravir plus rilpivirine administered every 2 months and cabotegravir plus rilpivirine administered every month (0.8; 95% CI: -0.6, 2.2) met the non-inferiority criterion (upper limit of the 95% CI below 4%). The efficacy results in Week 96 and Week 152 are consistent with the results for the primary endpoint in Week 48 (see Table 8).

Table 8: Virological outcomes of randomised treatment in ATLAS-2M after 48, 96 and 152 weeks (snapshot analysis)

	Dosing every 2 months (Q8W)	*Monthly dosing (Q4W)*
	N=522 (%)	*N=523 (%)*
Week 48		
HIV-1 RNA ≥50 copies/mL†, n (%)	9 (1.7)	5 (1.0)
*Treatment difference in % (95% CI)**	0.8 (-0.6, 2.2)	
HIV-1 RNA <50 copies/mL, n (%)	492 (94.3)	489 (93.5)
No virological data at the Week 48 window, n (%)	21 (4.0)	29 (5.5)
Reasons		
Discontinued study/treatment due to adverse events or death, n (%)	9 (1.7)	13 (2.5)
Discontinued study/treatment for other reasons, n (%)	12 (2.3)	16 (3.1)
No data during time window but continued study participation, n (%)	0	0
Week 96		
HIV-1 RNA ≥50 copies/mL†, n (%)	11 (2.1)	6 (1.1)
HIV-1 RNA <50 copies/mL, n (%)	475 (91.0)	472 (90.2)
No virological data at the Week 96 window, n (%)	36 (6.9)	45 (8.6)
Reasons		
Discontinued study/treatment due to adverse events or death, n (%)	17 (3.3)	17 (3.3)
Discontinued study/treatment for other reasons, n (%)	16 (3.1)	27 (5.2)
No data during time window but continued study participation, n (%)	3 (0.6)	1 (0.2)

Week 152		
HIV-1 RNA ≥50 copies/mL†, n (%)	14 (2.7)	5 (1.0)
HIV-1 RNA <50 copies/mL, n (%)	456 (87.4)	449 (85.9)
No virological data at the Week 152 window, n (%)	52 (10.0)	69 (13.2)
Reasons		
Discontinued study/treatment due to adverse events or death, n (%)	23 (4.4)	24 (4.6)
Discontinued study/treatment for other reasons, n (%)	28 (5.4)	44 (8.4)
No data during time window but continued study participation, n (%)	1 (0.2)	1 (0.2)

* adjusted for baseline stratification factors.
† Includes subjects who discontinued the study due to lack of efficacy or suppression.
N = Number of patients in each treatment group, CI = confidence interval

Table 9: Proportion of patients with plasma HIV-1 RNA ≥50 copies/mL at Week 48 for key baseline factors of patients (snapshot outcomes)

Baseline factors of patients		*Number of patients with HIV-1 RNA ≥50 copies/mL/ total assessed (%)*	
		Dosing every 2 months (Q8W) n/N (%)	*Monthly dosing (Q4W) n/N (%)*
Baseline CD4+ (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)
Sex	Male	4/385 (1.0)	5/380 (1.3)
	Female	5/137 (3.5)	0/143
Ethnicity	White	5/370 (1.4)	5/393 (1.3)

Baseline factors of patients		*Number of patients with HIV-1 RNA ≥50 copies/mL/ total assessed (%)*	
		Dosing every 2 months (Q8W) n/N (%)	*Monthly dosing (Q4W) n/N (%)*
	Non-white	4/152 (2.6)	0/130
	Black/African American	4/101 (4.0)	0/90
	Non-Black/Non-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 CAB/RPV exposure	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, CAB = cabotegravir, RPV = rilpivirine

In the ATLAS-2M study, the treatment differences for the primary endpoint across baseline characteristics of patients (CD4+ count, sex, ethnicity, BMI, age and prior exposure to cabotegravir/rilpivirine) were not clinically meaningful.

Post-hoc analysis – factors that are associated with virological failure

In multivariable analyses (MVA) of pooled Phase 3 studies (ATLAS up to Week 96, FLAIR up to Week 124 and ATLAS-2M up to Week 152), the influence of various factors on the risk of confirmed virological failure (CVF) was examined. The baseline factor analysis (BFA) examined baseline viral and patient characteristics, as well as the dosing regimen (Q4W or Q8W). The MVA incorporated the baseline factors and included the post-baseline predicted plasma drug concentrations for CVF using regression modelling with a variable selection procedure. After a total of 4,291 person-years, the unadjusted CVF incidence rate was 0.54 per 100 person-years; 23 cases of CVF were reported (1.4% of 1,651 persons in these studies).

The BFA showed that rilpivirine resistance mutations (incidence rate ratio IRR=21.65, p<0.0001), the 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/m^2, p=0.01) were associated with CVF. Other variables including Q4W or Q8W dosing, female sex or CAB/INSTI-resistant mutations, had no significant association with CVF. A combination of at least two 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/m^2 (see Table 10).

Table 10: Virological outcomes by presence of key baseline factors of rilpivirine resistance-associated mutations, subtype A6/A1[1] and BMI ≥30 kg/m^2

Baseline factors (number)	Virological success (%)[2]	Confirmed virological 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)	1,231/1,431 (86.0) (84.1%, 87.8%)	23/1,431 (1.6)[6] (1.0%, 2.4%) 18/1,224 (1.47)[7]

[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, Week 124 for FLAIR and 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 data set with all non-missing covariates for the baseline factors (for a total of 1,651 subjects).
[7] Analysis data set with all non-missing covariates for the multivariable modelling, including the drug concentrations.

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 no or only one risk factor, with CVF identified in 6/24 patients [25.0%, 95% CI (9.8%, 46.7%)] treated with the every-2-month dosing regimen and 5/33 patients [15.2%, 95% CI (5.1%, 31.9%)] treated with the monthly dosing regimen.

Adolescents

MOCHA

The safety, tolerability and pharmacokinetics of oral and injectable cabotegravir and injectable rilpivirine were investigated in a multicentre, open-label, non-comparative phase I/II study, MOCHA (IMPAACT 2017, study 208580).

Week 16 MOCHA cohort 1

55 HIV-1-infected and virologically suppressed adolescents aged 12 to <18 years and with a body weight of at least 35 kg were admitted to one of four subgroups: 1C monthly dosing, 1C every 2 months, 1R monthly dosing or 1R every 2 months.

In cohort 1C, the participants (n=30) received one 30 mg cabotegravir tablet every day for at least four weeks, followed by monthly cabotegravir injections over the course of three months (month 1: 600 mg injection, months 2 and 3: 400 mg injection), or cabotegravir injections every two months over the course of two months (months 1 and 2: 600 mg injection), while continuing to receive cART. In cohort 1R, subjects (n=25) received one 25 mg rilpivirine tablet every day for at least four weeks, followed by monthly rilpivirine injections over the course of three months (month 1: 900 mg injection, months 2 and 3: 600 mg injection) or rilpivirine injections every two months over the course of two months (months 1 and 2: 900 mg injection), while continuing to receive the standard cART.

At baseline, the average age of the participants in cohort 1 was 15.0 years, the average weight was 50.0 kg (range: 37.4 to 98.5), 47.3% were female, 92.7% were non-white, the mean CD4+ cell count was 725 cells per mm^3 (range: 397 to 1,808) and no participant had a CD4+ cell count of less than 350 cells per mm^3.

The primary objectives in Week 16, which consisted of using the adult dose by evaluating the safety and confirming the PK in HIV-infected, virologically suppressed adolescents, were achieved, meaning that the participants could pass forward into cohort 2 (see *"Undesirable effects", "Pharmacokinetics", "Specific patient groups"*).

Week 24 MOCHA cohort 2

Cohort 2 included suitable participants who had previously completed cohort 1 as well as suitable participants who had not yet taken part in the study. The participants in cohort 2 (n=144) discontinued their cART regimen prior to the study and received one 30 mg cabotegravir tablet plus one 25 mg rilpivirine tablet daily for at least four weeks, followed by every-2-month cabotegravir injections (month 1 and 2: 600 mg injection, then 600 mg injection every 2 months) and rilpivirine injections (month 1 and 2: 900 mg injection, then 900 mg injection every 2 months).

At baseline, the average age of the participants in cohort 2 was 15.0 years, the average weight was 48.5 kg (range: 35.2 to 100.9), 51.4% were female, 98.6% were non-white, the mean CD4+ cell count was 739.5 cells per mm^3 (range: 81 to 1,925) and 4 participants had a CD4+ cell count of less than 350 cells per mm^3.

The primary objective in Week 24 of confirming the safety of injectable cabotegravir plus injectable rilpivirine in HIV-infected, virologically suppressed adolescents, was achieved (see *"Undesirable effects"*). Antiviral activity was evaluated as a secondary objective, demonstrating that 139 out of 141 participants (98.6%) were still virologically suppressed (HIV-1 RNA plasma level <50 c/mL) based on available data in Week 24.

Oral bridging therapy with other ART

In a retrospective analysis of pooled data from 3 clinical studies (FLAIR, ATLAS-2M and LATTE-2/study 200056), 29 patients were included who received an oral bridging therapy for an average duration of 59 days (25th and 75th percentile 53-135) with an ART other than Vocabria plus rilpivirine (alternative oral bridging therapy) during treatment with intramuscular (i.m.) long-acting (LA) Vocabria plus rilpivirine injections. The median age of the patients was 32 years, 14% were female, 31% were non-Caucasian, 97% received an integrase inhibitor (INI)-based regimen as an alternative oral bridging therapy, 41% received an NNRTI as part of their alternative oral bridging therapy (including rilpivirine in 11 out of 12 cases) and 62% received an NRTI. Three patients stopped their treatment during or shortly after the oral bridging phase for non-safety-related reasons. In the majority (≥ 96%) of patients, viral suppression (plasma HIV-1 RNA < 50 copies/mL) could be maintained. During bridging with an alternative oral bridging therapy and during the phase after the alternative oral bridging therapy (up to 2 injections with Vocabria plus rilpivirine after oral bridging), no cases of CVF (plasma HIV-1 RNA ≥ 200 copies/mL) were observed.

Pharmacokinetics

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

Table 11: Pharmacokinetic parameters following once-daily oral use of cabotegravir in adult participants

Administration phase	*Dosing schedule*	*Geometric mean (5th/95th percentiles)*[a]		
		$AUC_{(0\text{-}tau)}$[b] *(µg•h/ml)*	*C_{max} (µg/ml)*	*C_{tau}*[b] *(µg/ml)*
Oral lead-in[c]	once daily 30 mg	145 (93.5; 224)	8.0 (5.3; 11.9)	4.6 (2.8; 7.5)

[a] The values for the pharmacokinetic (PK) parameters are based on individual post hoc estimates from population PK models for the oral regimen as well as the initial monthly regimen (in FLAIR and ATLAS) or the regimen with doses every 2 months (in ATLAS-2M).
[b] tau refers to the following administration intervals: 24 hours for oral use as well as 1 month for monthly (or 2 months for every 2 months) i.m. injection of a prolonged-release suspension.
[c] The values for the pharmacokinetic parameters for oral lead-in represent steady state.

Absorption

Cabotegravir is rapidly absorbed following oral administration, with a median T_{max} of 3 hours post-administration for the tablet formulation. The linearity of cabotegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of the tablet formulation, cabotegravir pharmacokinetics was dose-proportional to slightly less than proportional to dose from 5 mg to 60 mg. With once-daily administration, pharmacokinetic steady-state is achieved by 7 days.
Cabotegravir may be administered with or without food. Food increased the extent of absorption. The bioavailability of cabotegravir is not dependent on the fat content of the meal: high-fat meals increased the $AUC_{(0-\infty)}$ by 14% and increased C_{max} by 14% relative to fasting conditions. These increases are not clinically significant.
The absolute bioavailability of cabotegravir has not been established.

Distribution

In vitro data show that cabotegravir is highly bound (approximately >99%) to human plasma proteins. Following oral administration of cabotegravir tablets, the mean apparent volume of distribution (Vz/F) of cabotegravir in plasma was 12.3 L. In humans, the Vc/F in the plasma was estimated at 5.27 L and Vp/F at 2.43 L. These volume estimates, along with the assumption of high F, suggest some distribution of cabotegravir to the extracellular space.
Cabotegravir is detectable in the female and male genital tract. Median cervical and vaginal tissue:plasma ratios ranged from 0.16 to 0.28 and the median rectal tissue:plasma ratios was $\leq$0.08 following a single intramuscular injection of 400 mg cabotegravir at 4, 8 and 12 weeks after administration.
Cabotegravir is detectable in cerebrospinal fluid (CSF). In HIV-infected patients receiving cabotegravir plus rilpivirine injections, the cabotegravir CSF:plasma concentration ratio [median range] (n=16) was 0.003 (0.002 to 0.004) one week following a steady-state cabotegravir injection (Q4W or Q8W). Consistent with therapeutic cabotegravir concentrations in the CSF, CSF HIV-1 RNA (n=16) was <50 copies/mL in 16 subjects (100%) and <2 copies/mL in 15 subjects (94%). At the same time point, plasma HIV-1 RNA (n=18) was <50 copies/mL in 18 subjects (100%) and <2 copies/mL in 12 subjects (66.7%).

Metabolism

Cabotegravir is primarily metabolised by UGT1A1 with a minor UGT1A9 component. Cabotegravir is the predominant circulating compound in plasma, representing >90% of total radiocarbon in plasma. Following oral administration in humans, cabotegravir is primarily eliminated through metabolism; renal elimination of the unchanged active substance is low (<1% of the dose). 47% of the total oral

dose is excreted as the unchanged active substance in the faeces. It is unknown if all or part of this is due to unabsorbed active substance 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 samples. 27% of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (75% of urine radioactivity, 20% of the total dose).

Elimination

Based on population pharmacokinetic analyses, cabotegravir has a mean terminal half-life of 41 hours and an apparent clearance (CL/F) of 0.21 L/hour observed following oral administration to healthy subjects.

Kinetics in specific patient groups

Sex

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

Ethnicity

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

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 (see *“Clinical efficacy”*).

Patients with HBV and HCV co-infection

There are very limited data on the use of cabotegravir in subjects with HCV co-infection. There are no data on the use of cabotegravir in subjects with HBV co-infection.

Hepatic impairment

No clinically relevant pharmacokinetic differences between patients with moderate hepatic impairment and healthy subjects were observed. No dose adjustment is therefore 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.

Renal impairment

No clinically relevant pharmacokinetic differences between patients with severe renal impairment (creatinine clearance of ≥15 to <30 mL/min and not on dialysis) and healthy subjects were observed. No dose adjustment is therefore necessary for patients with mild, moderate or severe renal impairment. Cabotegravir has not been studied in patients on dialysis.

Elderly patients

Population pharmacokinetic analyses revealed no clinically relevant effect of age on cabotegravir exposure.

Pharmacokinetic data for cabotegravir in subjects aged >65 years are limited.

Children and adolescents

Population pharmacokinetic analyses showed no clinically relevant differences in exposure between adolescents (aged 12 or over and with a minimum body weight of 35 kg) and HIV-1-infected and non-infected adult participants of the cabotegravir development programme, meaning that no dose adjustment is required for adolescents with a body weight of ≥35 kg.

Table 12: Pharmacokinetic parameters following once-daily oral use of cabotegravir in adolescent participants aged 12 to <18 years (≥35 kg)

Administration phase	*Dosing schedule*	*Geometric mean (5th/95th percentiles)*[a]		
		$AUC_{(0\text{-}tau)}$[b] *(µg•h/mL)*	*C_{max} (µg/mL)*	*C_{tau}*[b] *(µg/mL)*
Oral lead-in[c]	once daily 30 mg	203 (136; 320)	11 (7.4; 16.6)	6.4 (4.2; 10.5)

[a] The values for the pharmacokinetic (PK) parameters are based on individual post hoc estimates from population PK models in an HIV-infected adolescent population (n=147) with a body weight of 35.2-98.5 kg as well as a non-HIV-1-infected adolescent population (n=62) with a body weight of 39.9-167 kg.

[b] tau refers to the dosing interval: 24 hours for oral use.

[c] The pharmacokinetic parameter values for oral lead-in represent steady state.

Genetic polymorphisms

In a meta-analysis of healthy and HIV-infected subjects, HIV-infected subjects with UGT1A1 genotypes conferring slow cabotegravir metabolism had an average 1.2-fold increase in steady-state cabotegravir AUC, C_{max} and C_{tau} following cabotegravir injection vs. an average 1.38-fold increase following administration of the oral formulation. This is similar to the average 1.3- to 1.5-fold increase in steady-state cabotegravir AUC, C_{max} and C_{tau} observed following administration of the oral formulation in healthy and HIV-infected subjects combined. These differences are not considered clinically relevant. Polymorphisms in UGT1A9 were not associated with differences in the

pharmacokinetics of cabotegravir. Therefore, no dose adjustment is required in subjects with either UGT1A1 or UGT1A9 polymorphisms.

Preclinical data

Long-term toxicity (or repeat dose toxicity)

The effect of long-term treatment with high doses of cabotegravir has been evaluated in toxicity studies with repeated oral administration in rats (26 weeks) and 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 at 27 times the maximum recommended human dose [MHRD] of 30 mg orally or 500 mg/kg/day at 3.7 times the MHRD of 30 mg orally, respectively.

In the 14-day oral toxicity study in monkeys, a dose of 1,000 mg/kg/day was not tolerated and resulted in gastrointestinal-associated disorders (weight loss, vomiting, loose/watery stools and moderate to severe dehydration).

In the 28-day oral toxicity study in monkeys, end-of-study cabotegravir exposure at a dose of 500 mg/kg/day was similar to that achieved in the 14-day study at a dose of 1,000 mg/kg/day. This suggests that the gastrointestinal intolerance observed in the 14-day study was the result of oral administration and not systemic toxicity.

In a 3-month study in rats, cabotegravir was administered as a once-monthly subcutaneous injection (up to 100 mg/kg/dose), once-monthly intramuscular injection (up to 75 mg/kg/dose) or once-weekly subcutaneous injection (100 mg/kg/dose) (at exposures >30 times the exposure in humans at the MRHD of 400 mg i.m.). No systemic adverse effects or target organ toxicities were identified. Local inflammatory reactions (erythema and oedema graded very slight to severe) were noted in animals given 75 mg/kg/dose (monthly i.m. injections, >30 times the exposure in humans at the MRHD of 400 mg i.m.). Treatment-related histology findings were limited to granulomatous inflammation and mixed inflammatory cell infiltration at the corresponding injection sites, with correlating macroscopic changes.

Mutagenicity and carcinogenicity

Cabotegravir did not prove to be 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 at ~7 times and the rat at ~26 times the MRHD of 30 mg orally.

Reproductive toxicity

When administered orally at 1,000 mg/kg/day cabotegravir (>25 times the exposure in humans at the MHRD of 30 mg orally) for up to 26 weeks, no adverse effects on male or

female reproductive organs or spermatogenesis were identified, and cabotegravir had no functional effects on the mating habits or fertility of male or female rats.
In embryo-foetal development studies, there was no teratogenicity following oral administration of cabotegravir to pregnant rats and rabbits at doses up to 1,000 or 2,000 mg/kg/day (30-fold or 0.66 times the exposure in humans at the MRHD of 30 mg orally). A reduction in foetal body weight occurred in caesarean-delivered rats at 1,000 mg/kg/day; however, as there was no reproducible effect at this dose on the birth weights or postnatal growth and development of naturally delivered pups, the foetal finding was not considered adverse. Cabotegravir was shown to cross the placenta of rats and was detected in foetal tissue. In pre- and postnatal studies in rats (PPN), cabotegravir at 1,000 mg/kg/day reproducibly delayed the onset of delivery and was associated with an increase in stillbirths and neonatal mortalities. There was no effect on survival when foetuses were delivered by caesarean section. A lower dose of 5 mg/kg/day (approximately 14 times the MRHD at 30 mg orally) was not associated with delayed delivery or neonatal mortality.

Other information

Shelf-life

Do not use this medicine after the expiry date marked as “EXP” on the pack.

Special precautions for storage

Do not store above 30°C. Store in the original packaging and keep out of the reach of children.

Authorisation number

67669 (Swissmedic)

Packs

Vocabria: 30 film-coated tablets (A)

Marketing authorisation holder

ViiV Healthcare GmbH, 6340 Baar

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