SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

REKAMBYS®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2 mL vial
Each vial contains 600 mg rilpivirine

3 mL vial
Each vial contains 900 mg rilpivirine

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release suspension for injection.
White to off-white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REKAMBYS is indicated, in combination with cabotegravir injection, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the non-nucleoside reverse transcriptase inhibitor (NNRTI) and integrase inhibitor (INI) class (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Therapy should be prescribed by a physician experienced in the management of HIV infection. Each injection should be administered by a healthcare professional.

Prior to starting REKAMBYS, the healthcare professional should carefully select patients who agree to the required injection schedule and counsel patients about the importance of adherenceto scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses.

Following discontinuation of REKAMBYS in combination with cabotegravir injection, it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the last every 1 month injection, or two months after the last every 2 months injection (see section 4.4).

The prescribing information for cabotegravir injection should be consulted for recommended dosing.

Posology

REKAMBYS (rilpivirine injection) may be initiated with oral lead-in or without (direct to injection).

The healthcare professional and patient may decide to use rilpivirine tablets as an oral lead-in prior to the initiation of rilpivirine injections to assess tolerability (see Table 1), or proceed directly to rilpivirine injection (see Tables 2 and 3, for monthly and every 2 months dosing recommendations, respectively).

Oral lead-in

When used for oral lead-in prior to the initiation of REKAMBYS, rilpivirine oral tablets, together with cabotegravir oral tablets,should be taken for approximately 1-month (at least 28 days) to assess tolerability to rilpivirine and cabotegravir. One rilpivirine 25-mg tablet should be taken with a meal with one cabotegravir 30-mg tablet once daily (see Table 1).

Table 1 Oral Lead-in Dosing Schedule in Adults

	Oral Lead-In
Drug	**For one month (at least 28 days), followed by the Initiation Injection[a]**
Rilpivirine	25 mg once daily with a meal
Cabotegravir	30 mg once daily

[a]see Table 2 for monthly injection dosing schedule and Table 3 for every 2 months injection dosing schedule

Every 1 month dosing

Initiation injection (900 mg corresponding to 3 mL)

On the final day of current antiretroviral therapy or oral lead-in, the recommended initiation injection dose of rilpivirine in adults is asingle 900 mg intramuscular injection.

Continuation injection (600 mg corresponding to 2 mL)

After the initiation injection, the recommended continuation injection dose of rilpivirine in adults is a single 600 mg monthly intramuscular injection. Patients may be given injections up to 7 days before or after the date of the monthly injection schedule.

Table 2 Recommended monthly intramuscular injection dosing schedule in adult patients

	Initiation injection	**Continuation injections**
Medicinal Product	**Initiate injection on the last day of either current ART therapy or oral lead-in (if used)**	**One month after initiation injection and monthly onwards**
Rilpivirine	900 mg	600 mg
Cabotegravir	600 mg	400 mg

Every 2 months dosing

Initiation Injections –1 month apart (900 mg corresponding to 3 mL)

On the final day of current antiretroviral therapy or oral lead-in, the recommended initial rilpivirine injection dose in adults is a single900 mg intramuscular injection.

One month later, a second 900 mg intramuscular injection should be administered. Patientsmay be given the second 900 mg injection up to 7 days before or after the scheduled dosing date.

Continuation Injections – 2 months apart (900 mg corresponding to 3 mL)

After the initiation injections, the recommended rilpivirine continuation injection dose in adults is a single 900 mg intramuscular injection administered every 2 months. Patients may be given injections up to 7 days before or after the date of the every 2-months injection schedule.

Table 3 Recommended every 2 months intramuscular injection dosing schedule in adult patients

	Initiation injections	**Continuation injections**
Medicinal Product	**Initiate injection on the last day of either current ART therapy or oral lead-in (if used). One month later, a second initiation injection should be administered.**	**Two months after last initiation injection and every 2 months onwards**
Rilpivirine	900 mg	900 mg

Cabotegravir	600 mg	600 mg

Dosing recommendations when switching from monthly to every 2 months injections
Patients switching from a monthly continuation injection schedule to an every 2-months continuation injection schedule should receive a single 900 mg intramuscular injection of REKAMBYS one month after the last 600 mg REKAMBYS continuation injection dose and then 900 mg every 2 months thereafter.

Dosing recommendations when switching from every 2 months to monthly injections
Patients switching from an every 2-months continuation injection schedule to a monthly continuation injection schedule should receive a single 600 mg intramuscular injection of REKAMBYS two months after the last 900 mg REKAMBYS continuation injection dose and then 600 mg monthly thereafter.

Missed doses
Patients who miss an injection visit should be clinically reassessed to ensure resumption of therapy is appropriate. See Table 4 and 5 for dosing recommendations after a missed injection.

Missed every 1 month injection (Oral Dosing to Replace Up to 2 Consecutive Monthly Injections)
If a patient plans to miss a scheduled injection by more than 7 days, daily oral therapy (one rilpivirine tablet [25 mg] and one cabotegravir tablet [30 mg]) may be used to replace up to 2 consecutive monthly injection visits. Limited data is available on oral bridging with other fully suppressive antiretroviral therapy (ART) (mainly INI-based), see section 5.1.

The first dose of oral therapy should be taken 1 month (± 7 days) after the lastinjection doses of REKAMBYS and cabotegravir. Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 4.
In case more than two months need to be covered for, i.e., missing more than two monthly injections, analternative oral regimen should be initiated one month (± 7 days) after the final injection of REKAMBYS.

Table 4 REKAMBYS dosing recommendations after missed injections or oral therapy for patients on monthly injection dosing

Time since last injection	Recommendation
≤ 2 months:	Continue with the monthly 600 mg injection schedule as soon as possible.
> 2 months:	Re-initiate the patient on the 900 mg dose, and then continue to follow the monthly 600 mg injection schedule.

Missed every 2 months injection (Oral Dosing to Replace 1 Every 2 Months Injection)
If a patient plans to miss a scheduled injection visit by more than 7 days, daily oral therapy (one rilpivirine tablet [25 mg] and one cabotegravir tablet [30 mg]) may be used to replace one 'every 2 months' injection visit. Limited data is available on oral bridging with other fully suppressive ART (mainly INI-based), see section 5.1.

The first dose of oral therapy should be taken approximately two months (±7 days) after the last injection doses of REKAMBYS and cabotegravir. Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 5.
In case more than two months need to be covered for, i.e., missing more than one 'every 2 months' injection, an alternative oral regimen should be initiated two months (± 7 days) after the final injection of REKAMBYS.

Table 5 REKAMBYS dosing recommendations after missed injections or oral therapy for patients on every 2 months injection dosing

Missed Injection Visit	Time since last injection	Recommendation (all injections are 3 mL)
Injection 2	**≤ 2 months**	Continue with the 900 mg injection as soon as possible and continue with every 2 months injection schedule.
	> 2 months	Re-initiate the patient on the 900 mg dose, followed by a second 900 mg initiation injection one month later. Then follow the every 2 months injection schedule.
Injection 3 or later	**≤ 3 months**	Continue with the 900 mg injection as soon as possible and continue with every 2 months injection schedule.
	> 3 months	Re-initiate the patient on the 900 mg dose, followed by a second 900 mg initiation injection one month later. Then follow the every 2 months injection schedule.

Special populations

Elderly
There is limited information regarding the use of REKAMBYS in patients > 65 years of age. No dose adjustment of REKAMBYS is required in older patients (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end stage renal disease, the combination of REKAMBYS with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. Subjects with estimated creatinine clearance < 50 mL/min/1.73 m^2 were not included in the Phase 3 studies. No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B), but caution is advised in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh score C); therefore REKAMBYS is not recommended in these patients (see section 5.2).

Paediatric population
The safety and efficacy of REKAMBYS in children and adolescents aged < 18 years have not been established. No data are available.

Method of administration

For intramuscular use.
Care should be taken to avoid inadvertent injection of REKAMBYS into a blood vessel. The suspension should be injected slowly (see section 4.4).

Prior to administration, the REKAMBYS vial should be brought to room temperature.

For instructions on administration,see “Instructions for Use” in the package leaflet. These instructions should be carefully followed when preparing the suspension for injection to avoid leakage.

REKAMBYS should always be co-administered with a cabotegravir injection. REKAMBYS and cabotegravir injections should be administered at separate gluteal injection sites during the same visit. The order of injections is not important.

When administering REKAMBYS, the healthcare professional should take into consideration the body mass index (BMI) of the patient to ensure that the needle length is sufficient to reach the gluteus muscle. The pack contains 1 injection needle (see section 6.5).

The vial should be held firmly and shaken vigorously for a full 10 seconds. The vial should be inverted and the resuspension should be checked. It should look uniform. If the suspension is not uniform, the vial should be shaken again. It is normal to see small air bubbles.

Injections must be administered to the ventrogluteal (recommended) or the dorsogluteal sites.

4.3 Contraindications

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

Co-administration with the following medicinal products (see section 4.5):
- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifabutin, rifampicin, rifapentine
- the systemic glucocorticoid dexamethasone, except as a single dose treatment
- St John's wort (*Hypericum perforatum*).

4.4 Special warnings and precautions for use

Risk of resistance following treatment discontinuation

To minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the last every 1 month injection of rilpivirine or two months after the last every 2 months injection of rilpivirine.

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

Long-acting properties of rilpivirine injection

Residual concentrations of rilpivirine may remain in the systemic circulation of patients for prolonged periods (up to 4 years in some patients) and should be considered upon discontinuation of rilpivirine (see sections 4.5, 4.6, 4.7, 4.9).

Baseline factors associated with virological failure

Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI $\geq$ 30 kg/m^2. Available data suggest that virologic failure occurs more often when these patients are treated according to the every 2 months dosing schedule as compared to the monthly dosing regimen. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI $\geq$ 30 kg/m^2 or HIV-1 subtypeA6/A1 (see section 5.1).

Post-injection reactions

Accidental intravenous administration may result in Adverse Reactions due to temporarily high plasma concentrations. In clinical studies, serious post-injection reactions were reported within minutes after the injection of rilpivirine. These events included symptoms such as dyspnoea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and pain (e.g., back and chest). These events were very rare and began to resolve within minutes after the injection. Some of the patients received symptomatic treatment, at the discretion of the treating physician.

Carefully follow the Instructions for Use when preparing and administering rilpivirine(see section 4.2). Patients should be briefly observed (approximately 10 minutes) after the injection. If a patient

experiences a post-injection reaction, monitoring and treatment should be provided as clinically indicated.

Cardiovascular

Rilpivirine should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes. At supra-therapeutic doses (75 and 300 mg once daily), oral rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG)(see sections 4.5, 4.8 and 5.2). Oral rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. Plasma rilpivirine concentrations after rilpivirine injections are comparable to those during such oral rilpivirine therapy.

HBV/HCV co-infection

Patients with hepatitis B co-infection were excluded from studies with rilpivirine. It is not recommended to initiate rilpivirine in patients with hepatitis B co-infection. In patients co-infected with hepatitis B receiving oral rilpivirine, the incidence of hepatic enzyme elevation was higher than in patients receiving oral rilpivirine who were not hepatitis B co-infected. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus.

Limited data is available in patients with hepatitis C co-infection. In patients co-infected with hepatitis C receiving oral rilpivirine, the incidence of hepatic enzyme elevation was higher than in patients receiving oral rilpivirine who were not hepatitis C co-infected. The pharmacokinetic exposure of oral and injectable rilpivirine in co-infected patients was comparable to that in patients without hepatitis C co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection.

Interactions with other medicinal products

Rilpivirine should not be administered with other antiretroviral medicinal products, except for cabotegravir injection for the treatment of HIV-1 infection (see section 4.5).

Pregnancy

There are limited data of rilpivirine in pregnant women. Rilpivirine is not recommended during pregnancy unless the expected benefit justifies the potential risk. Lower exposures of oral rilpivirine were observed when rilpivirine 25 mg once daily was taken during pregnancy. In the Phase 3 studies with oral rilpivirine, lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load should be monitored closely. Alternatively, switching to another ART regimen could be considered (see sections 4.6, 5.1 and 5.2).

Immune reactivation syndrome

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

Opportunistic infections

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

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Rilpivirine, in combination with cabotegravir injection, is intended for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral medicinal products for the treatment of HIV-1. Therefore, information regarding drug-drug interactions with other antiretroviral medicinal products is not provided. From a drug interaction perspective, there are no limitations on the use of other antiretroviral medicinal products after discontinuing rilpivirine.

For the oral lead-in rilpivirine treatment and in case missed doses are replaced by oral rilpivirine treatment, refer to the oral rilpivirine tablet Prescribing Information for information about drug interactions.

Medicinal products that affect rilpivirine exposure

Rilpivirine is primarily metabolised by cytochrome P450 (CYP)3A. Medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see section 5.2). Co-administration of rilpivirine and medicinal products that induce CYP3A has been observed to decrease the plasma concentrations of rilpivirine, which could reduce the therapeutic effect of rilpivirine.
Co-administration of rilpivirine and medicinal products that inhibit CYP3A has been observed to increase the plasma concentrations of rilpivirine.

When using oral rilpivirine, proton pump inhibitors are contraindicated (see rilpivirine tablet Prescribing Information, section 4.3).

Medicinal products that are affected by the use of rilpivirine

Rilpivirine is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes.

Rilpivirine inhibits P-glycoprotein *in vitro* (IC_{50} is 9.2 μM). In a clinical study, oral rilpivirine (25 mg once daily) did not significantly affect the pharmacokinetics of digoxin.

Rilpivirine is an *in vitro* inhibitor of the transporter MATE-2K with an IC_{50} of < 2.7 nM. The clinical implications of this finding are currently unknown.

Interaction table

Selected established and theoretical interactions between rilpivirine and co-administered medicinal products are listed in Table 6 and are based on the studies conducted with oral rilpivirine or are potential drug interactions that may occur (increase is indicated as "↑", decrease as "↓", no change as "↔", not applicable as "NA", confidence interval as "CI").

Table 6 Interactions and dose recommendations with other medicinal products

Medicinal products by therapeutic areas	Interaction Geometric mean change (%)Ω	Recommendations concerning co-administration

ANTIVIRAL AGENTS		
Cabotegravir	cabotegravir AUC ↔ cabotegravir Cmin↔ cabotegravir Cmax ↔ rilpivirine AUC ↔ rilpivirine Cmin ↓ 8% rilpivirine Cmax ↔	No dose adjustment is required.
Ribavirin	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
ANTICONVULSANTS		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with these anticonvulsants as co-administration may result in loss of therapeutic effect of rilpivirine (see section 4.3).
AZOLE ANTIFUNGAL AGENTS		
Ketoconazole*# 400 mg once daily	ketoconazole AUC ↓ 24% ketoconazole Cmin ↓ 66% ketoconazole Cmax ↔ (induction of CYP3A due to high rilpivirine dose in the study) rilpivirine AUC ↑ 49% rilpivirine Cmin ↑ 76% rilpivirine Cmax ↑ 30% (inhibition of CYP3A enzymes)	No dose adjustment is required.

Fluconazole Itraconazole Posaconazole Voriconazole	Not studied. Concomitant use of REKAMBYS with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine. (inhibition of CYP3A enzymes)	No dose adjustment is required.
ANTIMYCOBACTERIALS		
Rifabutin*# 300 mg once daily 300 mg once daily (+ 25 mg once daily rilpivirine) 300 mg once daily (+ 50 mg once daily rilpivirine)	rifabutin AUC ↔ rifabutin Cmin ↔ rifabutin Cmax ↔ 25-O-desacetyl-rifabutin AUC ↔ 25-O-desacetyl-rifabutin Cmin ↔ 25-O-desacetyl-rifabutin Cmax ↔ rilpivirine AUC ↓ 42% rilpivirine Cmin ↓ 48% rilpivirine Cmax ↓ 31% rilpivirine AUC ↑ 16%* rilpivirine Cmin ↔* rilpivirine Cmax ↑ 43%* * compared to 25 mg once daily rilpivirine alone (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with rifabutin as specific dosing recommendations have not been established. Co-administration is likely to result in loss of therapeutic effect of rilpivirine (see section 4.3).
Rifampicin*# 600 mg once daily	rifampicin AUC ↔ rifampicin Cmin NA rifampicin Cmax ↔ 25-desacetyl-rifampicin AUC ↓ 9% 25-desacetyl-rifampicin Cmin NA 25-desacetyl-rifampicin Cmax ↔ rilpivirine AUC ↓ 80% rilpivirine Cmin ↓ 89% rilpivirine Cmax ↓ 69% (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with rifampicin as co-administration is likely to result in loss of therapeutic effect of rilpivirine (see section 4.3).
Rifapentine	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with rifapentine as co-administration is likely to result in loss of therapeutic effect of rilpivirine (see section 4.3).
MACROLIDE ANTIBIOTICS		
Clarithromycin Erythromycin	Not studied. Increased exposure of rilpivirine is expected. (inhibition of CYP3A enzymes)	Where possible, alternatives such as azithromycin should be considered.
GLUCOCORTICOIDS OR CORTICOSTEROIDS		
Dexamethasone (systemic, except for single dose use)	Not studied. Dose dependent decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine should not be used in combination with systemic dexamethasone (except as a single dose) as co-administration may result in loss of therapeutic effect of rilpivirine (see section 4.3). Alternatives should be considered, particularly for long-term use.

NARCOTIC ANALGESICS		
Methadone* 60- 100 mg once daily, individualised dose	R(-) methadone AUC ↓ 16% R(-) methadone Cmin ↓ 22% R(-) methadone Cmax ↓ 14% rilpivirine AUC ↔* rilpivirine Cmin ↔* rilpivirine Cmax ↔* * based on historic controls	No dose adjustments are required when initiating co-administration of methadone with rilpivirine. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
ANTIARRHYTHMICS		
Digoxin*	digoxin AUC ↔ digoxin Cmin NA digoxin Cmax ↔	No dose adjustment is required.
ANTIDIABETICS		
Metformin*	metformin AUC ↔ metformin Cmin NA metformin Cmax ↔	No dose adjustment is required.
HERBAL PRODUCTS		
St John's wort (Hypericum perforatum)	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with products containing St John's wort as co-administration may result in loss of therapeutic effect of rilpivirine (see section 4.3).
ANALGESICS		
Paracetamol*# 500 mg single dose	paracetamol AUC ↔ paracetamol Cmin NA paracetamol Cmax ↔ rilpivirine AUC ↔ rilpivirine Cmin ↑ 26% rilpivirine Cmax ↔	No dose adjustment is required.
ORAL CONTRACEPTIVES		
Ethinylestradiol* 0.035 mg once daily Norethindrone* 1 mg once daily	ethinylestradiol AUC ↔ ethinylestradiol Cmin ↔ ethinylestradiol Cmax ↑ 17% norethindrone AUC ↔ norethindrone Cmin ↔ norethindrone Cmax ↔ rilpivirine AUC ↔* rilpivirine Cmin ↔* rilpivirine Cmax ↔* * based on historic controls	No dose adjustment is required.
HMG CO-A REDUCTASE INHIBITORS		
Atorvastatin*# 40 mg once daily	atorvastatin AUC ↔ atorvastatin Cmin ↓ 15% atorvastatin Cmax ↑ 35% rilpivirine AUC ↔ rilpivirine Cmin ↔ rilpivirine Cmax ↓ 9%	No dose adjustment is required.
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS		
Sildenafil*# 50 mg single dose	sildenafil AUC ↔ sildenafil Cmin NA sildenafil Cmax ↔ rilpivirine AUC ↔ rilpivirine Cmin ↔ rilpivirine Cmax ↔	No dose adjustment is required.
Vardenafil Tadalafil	Not studied.	No dose adjustment is required.

Ω % increase/decrease based on Drug-Drug Interaction studies with oral rilpivirine

* The interaction between rilpivirine and the medicinal product was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

\# This interaction study has been performed with a dose higher than the recommended dose for rilpivirine assessing

the maximal effect on the co-administered medicinal product. The dosing recommendation is applicable to the recommended dose of rilpivirine of 25 mg once daily.

QT prolonging medicinal products

Oral rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. Rilpivirine plasma concentrations after rilpivirine injections at the recommended dose of 600 mg monthly or 900 mg every 2 months, are comparable to those achieved with oral rilpivirine at a dose of 25 mg qd. In a study of healthy subjects, supratherapeutic doses of oral rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG (see section 5.1). Rilpivirine should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

The effect of rilpivirine on human pregnancy is unknown.

A moderate amount of data with oral rilpivirine in pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or foetal/neonatal toxicity of rilpivirine.

A study of 19 pregnant women treated with oral rilpivirine in combination with a background regimen during the second and third trimesters, and postpartum, showed lower exposures of oral rilpivirine during pregnancy, therefore viral load should be monitored closely if rilpivirine is used during pregnancy.

Animal studies do not indicate reproductive toxicity (see section 5.3).

Rilpivirine is not recommended during pregnancy unless the expected benefit justifies the potentialrisk.

An alternative oral regimen should be considered in line with current treatment guidelines. After discontinuation of rilpivirine, rilpivirine may remain in systemic circulation for up to 4 years insome patients (see section 4.4).

Breast-feeding

It is expected that rilpivirine will be secreted into human milk based on animal data, although this has not been confirmed in humans. Rilpivirine may be present in human milk for up to 4 years in some patients after discontinuation of rilpivirine.

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed.

Fertility

No human data on the effect of rilpivirine on fertility are available. No clinically relevant effects on fertility were seen in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients should be informed that fatigue, dizziness and somnolence could occur when treated with rilpivirine (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported ARs were injection site reactions, headache, and pyrexia.

Tabulated summary of adverse reactions

The ARs identified for rilpivirine and/or cabotegravir are listed by system organ class (SOC) and frequency (see Table 7). Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100).

Table 7 Tabulated summary of adverse reactions[1]

MedDRA System Organ Class (SOC)	Frequency Category	ARs for rilpivirine + cabotegravir regimen
Blood and lymphatic system disorders	Common	decreased white blood cell count[2], decreased haemoglobin[2], decreased platelet count[2]
Immune System Disorders	Uncommon	immune reactivation syndrome[2]
Metabolism and nutrition disorders	Very common	increased total cholesterol (fasted)[2], increased LDL cholesterol (fasted)[2]
	Common	decreased appetite[2], increased triglycerides (fasted)[2]
Psychiatric disorders	Common	depression, anxiety, abnormal dreams, insomnia, sleep disorder[2], depressed mood[2]
Nervous system disorders	Very common	headache
	Common	dizziness
	Uncommon	somnolence, vasovagal reactions (in response to injections)
Gastrointestinal disorders	Very common	increased pancreatic amylase[2]
	Common	nausea, vomiting, abdominal pain[3], flatulence, diarrhoea, abdominal discomfort[2], dry mouth[2], increased lipase[2]
Hepatobiliary disorders	Uncommon	hepatotoxicity
Skin and subcutaneous tissue disorders	Common	rash[4]
Musculoskeletal and connective tissue disorders	Common	myalgia
General disorders and administrative site conditions	Very common	injection site reactions (pain and discomfort, nodule, induration), pyrexia[5]
	Common	injection site reactions (swelling, erythema, pruritus, bruising, warmth, haematoma), fatigue, asthenia, malaise
	Uncommon	injection site reactions (cellulitis, abscess, anaesthesia, haemorrhage, discolouration)
Investigations	Common	weight increased
	Uncommon	transaminase increased, blood bilirubin increased

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

2 Additional adverse reactions seen with oral rilpivirine in other studies.

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

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

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

The overall safety profile at week 96 and week 124 in the FLAIR study was consistent with that observed at week 48, with no new safety findings identified. In the extension phase of the FLAIR study, initiating the rilpivirine plus cabotegravir injection regimen without oral lead-in (direct to injection) was not associated with any new safety concerns related to omitting the oral lead-in phase.

Description of selected adverse reactions

Local Injection Site Reactions (ISRs)
Up to 1% of subjects discontinued treatment with rilpivirine and cabotegravir injections because of ISRs.

Injection site reactions were generally mild (Grade 1, 70%-75% of subjects) or moderate (Grade 2, 27%-36% of subjects). 3-4% of subjects experienced severe (Grade 3) ISRs. The median duration of ISR events was 3 days. The percentage of subjects reporting ISRs decreased over time.

Weight increased
At the week 48 time point, subjects in Phase 3 Studies FLAIR and ATLAS, who received rilpivirine plus cabotegravir gained a median of 1.5 kg in weight; subjects continuing on their current antiretroviral regimen (CAR) group gained a median of 1.0 kg (pooled analysis).

In the individual studies FLAIR and ATLAS, the median weight gains in the rilpivirine plus cabotegravir arms were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR arms.

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

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

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

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

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

4.9 Overdose

There is currently limited experience with rilpivirine overdose. If overdose occurs, the patient should be treated supportively and as clinically indicated, with monitoring of vital signs and ECG (QT interval), as necessary. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral for systemic use, non-nucleoside reverse transcriptase inhibitors, ATC code: J05AG05

Mechanism of action

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α, β and γ.

Antiviral activity *in vitro*

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM (0.27 ng/mL). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2,510 to 10,830 nM (920 to 3,970 ng/mL), treatment of HIV-2 infection with rilpivirine is not recommended in the absence of clinical data.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/mL) and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL).

Resistance

Considering all of the available *in vitro* data and *in vivo* data generated with oral rilpivirine in previously untreated patients, the following resistance-associated mutations, when present at baseline, may affect the activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, M230L, and the combination of L100I and K103N.

In cell culture
Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1. The most commonly observed resistance-associated mutations that emerged included L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

Virologically suppressed patients:
The number of subjects who met confirmed virologic failure (CVF) criteria was low across the pooled Phase 3 studies ATLAS and FLAIR. There were 7 CVFs on rilpivirine plus cabotegravir (7/591, 1.2%) and 7 CVFs on current antiretroviral regimen (7/591, 1.2%) through week 48. In the rilpivirine plus cabotegravir group in the pooled analysis, 5/591 (0.8%) subjects had resistance development: 5/591 (0.8%) and 4/591 (0.7%) with resistance-associated mutations to rilpivirine (K101E [n=1], E138A/E/K/T [n=1], E138A [n=1], or E138K [n=2]) and/or cabotegravir (G140R [n=1], Q148R [n=2], or N155H [n=1]), respectively. The 4 CVFs on cabotegravir plus rilpivirine in FLAIR had HIV-1 subtype A1 (n=3) or AG (n=1). One CVF in FLAIR never received an injection. The 3 CVFs on cabotegravir plus rilpivirine in ATLAS had HIV-1 subtype A, A1, or AG. In 2 of these 3 CVFs the rilpivirine resistance-associated mutations observed at failure were also observed at baseline in PBMC HIV-1 DNA.

In the ATLAS-2M study 10 subjects met CVF criteria through week 48: 8/522 (1.5%) in the Q8W arm and 2/523 (0.4%) in the Q4W arm. In the Q8W group 5/522 (1.0%) had resistance development: 4/522 (0.8%) and 5/522 (1.0%) with resistance-associated mutations to rilpivirine (E138A [n=1], E138K [n=1], K101E [n=2], or Y188L [n=1]) and/or cabotegravir (Q148R [n=3] or N155H [n=4]), respectively. In the Q4W group 2/523 (0.4%) had resistance development: 1/523 (0.2%) and 2/523 (0.4%) had rilpivirine (K101E [n=1], M230L [n=1]) and/or cabotegravir (E138K [n=1], Q148R [n=1], or N155H [n=1]) resistance-associated mutations, respectively. At baseline in the Q8W arm, 5 subjectshad rilpivirine resistance-associated mutations and 1 of those subjects carried a cabotegravir resistance-associated

mutation. Neither subject in the Q4W arm had any rilpivirine or cabotegravir resistance-associated mutation at baseline. The 10 CVFs on cabotegravir plus rilpivirine in ATLAS-2M had HIV-1 subtype A (n=1), A1 (n=2), B (n=4), C (n=2), or Complex (n=1).

Cross-resistance

Site-directed NNRTI mutant virus
In a panel of 67 HIV-1 recombinant laboratory strains with one mutation at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96%) of these strains. The single resistance-associated mutations associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V. The K103N mutation did not result in reduced susceptibility to rilpivirine by itself, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine.

Recombinant clinical isolates
Rilpivirine retained sensitivity (fold change ≤ biological cut-off) against 62% of 4,786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

Virologically suppressed patients
In the week 48 analysis of the Phase 3 studies ATLAS and FLAIR, 5/7 CVFs had phenotypic resistance against rilpivirine at failure. Among these 5 patients, phenotypic cross-resistance was observed against efavirenz (n=4), etravirine (n=3), and nevirapine (n=4).

Effects on electrocardiogram

No effect on QTcF interval was shown for oral rilpivirine at the recommended dose of 25 mg once daily in a randomised, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady-state. Plasma rilpivirine concentrations after REKAMBYS injections are comparable to those achieved with oral rilpivirine at dose of 25 mg qd. REKAMBYS at the recommended dose of 600 mg monthly or 900 mg every 2 months is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of oral rilpivirine were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) ms, respectively. Steady-state administration of oral rilpivirine 75 mg once daily and 300 mg once daily resulted in a mean C_{max} approximately 4.4-fold and 11.6-fold, respectively, higher than the mean steady-state C_{max} observed with the recommended 600 mg once monthly dose of REKAMBYS. Steady state administration of oral rilpivirine 75 mg once daily and 300 mg once daily resulted in a mean C_{max} approximately 4.1-fold and 10.7-fold, respectively, higher than the mean steady state C_{max} observed with the recommended 900 mg every 2 months dose of REKAMBYS.

Clinical efficacy and safety

Every 1 month dosing

The efficacy of REKAMBYS plus cabotegravir injection has been evaluated in two Phase 3 randomised, multicentre, active-controlled, parallel-arm, open-label, non-inferiority studies, FLAIR (201584) and ATLAS (201585). The primary analysis was conducted after all subjects completed their week 48 visit or discontinued the study prematurely.

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

In FLAIR, 629 HIV-1-infected, antiretroviral treatment (ART)-naive subjects received a dolutegravir INI containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir + 2 other nucleoside reverse transcriptase inhibitors if subjects were HLA-B*5701 positive). Subjects who were virologically suppressed (HIV-1 RNA

< 50 copies per mL, n=566) were then randomised (1:1) to receive either a rilpivirine plus cabotegravir regimen or remain on the CAR. Subjects randomised to receive the rilpivirine plus cabotegravir regimen, initiated treatment with oral lead-in dosing with a cabotegravir (30 mg) tablet plus a rilpivirine (25 mg) tablet once daily for at least 4 weeks, followed by treatment with cabotegravir injection (month 1: 600 mg, month 2 onwards: 400 mg injection) plus rilpivirine injection (month 1: 900 mg injection, month 2 onwards: 600 mg injection), monthly, for up to 96 weeks.

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

Pooled Phase 3 studies
At baseline, in the pooled analysis, in the rilpivirine plus cabotegravir arm the median age of subjects was 38 years, 27% were female, 27% were non-white, 1% were ≥ 65 years and 7% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment arms.

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

In a pooled analysis of the two Phase 3 studies, rilpivirine plus cabotegravir was non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA ≥ 50 c/mL (1.9% and 1.7% respectively) at week 48. The adjusted treatment difference between rilpivirine plus cabotegravir and CAR (0.2; 95% CI: -1.4, 1.7) met the non-inferiority criterion (upper bound of the 95% CI below 4%) [See Table 8].

The primary endpoint and other week 48 outcomes, including outcomes by key baseline factors, for FLAIR, ATLAS, and pooled data are shown in Table 8 and Table 9.

Table 8 Virologic outcomes of randomised treatment in FLAIR and ATLAS at week 48 (Snapshot analysis)

	FLAIR		**ATLAS**		**Pooled Data**	
	RPV+ CAB N=283	**CAR N=283**	**RPV+ CAB N=308**	**CAR N=308**	**RPV+ CAB N=591**	**CAR N=591**
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 % (95% CI)*	-0.4 (-2.8, 2.1)		0.7 (-1.2, 2.5)		0.2 (-1.4, 1.7)	
HIV-1 RNA < 50 copies/mL	265 (93.6)	264 (93.3)	285 (92.5)	294 (95.5)	550 (93.1)	558 (94.4)
Treatment Difference % (95% CI)*	0.4 (-3.7, 4.5)		-3.0 (-6.7, 0.7)		-1.4 (-4.1, 1.4)	
No virologic data at week 48 window	12 (4.2)	12 (4.2)	18 (5.8)	11 (3.6)	30 (5.1)	23 (3.9)
Reasons						
Discontinued study/study drug due to adverse event or death	8 (2.8)	2 (0.7)	11 (3.6)	5 (1.6)	19 (3.2)	7 (1.2)

Discontinued study/study drug for other reasons	4 (1.4)	10 (3.5)	7 (2.3)	6 (1.9)	11 (1.9)	16 (2.7)
Missing data during window but on study	0	0	0	0	0	0

* Adjusted for baseline stratification factors.

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

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

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

BMI=body mass index, PI=Protease inhibitor, INI=Integrase inhibitor, NNRTI=non-nucleoside reversetranscriptase inhibitor, RPV=rilpivirine, CAB=cabotegravir, CAR=current antiretroviral regimen

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

Week 96 FLAIR

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

Week 124 FLAIR Direct to Injection versus Oral Lead-In

In the FLAIR study, an evaluation of safety and efficacy was performed at week 124 for patients electing to switch at week 100 from abacavir/dolutegravir/lamivudine to rilpivirine plus cabotegravir in the Extension Phase. Subjects were given the option to switch with or without an oral lead-in phase, creating an oral lead-in group and a direct to injection group.

At week 124, the proportion of subjects having plasma HIV-1 RNA ≥ 50 c/mL was 1/121 (0.8%) and 1/111 (0.9%) for the oral lead-in and direct to injection groups, respectively. The rates of virologic suppression (HIV-1 RNA <50 c/mL) were similar in both the oral lead-in group (113/121 [93.4%]) and

direct to injection group (110/111 [99.1%]).

Every 2 months dosing

Patients virologically suppressed (stable on prior ART for at least 6 months)
The efficacy and safety of rilpivirine injection given every 2 months, has been evaluated in one Phase 3b randomised, multicentre, parallel-arm, open-label, non-inferiority study, ATLAS-2M (207966). The primary analysis was conducted after all subjects completed their week 48 visit or discontinued the study prematurely.

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

At baseline, the median age of subjects was 42 years, 27% were female, 27% were non-white, 4% were ≥65 years, and 6% had a CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between the treatment arms.

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

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

Table 10 Virologic outcomes of randomised treatment of ATLAS-2M at 48 weeks (Snapshot analysis)

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

* Adjusted for baseline stratification factors.
† Includes subjects who discontinued for lack of efficacy, discontinued while not suppressed.
N=Number of subjects in each treatment group, CI=confidence interval, CAR=current antiretroviral regimen.

Table 11 Proportion of subjects with plasma HIV-1 RNA ≥ 50 copies/mL in ATLAS-2M at week 48 for key baseline factors (Snapshot outcomes).

Baseline factors		Number of HIV-1 RNA ≥ 50 c/mL/ Total Assessed (%)	
		Every 2 months dosing (Q8W)	Monthly dosing (Q4W)
Baseline CD4+ cell count (cells/mm^3)	< 350	1/ 35 (2.9)	1/ 27 (3.7)
	350 to < 500	1/ 96 (1.0)	0/ 89
	≥ 500	7/391 (1.8)	4/407 (1.0)
Gender	Male	4/385 (1.0)	5/380 (1.3)
	Female	5/137 (3.5)	0/143
Race	White	5/370 (1.4)	5/393 (1.3)
	Non-White	4/152 (2.6)	0/130
	Black/African American	4/101 (4.0)	0/ 90
	Non-Black/African American	5/421 (1.2)	5/421 (1.2)
BMI	< 30 kg/m^2	3/409 (0.7)	3/425 (0.7)
	≥ 30 kg/m^2	6/113 (5.3)	2/98 (2.0)
Age (years)	< 35	4/137 (2.9)	1/145 (0.7)
	35 to < 50	3/242 (1.2)	2/239 (0.8)
	≥ 50	2/143 (1.4)	2/139 (1.4)
Prior exposure CAB/RPV	None	5/327 (1.5)	5/327 (1.5)
	1-24 weeks	3/69 (4.3)	0/68
	> 24 weeks	1/126 (0.8)	0/128

BMI=body mass index, CAB=cabotegravir, RPV=rilpivirine

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

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

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

Post-hoc analyses

Multivariable analyses of pooled Phase 3 studies (ATLAS through 96 weeks, FLAIR through 124 weeks, ATLAS-2M through 152 weeks) examined the influence of various factors on the risk of CVF. The baseline factors analysis (BFA) examined baseline viral and participants characteristics and dosing regimen; and the multivariable analysis (MVA) included the baseline factors and incorporated post-baseline predicted plasma drug concentrations on CVF using regression modelling with a variable selection procedure. Following a total of 4291 person-years, the unadjusted CVF incidence rate was 0.54 per 100 person-years; 23 CVFs were reported (1.4% of 1651 individuals in these studies).

The BFA demonstrated rilpivirine resistance mutations (incidence rate ratio IRR=21.65, p<0.0001), HIV-1 subtype A6/A1 (IRR=12.87, p<0.0001), and body mass index IRR=1.09 per 1 unit increase, p=0.04; IRR=3.97 of ≥30 kg/m2, p=0.01) were associated with CVF. Other variables including Q4W or Q8W dosing, female gender, or CAB/INI resistance mutations had no significant association with CVF. A combinationof at least 2 of the following key baseline factors was associated with an increased risk of CVF: rilpivirine resistance associated mutations, HIV-1 subtype A6/A1, or BMI ≥ 30 kg/m^2 (Table 12).

Table 12 Virologic outcomes by presence of key baseline factors of rilpivirine resistance mutations, HIV-1 Subtype A6/A1[1] and BMI ≥ 30 kg/m^2

Baseline Factors (number)	Virologic Successes[2]	Confirmed Virologic Failure (%)[3]
0	844/970 (87.0)	4/970 (0.4)
1	343/404 (84.9)	8/404 (2.0)[4]
≥ 2	44/57 (77.2)	11/57 (19.3)[5]
TOTAL (95% Confidence Interval)	1231/1431 (86/0) (84.1%, 87.8%)	23/1431 (1.6)[6] (1.0%, 2.4%)

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

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

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

4 Positive Predictive Value (PPV) <1%; Negative Predictive Value (NPV) 98.5%; sensitivity 34.8%; specificity 71.9%

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

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

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

Oral bridging with other ART

In a retrospective analysis of pooled data from 3 clinical studies (FLAIR, ATLAS-2M, and LATTE-2/study 200056), 29 subjects were included who received oral bridging for a median duration of 59 days (25th and 75th percentile 53-135) with ART other than rilpivirine plus cabotegravir (alternative oral bridging) during treatment with rilpivirine plus cabotegravir long-acting (LA) intramuscular (IM) injections. The median age of subjects was 32 years, 14% were female, 31% were non-white, 97% received an INI-based regimen for alternative oral bridging, 41% received an NNRTI as part of their alternative oral bridging regimen (including rilpivirine in 11/12 cases) and 62% received an NRTI. Three subjects withdrew during oral bridging or shortly following oral bridging for non-safety reasons. The majority (≥96%) of subjects maintained virologic suppression (plasma HIV-1 RNA <50 c/mL). During bridging with alternative oral bridging and during the period following alternative oral bridging (up to 2 rilpivirine plus cabotegravir injections following oral bridging), no cases of CVF (confirmed plasma HIV-1 RNA ≥200 c/mL) were observed.

5.2 Pharmacokinetic properties

The population pharmacokinetic properties of rilpivirine have been evaluated in healthy and HIV-1 infectedadults.

Table 13 Pharmacokinetic parameters of rilpivirine following once daily oral dosing, and after initial, monthly, or every two months intramuscular injections of rilpivirine in adults

Dosing phase	Dose regimen	Geometric mean (5th; 95th Percentile)		
		$AUC_{(0\text{-}tau)}$[b] (ng•h/mL)	Cmax (ng/mL)	Ctau[b] (ng/mL)
Oral Lead-In[c]	25 mg PO once daily	2,083 (1,125; 3,748)	116 (49; 244)	79 (32; 177)
Initial Injection[a,d]	900 mg IM initial dose	44,842 (21,712; 87,575)	144 (94; 221)	42 (22; 79)
Monthly Injection[a,c]	600 mg IM monthly	68,324 (39,042; 118,111)	121 (68; 210)	86 (50; 147)
Every 2 months Injection[a,c]	900 mg IM every 2 months	132,450 (76,638; 221,783)	138 (81; 228)	69 (38; 119)

a. Based on individual post-hoc estimates from rilpivirine IM population pharmacokinetic model (pooled data FLAIR, ATLAS and ATLAS-2M).

b. tau is dosing interval: 24 hours for oral; 1 or 2 months for monthly or every 2 months IM injections.

c. For oral rilpivirine, C_{tau} represents observed pooled data FLAIR, ATLAS and ATLAS-2M, AUC(0-tau) and C_{max} represent pharmacokinetic data from oral rilpivirine Phase 3 studies

d. When administered with oral lead-in, initial injection C_{max} primarily reflects oral dosing because the initial injection was administered on the same day as the last oral dose. When administered without oral lead-in (direct to injection, n=110), the rilpivirine observed geometric mean (5th, 95th percentile) Cmax (1 week post initial injection) was 68 ng/mL (28, 220) and the Ctau was 49 ng/mL (18, 138).

e. Week 48 data.

Absorption

Rilpivirine prolonged-release injection exhibits absorption rate-limited kinetics (i.e., flip-flop pharmacokinetics) resulting from slow absorption from the gluteal muscle into the systemic circulation resulting in sustained rilpivirine plasma concentrations.

Following a single intramuscular dose, rilpivirine plasma concentrations are detectable the first day and gradually rise to reach maximum plasma concentrations after a median of 3-4 days. Rilpivirine has been detected in plasma up to 52 weeks or longer after administration of a single dose of rilpivirine. After 1 year of monthly or every 2 months injections, approximately 80% of the rilpivirine pharmacokinetic steady-state exposure is reached.

Plasma rilpivirine exposure increases in proportion or slightly less than in proportion to dose following single and repeat IM injections of doses ranging from 300 to 1200 mg.

Distribution

Rilpivirine is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. Based on population pharmacokinetics analysis, the typical apparent volume of the central compartment (Vc/F) for rilpivirine after IM administration was estimated to be 132 L, reflecting a moderate distribution to peripheral tissues.

Rilpivirine is present in cerebrospinal fluid (CSF). In HIV-1-infected subjects receiving a regimen of rilpivirine injection plus cabotegravir injection, the median rilpivirine CSF to plasma concentration ratio (n=16) was 1.07 to 1.32% (range: not quantifiable to 1.69%). Consistent with therapeutic rilpivirine concentrations in the CSF, CSF HIV-1 RNA (n=16) was < 50 c/mL in 100% and < 2 c/mL in 15/16 (94%) of subjects. At the same time point, plasma HIV-1 RNA (n=18) was < 50 c/mL in 100% and < 2 c/mL in 12/18 (66.7%) of subjects.

Biotransformation

In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system.

Elimination

The mean apparent half-life of rilpivirine following rilpivirine administration is absorption rate-limited and was estimated to be 13-28 weeks.

The apparent plasma clearance (CL/F) of rilpivirine was estimated to be 5.08 L/h.

After single dose administration of oral ^{14}C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.

Special patient populations

Gender
No clinically relevant differences in the rilpivirine exposure after intramuscular (IM) administration have been observed between men and women.

Race
No clinically relevant effect of race on the rilpivirine exposure after intramuscular administration has been observed.

BMI
No clinically relevant effect of BMI on the rilpivirine exposure after intramuscular administration has been observed.

Elderly
No clinically relevant effect of age on the rilpivirine exposure after intramuscular administration has been observed. Pharmacokinetic data for rilpivirine in subjects of > 65 years old are limited.

Renal impairment
The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. No dose adjustment is needed for patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, rilpivirine should be used with caution, as plasma concentrations may be increased due to alteration of drug absorption, distribution and/or metabolism secondary to renal dysfunction. In patients with severe renal impairment or end-stage renal disease, the combination of rilpivirine with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. As rilpivirine ishighly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see section 4.2).

Hepatic impairment
Rilpivirine is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of oral rilpivirine was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. However, it may not be excluded that the pharmacologically active, unbound, rilpivirine exposure is significantly increased in moderate hepatic impairment. No dose adjustment is suggested but caution is advised in patients with moderate hepatic impairment. Rilpivirine has not been studied in patients with severe hepatic impairment (Child-Pugh score C).

Therefore, rilpivirine is not recommended in patients with severe hepatic impairment (see section 4.2).

HBV/HCV Co-infected Patients
Population pharmacokinetic analysis indicated that hepatitis B and/or C virus co-infection had no clinically relevant effect on the rilpivirine exposure after oral rilpivirine intake.

Paediatric Patients
The phamacokinetics of rilpivirine in children and adolescents aged < 18 years have not been established with rilpivirine.

5.3 Preclinical safety data

All studies were performed with rilpivirine for oral use except for the studies on local tolerance with rilpivirine injections.

Repeated dose toxicity

Liver toxicity associated with liver enzyme induction was observed in rodents. In dogs, cholestasis-like effects were noted.

Reproductive toxicology studies

Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no teratogenicity with oral rilpivirine in rats and rabbits. The exposures at the embryo-foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively ≥ 12 times and ≥ 57 times the exposure in humans at the maximum recommended human daily dose of 25 mg once daily in HIV-1 infected patients or 600 mg or 900 mg intramuscular injection dose of rilpivirine long-acting injectable suspension.

Carcinogenesis and mutagenesis

Oral rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were ≥ 17 times (mice) and ≥ 2 times (rats) the exposure in humans at the maximum recommended human daily dose of 25 mg once daily in HIV-1 infected patients or 600 mg or 900 mg intramuscular injection dose of rilpivirine long-acting injectable suspension. In rats, there were no drug-related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific.

Rilpivirine has tested negative in the absence and presence of a metabolic activation system in the *in vitro* Ames reverse mutation assay and the *in vitro* clastogenicity mouse lymphoma assay. Rilpivirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Local tolerance for rilpivirine

After long-term repeated IM administration of rilpivirine in dogs and minipigs, slight, short-lasting (i.e., 1-4 days in minipigs) erythema was observed, and white deposits were noted at the injection sites at necropsy, accompanied by swelling and discolouration of draining lymph nodes. Microscopic examination showed macrophage infiltration and eosinophilic deposits at the injection sites. A macrophage infiltration response was also noted in the draining/regional lymph nodes. These findings were considered to be a reaction to the deposited material rather than a manifestation of local irritation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

poloxamer 338
glucose monohydrate
sodium dihydrogen phosphate monohydrate
citric acid monohydrate
sodium hydroxide (to adjust pH)
water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or diluents.

6.3 Shelf life

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

Chemical and physical in-use stability has been demonstrated for 6 hours at 25°C.

Once the suspension has been drawn into the syringe, the injection should be administered as soon as possible, but may remain in the syringe for up to 2 hours. If 2 hours are exceeded, the medicine, syringe, and needle must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.

Prior to administration, the vial should be brought to room temperature (not to exceed 25°C). The vial may remain in the carton at room temperature for up to 6 hours; do not put back into the refrigerator. If not used within 6 hours, the vial must be discarded (refer to section 6.3).

6.5 Nature and contents of container

Type I glass vial.

600 mg pack

Each pack contains one clear 4-mL glass vial, with a butyl elastomer stopper and an aluminium overseal with a plastic flip-off button, 1 syringe (0.2 mL graduation), 1 vial adaptor and 1 needle for injection (23 gauge, 1½ inch).

900 mg pack

Each pack contains one clear 4-mL glass vial, with a butyl elastomer stopper and an aluminium overseal with a plastic flip-off button, 1 syringe (0.2 mL graduation), 1 vial adaptor and 1 needle for injection (23 gauge, 1½ inch).

6.6 Special precautions for disposal and other handling

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

Full instructions for use and handling of REKAMBYS are provided in the package leaflet (see Instructions for Use).

7. MARKETING AUTHORISATION HOLDER

J-C Health Care Ltd., Kibbutz Shefayim 6099000, Israel.

8. MARKETING AUTHORISATION NUMBER

170-12-36949-99

9. MANUFACTURER

Cilag AG, Hochstrasse 201, 8200 Schaffhausen Switzerland.

Revised in September 2025.