Module 2.2-Introduction

1 INTRODUCTION

A collaboration agreement exists between Janssen Sciences Ireland and ViiV Healthcare for the development of a dual regimen for the treatment of HIV, consisting of Rilpivirine (RPV, JNJ-16150108-AAA, R278474, TMC278 free base) prolonged release suspension (also referred to as RPV LA) and a prolonged release suspension of Cabotegravir (also referred to as CAB long-acting (LA)) for intramuscular injection.
The proposed trade name for RPV LA is REKAMBYS.

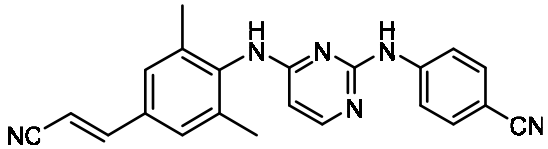
Submission of marketing authorization applications (MAAs) for RPV LA and CAB oral and LA, will occur in parallel to the EMA by each Applicant (Janssen-Cilag International NV and ViiV Healthcare BV, respectively). The current proposed REKAMBYS MAA application discusses the RPV LA component of this proposed 2-drug regimen. The oral formulation of RPV is already licensed since November 2011 as EDURANT, with Janssen-Cilag International NV as MAH.

2 PRODUCT BACKGROUND

2.1 Drug Substance

The chemical information on the active substance, RPV (free base), is summarized in Table 1.

Table 1: Chemical Information of the Compound

Chemical Name	4-[[4-[[4-[(*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile
JNJ-number:	JNJ-16150108-AAA
R-number:	R278474
TMC-number:	TMC278 free base
Molecular Formula	$C_{22}H_{18}N_6$
Molecular Weight	366.43
Stereochemistry	Achiral molecule, with the *E* configuration for the cyanoethenyl double bond.
Chemical structure	

The development of RPV free base was based on work previously performed on the hydrochloride salt of rilpivirine, which has already been described in the approved marketing authorization for EDURANT® (EU/1/11/736). Rilpivirine as free base is manufactured [redacted], with [redacted], [redacted] and [redacted] process steps to generate the rilpivirine drug substance [redacted] and [redacted] in use in the drug product RPV LA.

The proposed drug substance specifications and limits are [redacted] to those currently approved for rilpivirine HCl with additional testing for [redacted] and [redacted] since the drug substance is for use in an injectable preparation.

2.2 Drug Product

The composition of the RPV LA is provided in Table 2.

Table 2: Nominal composition of Rilpivirine 300-mg/mL prolonged release suspension for injection (G001)

Components	Quality Reference[a]	Function	Composition per Unit Dose (mg/vial)	
			2-mL dose	3-mL dose
Rilpivirine (R278474) [redacted]	[redacted]	Active drug substance	600	900
Poloxamer 338	[redacted]	[redacted]	100	150
Glucose Monohydrate	[redacted]	[redacted]	38.50	57.75
Sodium Dihydrogen Phosphate Monohydrate	[redacted]	[redacted]	4	6
Citric Acid Monohydrate	[redacted]	[redacted]	2	3
Sodium Hydroxide	[redacted]	[redacted]	1.732	2.598
Water for Injection	[redacted]	[redacted]	q.s. ad 2 mL	q.s ad 3 mL

[a] Where multiple compendia are listed, the compendium specific to the region of the submission is applied.

The 300-mg/mL drug product is packaged in a 4-mL clear glass vial with rubber injection stopper and sealed with an aluminum cap, and stored at 5 °C. The drug product is supplied as a medicinal product kit which contains the drug product vial, a sterile-packed plastic syringe, a sterile-packed safety needle and a sterile-packed vial adapter.

The drug product is aseptically manufactured by [redacted] and aseptically filling it into glass vials.

Two different dosage units, 600-mg and 900-mg dose, are obtained by filling the vials to a fill volume allowing an extractable volume of 2.0 mL and 3.0 mL, respectively.

3 PROPOSED CLINICAL USE

REKAMBYS is proposed to be 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) and have no known or suspected resistance to either RPV or CAB.

4 DEVELOPMENT PROGRAM OF REKAMBYS

4.1 Non-clinical development

RPV LA nonclinical development is largely derived from RPV oral (EDURANT).
The active drug moiety in the oral and injectable formulation is the same, and exposures are comparable with oral RPV and RPV LA. Therefore, results can be extrapolated and the nonclinical safety of RPV LA is largely based upon the nonclinical findings from the oral RPV program.

In addition, for RPV LA a bridging toxicity program was performed consisting of local tolerance studies and repeat toxicity studies up to 1 month in dogs and up to 9 months in minipigs. These studies specifically performed with RPV LA are included in this MAA, in accordance with scientific advice performed (Mod1.2/Annex 5.14/ EMEA/H/SA/919/1/FU/3/2014/I):

- PK studies including distribution in rats (Mod4.2.2.3/ADME-58575)
- Bridging toxicity program (Mod4.2.3.2/TOX10759 and Mod4.2.3.2/TOX9517)

Studies related to the excipient Poloxamer 338 are described in this MAA:

- A combined male and female fertility and embryo-foetal toxicity study by the intramuscular (IM) route in the rat (Segment I & II) (Mod4.2.3.7.7/TOX13391)

- Embryo-foetal toxicity study by the IM route in the rabbit (Segment II) (Mod4.2.3.7.7/TOX13376),

and

- Pre- and post-natal development study by the IM route in the rat (Mod4.2.3.7.7/TOX13546)

Additional bridging data from Poloxamer 188 is included, in accordance with follow-up scientific advices (Mod1.2/Annex 5.14/EMEA/H/SA/919/1/FU/4/2016/I and Mod1.2/Annex 5.14/EMEA/H/SA/919/1/FU/5/2018/II).

For those sections for which no specific RPV LA data are available, all the relevant nonclinical pharmacology, PK and toxicology studies performed after oral administration of RPV and as previously submitted for EDURANT are re-included to support this REKAMBYS MAA.

Documents associated with RPV LA which are not included in Module 4 of this MAA as well as a justification for their absence are listed in Appendix 1 of the Non-Clinical Overview (Mod2.4/Appendix 1).

4.2 Clinical development

The clinical development for RPV LA was initiated in 20[redacted]. In [redacted]20[redacted], Janssen Sciences Ireland UC and ViiV Healthcare signed a collaboration agreement enabling the Phase III clinical development of RPV + CAB regimen. The primary objective of this joint development programme was to generate sufficient evidence of safety and efficacy to support the combined use of the two injectable LA formulations, CAB LA and RPV LA, as a novel two-drug regimen for the maintenance of virologic suppression in HIV-1 infected patients.

The current REKAMBYS MAA includes Week 48 (primary endpoint) data from the two ongoing pivotal phase III non-inferiority switch studies ATLAS and FLAIR, evaluating monthly dosing of CAB LA + RPV LA compared to oral standard of care (SOC) regimens, to support the proposed indication:

- In the first study, FLAIR (201584), 629 ARV-naive subjects initiated an INI-based 3-drug regimen (dolutegravir/abacavir/lamivudine). After achieving virologic suppression (HIV-1 RNA <50 copies/mL), 566 subjects were randomised to either continue the current antiretroviral regimen (CAR) regimen, or to switch to an injectable regimen of CAB LA + RPV LA. Patients randomised to the LA regimen received a 1-month (at least 28 days) oral lead-in (OLI) of CAB + RPV prior to initiating LA therapy. Following the OLI phase, an initiation dose of RPV LA 3mL was given followed by monthly continuation injection of 2mL.

- In the second study, ATLAS (201585), 618 virologically-suppressed (HIV-1 RNA < 50 copies/mL) subjects already on a CAR regimen for at least 6 months were randomized to either continue their CAR regimen or switched to an injectable regimen of CAB LA + RPV LA, after a 1-month (at least 28 days) oral lead-in CAB + RPV. Following the OLI phase, an initiation dose of RPV LA 3mL was given followed by monthly continuation injection of 2mL.

In addition, the 24 Week results from an ongoing Ph IIIb study ATLAS 2M (207966) are described in this MAA. ATLAS 2M evaluates whether a bi-monthly dosing of RPV LA + CAB LA is non-inferior to the monthly regimen. Pending Week 48 primary endpoint data, the applicant aims at extending the posology of the long acting regimen to 2-monthly use, within the same indication supported by ATLAS and FLAIR.

The REKAMBYS MAA is further supported by data from the following Phase II studies:

- The Phase IIb LATTE study (LAI116482) provides supportive safety and efficacy data; the study was designed for oral CAB dose selection, which led to the selection of oral CAB 30mg once daily for use in future HIV-1 treatment studies. Week 144 results are included in this submission.

- The Phase IIb LATTE-2 Study (200056) provides supportive safety and efficacy data for the two-drug injectable regimen of CAB LA and RPV LA in virologically suppressed HIV-1 infected patients. LATTE-2 has now reported results out to Week 160.

This MAA also describes data to inform the appropriate uses of the two-drug regimen of oral CAB 30 mg and RPV 25 mg (EDURANT®) once daily:

- As short-term (approximately 1 month) oral lead-in therapy to establish tolerability to the individual agents prior to the first CAB LA and RPV LA IM injections.
- For use during a short-term injection-free period in the event of planned interruptions in the LA dosing schedule