22 October 2015
EMA/742847/2015 adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Edurant

International non-proprietary name: rilpivirine

Procedure No. EMEA/H/C/002264/II/0017/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

3TC	lamivudine
ABC	abacavir
ACTH	adrenocorticotropic hormone
ADR	adverse drug reaction
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC_{24h}	AUC from time of administration up to 24 hours post dosing, calculated by linear trapezoidal summation
AZT	zidovudine
BCO	biologic cut-off
C_{min}	minimum plasma concentration
C_{0h}	trough (predose) plasma concentration
ECG	electrocardiogram
EFV	efavirenz
ETR	etravirine
EU	European Union
FDA	Food and Drug Administration
FC	fold change in EC_{50} values in cell-based assay
FTC	emtricitabine
GAM	generalized additive models
GCP	good clinical practice
HIV(-1)	human immunodeficiency virus (type 1)
ITT	intent-to-treat
NC=F	non-completer = failure
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide analogue reverse transcriptase inhibitor; N(t)RTI in the protocol
NVP	nevirapine
qd	once daily
RAM	resistance associated mutation
RPV	rilpivirine, or TMC278, formerly known as R278474
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	system organ classes
TDF	tenofovir disoproxyl fumarate
TLOVR	time to loss of virologic response algorithm
USA	United States of America
VF	virologic failure
VL	viral load
WT	wild type

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 9 March 2015 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None

Extension of indication to include treatment of ARV treatment-naïve paediatric patients aged 12 to <18 years of age based on the results of the 48-week data of study TMC278-TiDP38-C213 (PAINT), undertaken to evaluate the pharmacokinetics, safety/ tolerability, and efficacy of rilpivirine 25 mg qd in combination with an investigator-selected background regimen containing two nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs) in this adolescent population. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly.
A revised RMP version 6.0 was included as part of this application.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0344/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP, EMEA-317-PIP-01-08-M07 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	9 March 2015
Start of procedure	28 March 2015
CHMP Rapporteur Assessment Report	26 May 2015
PRAC Rapporteur Assessment Report	26 May 2015
PRAC members comments	4 June 2015
PRAC Outcome	11 June 2015
CHMP members comments	15 June 2015
Updated CHMP Rapporteur Assessment Report	18 June 2015
Request for supplementary information (RSI)	25 June 2015
Submission of responses	21 August 2015
Restart of procedure	24 August 2015
CHMP Rapporteur response Assessment Report	22 September 2015
PRAC Rapporteur response Assessment Report	22 September 2015
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	08 October 2015
CHMP members comments	12 October 2015
Updated CHMP Rapporteur Assessment Report	N/A
CHMP Opinion	22 October 2015

2. Scientific discussion

2.1. Introduction

Product

Edurant 25 mg film-coated tablets contain rilpivirine hydrochloride equivalent to 25 mg rilpivirine (RPV). RPV, a diarylpyrimidine derivate is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Edurant was licensed in EU on 28 November 2011. Edurant, in combination with other antiretroviral medicinal products, is indicated for the treatment of human-immunodeficiency-virus-type-1 (HIV-1) infection in antiretroviral-treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml. The dosing regimen for adults is 25 mg taken qd with a meal.

Rilpivirine as part of a fixed-dose combination tablet is also approved in several countries, including the EU, as Complera/Eviplera (emtricitabine (200 mg), rilpivirine (25 mg) and tenofovir disoproxil (245 mg)).

Scope of Application / Problem statement

The data submitted in this application are the results from the Week 48 analysis of the C213 clinical trial. The MAH aims to extent the current indication of RPV to also include HIV-1 infected ARV treatment-naïve paediatric patients 12 to less than 18 years of age with a viral load ≤100,000 copies/mL at start of treatment.

An updated RMP (version 6.0) is enclosed to support this application. In addition to the updated paediatric information, the RMP has also been updated with the following information:

- Section SVII.4.2. (Important Identified and Potential interactions) of the RMP has been updated to include information on the interaction of RPV with telaprevir (as submitted to EMA in procedure EMEA/H/C/002264/II/002).
- The Pharmacovigilance Plan of the RMP has been updated to indicate that the results of the EDURANT/EVIPLERA Health Care Professional Survey (PASS) have been submitted to the Agency (procedure EMEA/H/C/002264/II/15). This submission was made in order to fulfill the Post-Authorization Measure (PAM) MEA 011.3 - HCP survey (PASS). The results of the survey are described in the RMP.
- As requested by EMA on 20 January 2015 (EMA/43598/2015), the Pharmacovigilance Plan of the RMP (Section III.1) also has been updated to state that the data of the Antiretroviral Pregnancy Registry Interim Reports will be submitted together with the PSUR.
- The MAH no longer considers 'Drug-drug interactions' as 'missing information'. The RMP has been updated accordingly.
- The MAH introduced a revised due date for the submission of the results of the TMC114HIV3015 study. The study is currently ongoing but additional subjects need to be recruited to study the pharmacokinetics of RPV in at least 12 HIV-1 infected pregnant women. Submission of the final trial study report (data from the RPV cohort) is planned in 4Q2016.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

An updated ERA is not required as this extension of indication is not expected to impact the total environmental exposure.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

The MAH claims that the C213 study, included in this submission, was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and in compliance with the protocol.

One site in South Africa was closed during the study following an inspection by the South African Medicines Control Council (local health authority), which identified GCP non-compliance. Four patients were enrolled at this site. Ongoing patients were transferred to another site. To evaluate whether the GCP non-compliance at site ZA00168 affected the results of the study, sensitivity analysis was performed excluding the data from this site for the primary efficacy endpoint, and for safety.

2.3.2. Pharmacokinetics

ARV treatment-naïve, HIV-1 infected adolescents aged ≥12 to <18 years, and weighing ≥32 kg were included in this study. Pharmacokinetics of RPV was evaluated over a 48-week treatment period (see for further study details section 2.4 of this report).

For measurement of rilpivirine plasma concentrations, a previous validated liquid chromatography with tandem mass-spectrometry [LS-MS/MS] method (BA1674) was applied over a calibration concentration range of 1 – 2000 ng/ml and showing a good accuracy and precision. Within–study results showed that accuracy was within normal run criteria.

Part 1 of the study (consisting of Part 1a and Part 1b) was designed to evaluate the steady-state pharmacokinetic (PK) profile and the short-term safety and antiviral activity of RPV 25 mg qd.
In Part 1a, a group of 11 patients was enrolled, 4 patients in the age group ≥12 to <15 years and 7 patients in the age group ≥15 to <18 years. At Week 2, when these first 11 patients had been treated for at least 2 weeks or discontinued earlier, an analysis of RPV pharmacokinetics together with short-term safety and antiviral activity was performed, which was reviewed by an independent data monitoring committee (IDMC). Based on these Week 2 interim data the IDMC agreed for these patients to continue treatment with RPV 25 mg qd and their background regimen.

Part 1 of the study was for various reasons expanded to include another 14 patients (Part 1b), 8 patients in the age group ≥12 to <15 years and 6 patients in the age group ≥15 to <18 years, amounting to a total of 25. At Week 4, when these additional 14 patients had been treated for at least 4 weeks or discontinued earlier, another Part 1 analysis was performed, which was evaluated by the IDMC before the start of Part 2 of the study.

Full 24-hour pharmacokinetic profiles were determined at Week 2 (Part 1a) or at Week 4 (Part 1b) for 23 of the 25 patients included in Part 1 of the study (2 patients in Part 1 discontinued before any pharmacokinetic assessments were done). The results are shown in table PK 1.

Table PK 1. Pharmacokinetic parameters of RPV after multiple dose administration of RPV 25 mg qd in adolescents (part 1) in comparison with pharmacokinetic parameters observed in adults (pooled data of study TMC278-C209 and C215).

Pharmacokinetics of RPV (mean±SD, t_{max}: median [range])	TMC278-C213 Part 1a (test)	TMC278-C213 Part 1b (test)	TMC278-C213 Part 1a + 1b (test)	TMC278-C209 + TMC278-C215 (reference)
N	11	12	23	44
C_{trough}, ng/mL	68.5 ± 29.0	92.1 ± 47.0	80.8 ± 40.4	67.6 ± 39.0
C_{min}, ng/mL	47.0 ±18.1	66.4 ± 29.9	57.1 ± 26.3	53.7 ± 28.3
C_{max}, ng/mL	88.7 ± 25.5	127 ± 38.9	109 ± 38.0	134 ± 72.0
t_{max}, h	5.00 (2.00 - 9.03)	5.00 (4.00 - 6.00)	5.00 (2.00 - 9.03)	4.00 (1.00-12.00)
AUC_{24h}, ng.h/mL	1551 ± 460	2167 ± 800	1872 ± 717	2005 ± 970

In comparison to adults, the ratio of the least squares (LS) means for adolescents/adults was close to 100% for the different RPV PK parameters (see table PK 2). AUC24h, Ctrough, Cmin and Cmax were all within the range to conclude comparability in RPV pharmacokinetics between adults and adolescents (geometric mean ratio of >0.80 and <1.25).

Table PK 2. Steady-state pharmacokinetic parameters of RPV after multiple dose administration of RPV 25 mg qd in adolescents (study Part 1) and in adults (pooled data of TMC278-C209/C215 PK substudies).

Parameter	LS means[a]		LS means ratio, %	90% CI,% [b]
	TMC278-C209 + TMC278-C215 (reference)	TMC278-C213 (Part 1a + 1b) (test)		
C_{trough}, ng/mL	58.3	70.6	121.07	95.45 – 153.58
C_{min}, ng/mL	47.5	51.3	108.09	87.44 – 133.61
C_{max}, ng/mL	116	102	88.24	71.09 – 109.54
AUC_{24h}, ng.h/mL	1782	1750	98.19	80.53 - 119.73

[a] N=44 for reference and N=23 for test
[b] 90% confidence intervals
LS: least squares

Based upon these data, next to short-term safety and efficacy data, patients continued their treatment with RPV 25 mg qd for Part 2. Here, sparse samples for the determination of RPV plasma concentrations were gathered in all patients at Week 2 (except Part 1a patients), Week 4 (except Part 1b patients), Week 8, Week 12, Week 24 and Week 48.

Pharmacokinetic parameters (AUC24h and Ctrough) of RPV for all patients were determined by means of empirical Bayes' estimation using a population pharmacokinetic model previously developed for adults, and adjusted for adolescents using the intensive and sparse pharmacokinetic sampling data from the current study. In summary, the population pharmacokinetic model that best describes the pharmacokinetics of RPV when given as 25 mg qd with a meal in adolescents was (similar to adults) a 2-compartment disposition model in which absorption was described by a lag time followed by a sequential zero- and first-order absorption process. The population pharmacokinetic analysis did not necessitate a change to the structural fixed parameters of the previously established RPV population pharmacokinetic model, but included a modification of the random parameters with the addition of an inter-occasion variability on clearance. As such, individual pharmacokinetic parameter estimates were derived for each visit with pharmacokinetic sampling.

[VBA[1]

The AUC24h (2391 ± 991 ng.h/ml) and Ctrough (84 ± 39 ng/ml) in adolescents at week 48 were similar to those obtained in adults (AUC24h: 2397 ± 1032 ng.h/ml; Cmax 80 ± 37 ng/ml) (see table PK 3).

Table PK 3. Summary statistics of individual population pharmacokinetic model-derived parameters of RPV 25 mg qd in adolescents and adults (Week 48 Analysis).

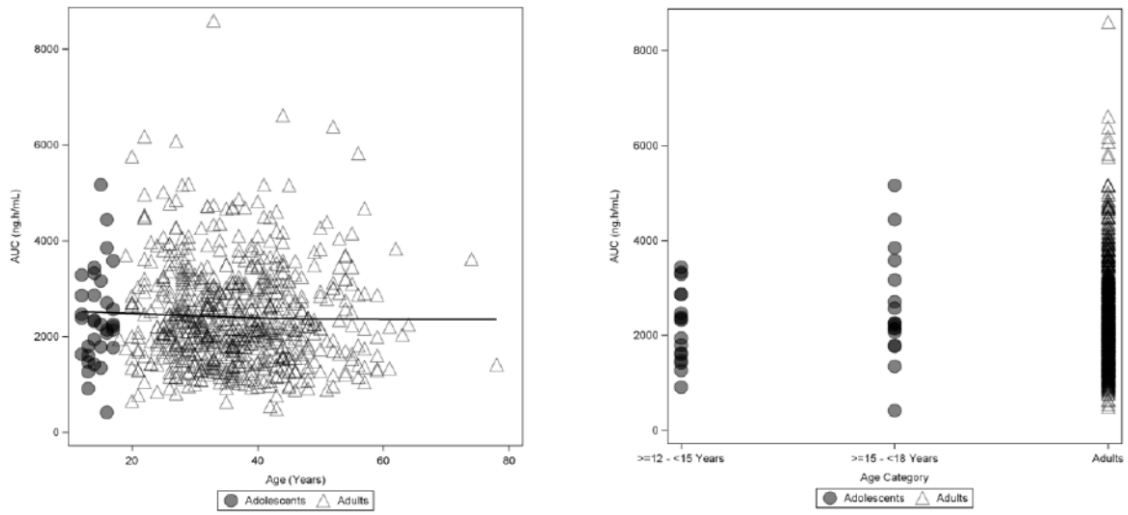
Pharmacokinetics of RPV mean±SD (range)	**Adolescents TMC278-C213**	**Adults TMC278-C209/C215**
N	34	679
C_{0h}, ng/mL	84 ± 39	80 ± 37
	(7 - 202)	(1.45 - 300)
AUC_{24h}, ng.h/mL	2391 ± 991	2397 ± 1032
	(417 - 5166)	(482 - 8601)

N=number of subjects with data

Effect of age

There was no clear relation between the RPV pharmacokinetics and age as a continuous variable and no relevant difference by age category (≥12 to <15 years and ≥15 to <18 years), with ranges of pharmacokinetic parameters overlapping between categories. This was also confirmed in the graphical evaluation of potential covariates in the population pharmacokinetic analysis for C213, where age was not found to impact the RPV apparent oral clearance (CL/F) or apparent volume of distribution (Vd/F). In addition, these results are in line with the data in adults, where no age effect was observed (see figure PK 1 next page).

Figure PK 1. RPV pharmacokinetics (AUC24h) by age (left figure) and age category (right figure) in adolescents (C213) and adults (C209/C215).



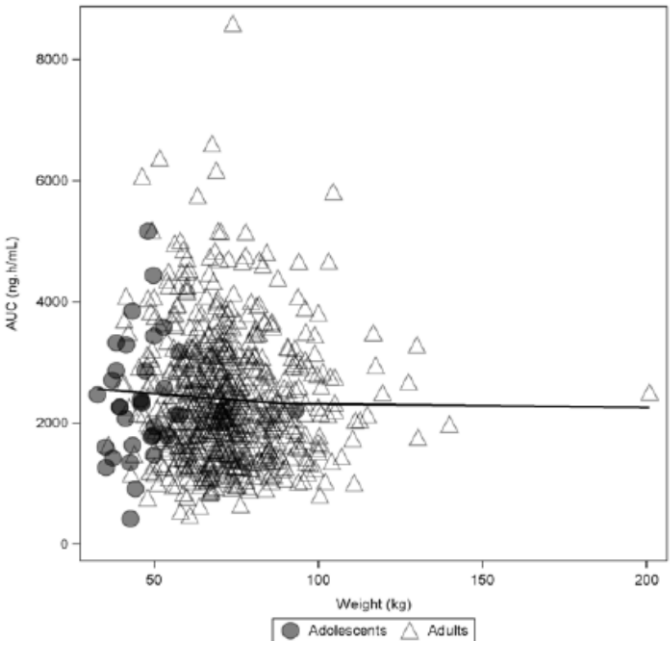
Effect of gender

Twenty (55.6%) of the patients in C213 were female, and 16 (44.4%) were male. In adolescents in C213, there was no clinically relevant difference by gender, with ranges overlapping between males and females. This is in line with the data observed in adults.

Effect of body weight

The median (range) bodyweight at screening for patients in C213 was 45.2 (33 - 93) kg. Bodyweight did not impact the RPV pharmacokinetics in adolescent patients, across the bodyweight range in C213 (33 – 93 kg). This was also confirmed in the graphical evaluation of potential covariates in the population pharmacokinetic analysis for C213, where bodyweight was not found to impact the RPV CL/F or Vd/F. These results are similar for the RPV pharmacokinetics in adults, across a wider bodyweight (see figure PK 2).

Figure PK 2. RPV pharmacokinetics (AUC24h) by bodyweight in adolescents (C213) and adults (C209/C215) range (36.2 - 200.9 kg).



2.3.3. Discussion on clinical pharmacology

The results at week 48 showed that pharmacokinetics at week 24 and 48 were comparable. Moreover, week 48 data showed that AUC24h and Ctrough were comparable to those in adults. These data support the efficacy of RPV 25 qd in adolescents. In adolescents no effect of age on the pharmacokinetics of RPV were seen. This is in line with what previous was observed for adults, in the age range of the Phase 3 studies. No clinical relevant effect of gender or body weight was observed in adolescents.

2.3.4. Conclusions on clinical pharmacology

AUC24h and Ctrough values were comparable to those observed in adults, which in principle supports the efficacy of RPV 25 qd also in adolescents.

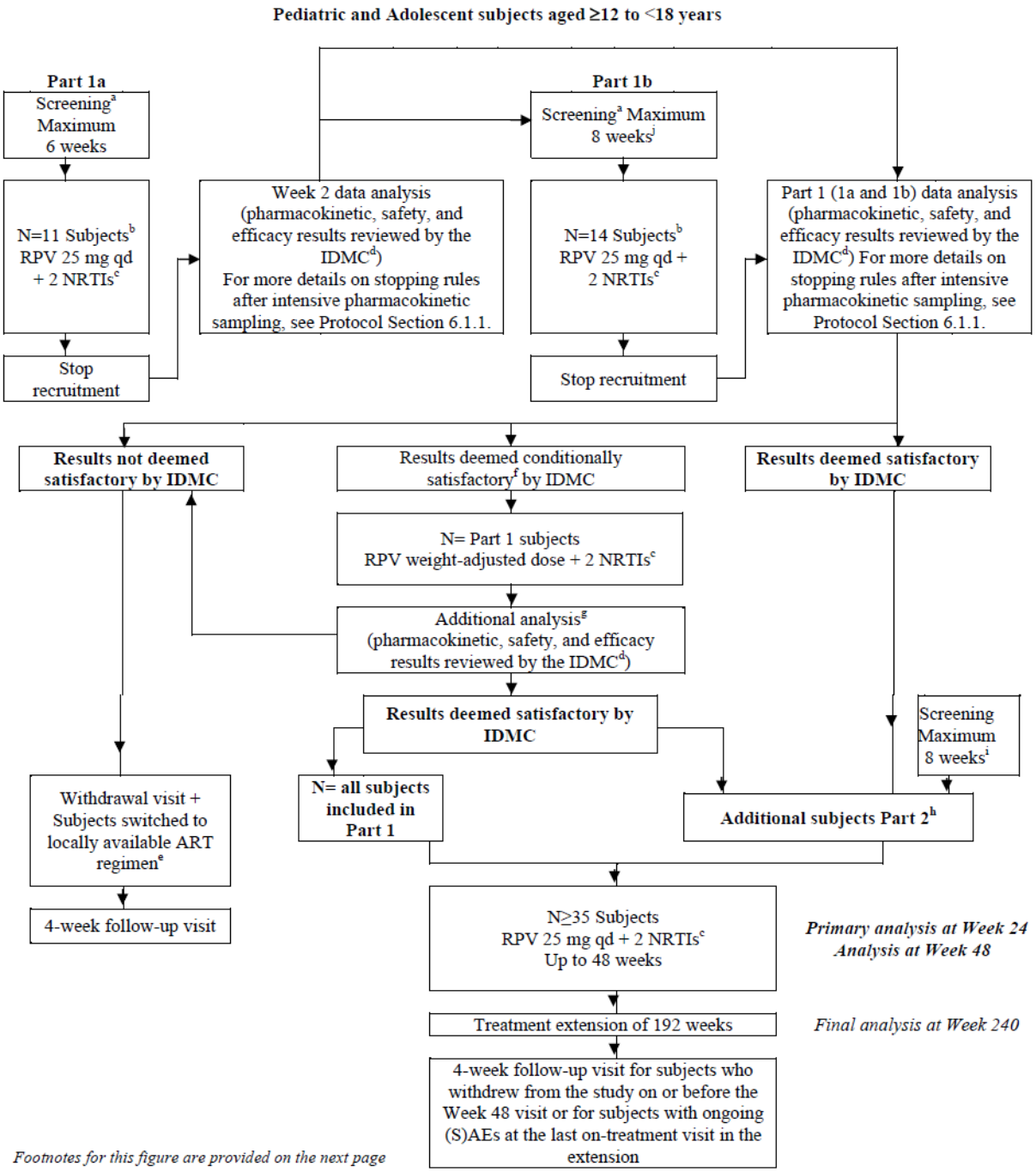
2.4. Clinical efficacy

2.4.1. Main study

Study TMC278-TiDP38-C213: A Phase II, open-label, single arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of TMC278 in antiretroviral-naïve HIV-1 infected adolescents aged 12 to <18 years (EudraCT: 2008-001696-30).

Methods

The design of the study C213 is shown in Figure 1.



a To ensure that the duration between baseline and the review by the IDMC for subjects in Part 1a of the study was kept as short as possible, investigators were to identify eligible subjects in advance. Recruitment was to be started when the majority of the sites had the necessary documentation and approvals in place and were therefore considered activated for enrollment.
For Part 1b of the study, recruitment could start at the individual sites as soon as the necessary documentation and approvals were in place, and was closed once the required number of subjects was recruited. Study sites were informed in advance regarding stop of recruitment.
b For Part 1a of the study, at least 5 subjects in the age group ≥12 to <15 years and at least 5 subjects in the age group ≥15 to <18 years were to be recruited (simultaneously). Part 1a included 11 subjects, 4 subjects in the age group ≥12 to <15 years and 7 subjects in the age group 15 to <18 years. In Part 1b of the study, approximately 12 subjects (in order to have at least 10 evaluable subjects at Week 4) were to be enrolled, aiming at an equal distribution of subjects between the two age groups (i.e., subjects 12 to <15 years and subjects ≥15 to <18 years). Part 1b of the study included 14 subjects, 8 subjects in the age group 12 to <15 years and 6 subjects in the age group ≥ 15 to <18 years.
c Investigator-selected with a choice limited to zidovudine (AZT), abacavir (ABC), or tenofovir disoproxil fumarate (TDF) in combination with lamivudine (3TC) or emtricitabine (FTC), given as the co-formulation or as the separate components.
d Subjects included in Part 1 of the study continued their ART regimen and the study during this review period.
e In case the study would have been stopped after Part 1, a sample was to be analyzed in real time for the determination of HIV-1 genotype (as long as the plasma viral load was sufficiently high to allow the HIV-1 genotype to be determined), in order to assist in the selection of

a new ART. When determination of HIV-1 genotype on this sample would not have been possible due to a too low plasma viral load, the new ART would have been based on the screening HIV-1 genotyping result.
f In case the results of Part 1 of the study would have shown a safety concern as deemed by the IDMC, which could have been avoided by a lower RPV exposure.
g Analysis would have been done when these subjects would have been treated for 4 weeks (+/- 1 week) with the weight-adjusted dose.
h Because no dose switch was required, Part 2 of the study could start immediately after the positive IDMC evaluation of the results of Part 1 of the study. In case a dose switch would have been required, Part 2 of the study would have started after re-evaluation by the IDMC of the analysis when subjects would have been treated for 4 weeks (+/- 1 week) with the weight-adjusted dose.
i The screening period could be prolonged to maximum 8 weeks in order to allow plasma viral load and CD4+ cell count to be assessed before continuing with the other screening assessments. After obtaining informed consent, samples were taken for determination of plasma viral load and CD4+ cell count. If plasma viral load results met the inclusion criteria and the investigator considered initiation of ART appropriate (taking into account current treatment guidelines, including CD4+ cell count and the subject's clinical situation), the subject returned within 2 weeks after availability of these results, for the remainder of the screening procedures. If plasma viral load results did not meet the inclusion criteria, the subject was considered a screen failure.

Study participants

The study population consisted of boys and girls, aged ≥12 to <18 years, weighing ≥32 kg, with documented chronic HIV-1 infection who were treatment naïve at screening. Patients' HIV-1 plasma viral load at screening was ≥500 HIV-1 RNA copies/mL but ≤100,000 HIV-1 RNA copies/mL for Part 1b and Part 2 of the study. For Part 1a, patients with a screening viral load ≥ 5,000 HIV-1 RNA copies/mL were allowed. Main exclusion criteria were: NNRTI resistance at screening or from historical data available in the source documents; any currently active Acquired Immunodeficiency Syndrome (AIDS) defining illness; any active clinically significant disease; Risk factors for QTc prolongation.

Treatments

The ART regimen consisted of RPV 25 mg qd, in combination with 2 NRTIs (zidovudine (AZT), abacavir (ABC), or tenofovir disoproxyl fumarate (TDF) in combination with lamivudine (3TC) or emtricitabine (FTC), whichever was approved and marketed). The NRTIs were selected by the investigator.
Switching to alternative NRTIs was allowed for some predefined toxicities. The use of ABC needed to be preceded by a negative HLA-B*5701-test.

Objectives

The objectives of Part 1 of this study were:

- to evaluate the steady-state pharmacokinetics of RPV 25 mg qd in patients aged ≥12 to <18 years;
- to evaluate short-term safety and antiviral activity of RPV in this age group.

The objectives of Part 2 of this study were:

- to evaluate long-term safety and efficacy over a 24- and 48-week treatment period of RPV;
- to evaluate immunologic changes (as measured by CD4+ cell parameters) over a 24- and 48-week treatment period of RPV;
- to assess the evolution of viral genotype and phenotype over a 24- and 48-week treatment period of RPV;
- to evaluate pharmacokinetics (by means of population pharmacokinetics) and pharmacokinetic-pharmacodynamic relationships for safety and efficacy of RPV;
- to evaluate treatment adherence as measured by the Study Adherence Questionnaire for Children and Teenagers.

Outcomes/endpoints

Antiviral Activity:

The efficacy parameters for this study that were tabulated, analyzed descriptively (eg, n, mean,

SD, minimum, median, maximum) and presented graphically include:

Proportion of subjects with plasma viral load <50 HIV-1 RNA copies/mL at Week 24 and Week 48.

The changes from baseline in the log10 HIV-1 RNA copies/mL values by analysis time point.

The changes in plasma viral load from baseline by subgroups (≤100,000 and >100,000 HIV-1 RNA copies/mL).

Proportion of subjects with a plasma viral load <50 and <400 HIV-1 RNA copies/mL at all-time points, and time to achieve these.

Proportion of subjects with a decrease from baseline in plasma viral load of 1.0 log10 HIV-1 RNA copies/mL at Week 12

Time to loss of virologic response.

The change from baseline in CD4+ cell count (absolute and %) was the immunology parameter, which was presented by analysis time point and by subgroups (≤100,000 and >100,000 HIV-1 RNA copies/mL).

Immunologic Change:

The change from baseline in CD4+ cell count (absolute and %) was the immunology parameter, which

was presented by analysis time point and by subgroups (≤100,000 and >100,000 HIV-1 RNA copies/mL).

Resistance Determinations:

Relevant changes in the viral phenotype and genotype (emerging mutations, incidence of mutations, subjects with post-baseline genotypic data by emerging resistance-associated mutations [RAMs] and by phenotypic resistance and cross-resistance) were tabulated and analysed descriptively particularly for subjects with virologic failure (VF).

Safety: Only treatment-emergent events are described in the results.

Randomisation

This is an open design study.

Blinding (masking)

None.

Results

Participant flow

36 patients were enrolled. Of these 36 patients, 24 (66.7%) patients were ongoing at the Week 48 analysis cut-off date (12 June 2014), while 8 (22.2%) patients prematurely discontinued the study prior to that time. Four (11.1%) patients completed the study at Week 48 and did not continue in the post Week 48 extensions.

Among the 8 patients who prematurely discontinued, 6/36 (16.7%) patients reached a virologic endpoint, 1 (2.8%) subject had been dosed despite the presence of an exclusionary NNRTI RAM at screening (protocol

deviation) and was therefore discontinued after 7 days of dosing, and another subject was diagnosed with pulmonary tuberculosis during the study and was withdrawn from the study before the Week 48 analysis cut-off date as per withdrawal criteria.

Conduct of the study

Major protocol deviations were observed for 3 (8.3%) patients, table below. One patient entered the study despite the presence of an exclusionary NNRTI RAM at screening and was discontinued after 7 days. The major protocol deviations reported for the other 2 patients were related to lack of RPV intake and/or intake without food.

Table E1: Protocol deviations

Class/ Coded Term, n (%)	RPV 25 mg qd (N=36)
Any major protocol deviation	3 (8.3%)
Entered but did not satisfy criteria	1 (2.8%)
Other	1 (2.8%)
Received wrong treatment or incorrect dose	2 (5.6%)

A subject may have more than one deviation.
N=number of subjects with data, n=number of subjects with that observation

One site in South Africa was closed during the study following an inspection by the South African Medicines Control Council (local health authority), which identified GCP non-compliance. Four patients were enrolled at this site. Ongoing patients were transferred to another site. To evaluate whether the GCP non-compliance at site ZA00168 affected the results of the study, sensitivity analysis was performed excluding the data from this site for the primary efficacy endpoint, and for safety.

Adherence to RPV treatment was assessed by pill count and by questionnaires. Based on pill count, the mean RPV treatment adherence until Week 48 was 97.5% (4.80).

The majority of patients, 28/36 (77.8%), had an adherence of >95% to RPV treatment at Week 48, while 8/36 (22.2%) patients had an adherence of <95% to RPV treatment at Week 48. All patients had a mean adherence of at least 80%.

Baseline data

Patients were enrolled and treated at sites in the following countries: South Africa (3 sites), India (1 site), Thailand (1 site), USA (1 site), Uganda (1 site).

The majority of patients were black or African American (32/36 [88.9%] patients), 20/36 (55.6%) were female. There were 18 (50.0%) patients in each of the following age categories: ≥12 to <15 years and ≥15 to <18 years.

The majority of patients were infected with HIV-1 clade C (23/36 [63.9%] patients), followed by clade A1 (9/36 [25.0%] patients). The combination of NRTIs most frequently used together with RPV was FTC/TDF (24/36 [66.7%] subjects). TDF/3TC was used by 8/36 (22.2%) subjects and AZT/3TC was used by 4/36 (11.1%) subjects. See next table for more details.

Table E2: Main demographics and characteristics

Male gender, n (%)	16 (44.4%)
Age, n (%)	
≥12 - <15 Years	18 (50.0%)
≥15 - <18 Years	18 (50.0%)
Race, n (%)	
Asian	4 (11.1%)
Black or African American	32 (88.9%)
HIV-1 Clade, n (%)	
A1	9 (25.0%)
B	1 (2.8%)
C	23 (63.9%)
CRF01_AE	1 (2.8%)
D	2 (5.6%)
Hepatitis B/C co-infection status, n (%)	
Unknown	8 (22.2%)
Yes	3 (8.3%)
Mode of HIV infection, n (%)	
Heterosexual contact	4 (11.1%)
Mother to child transmission	30 (83.3%)
Other	1 (2.8%)
Unknown	1 (2.8%)
Baseline HIV-1 RNA (categorical), n (%)	
≤100000 copies/mL	28 (77.8%)
>100000 - ≤500000 copies/mL	6 (16.7%)
>500000 copies/mL	2 (5.6%)
Baseline $CD4^+$ cell count (cells/µL)	
Median (min - max)	414.0 (25 - 983)
≤200 cells/µL	4 (11.1%)
>200 cells/µL	32 (88.9%)
Duration of known HIV infection (years)	
Median (min - max)	1.30 (0.0 - 11.2)

Outcomes and estimation

Table E3: Virologic Response (TLOVR) - Week 24 and Week 48 Tabulation

n (%)	RPV 25 mg qd (N=36)
Week 24	
Responder	27 (75.0%)
Virologic failure	7 (19.4%)
never suppressed	6 (16.7%)
initial lack of response	1 (2.8%)
rebounder	1 (2.8%)
Discontinued due to AE	1 (2.8%)
Discontinued due to reason other than AE	1 (2.8%)
Week 48	
Responder	26 (72.2%)
Virologic failure	8 (22.2%)
never suppressed	4 (11.1%)
initial lack of response	1 (2.8%)
rebounder	4 (11.1%)
Discontinued due to AE	1 (2.8%)
Discontinued due to reason other than AE	1 (2.8%)

One subject (213-0026) discontinued due to an AE of pulmonary tuberculosis (mandatory withdrawal criterion).

N=number of subjects with data, n=number of subjects with that observation

Table E 4: Virologic Response (TLOVR) - Week 24 and Week 48 Tabulation, grouped per Baseline Viral Load

	RPV 25 mg qd	
	Baseline Viral load	
n (%)	≤100000 copies/mL N=28	>100000 copies/mL N=8
Week 24		
Virologic responder	24 (85.7%)	3 (37.5%)
Virologic failure	3 (10.7%)	4 (50.0%)
never suppressed	3 (10.7%)	3 (37.5%)
initial lack of response	0	1 (12.5%)
rebounder	0	1 (12.5%)
Discontinued due to AE*	0	1 (12.5%)
Discontinued due to reason other than AE**	1 (3.6%)	0
Week 48		
Virologic responder	22 (78.6%)	4 (50.0%)
Virologic failure	5 (17.9%)	3 (37.5%)
never suppressed	2 (7.1%)	2 (25.0%)
initial lack of response	0	1 (12.5%)
rebounder	3 (10.7%)	1 (12.5%)
Discontinued due to AE*	0	1 (12.5%)
Discontinued due to reason other than AE**	1 (3.6%)	0

Resistance determination

Baseline resistance

For all 36 patients, genotypic data were available at baseline and/or screening. One subject carrying V179T at screening and baseline was enrolled in error. This subject discontinued the study at Week 1 for this reason, and was identified as VF in the Week 48 TLOVR efficacy analysis.

A total of 8/36 (22.2%) patients carried at least 1 NNRTI RAM at (pre-) baseline. These were V179I (n=7) (non-exclusionary) and V179T (n=1) (as indicated above). None of the patients carried RPV RAMs or NRTI RAMs at baseline.

Analysis of virologic failures

Of the 20 patients with post-baseline genotypic data, 8 patients experienced VF in the first 48 weeks according to the TLOVR imputation (4 patients 'never suppressed' and 4 patients 'rebounder'), 2 patients discontinued due to other reasons than VF (1 due to an AE and 1 due to other reasons), and 10 patients were responders at Week 48. Of these 10 responders at Week 48, 4 patients experienced VF (TLOVR; all 'rebounder') after their Week 48 visit (before the cut-off for the Week 48 analysis), while 6 patients remained responders.

The next table shows the emergence of resistance in the mentioned 20 patients, for who paired data was available.

Table E5. Emerging resistance to NNRTI / NRTI- Week 48

Virologic outcome (TLOVR) category Week 48

	RPV 25 mg qd			
Last post-baseline time point / Emerging RAMs, n (%)	VF (≤W48) N=8	Discontinuer N=2	Virologic responder N=10	Overall N=20
Last post-baseline time point with genotypic data				
None	2 (25.0%)	2 (100.0%)	10 (100.0%)	14 (70.0%)
NNRTI – at least 1	6 (75.0%)	0	0	6 (30.0%)
RPV RAM – at least 1*	5 (62.5%)	0	0	5 (25.0%)
V90I	1 (12.5%)	0	0	1 (5.0%)
K101E*	2 (25.0%)	0	0	2 (10.0%)
E138G*	1 (12.5%)	0	0	1 (5.0%)
E138K*	4 (50.0%)	0	0	4 (20.0%)
E138R*	1 (12.5%)	0	0	1 (5.0%)
Y181I*	1 (12.5%)	0	0	1 (5.0%)
V189I	1 (12.5%)	0	0	1 (5.0%)
H221Y*	1 (12.5%)	0	0	1 (5.0%)
M230L*	2 (25.0%)	0	0	2 (10.0%)
NRTI – at least 1	4 (50.0%)	0	0	4 (20.0%)
K65R	1 (12.5%)	0	0	1 (5.0%)
Y115F	1 (12.5%)	0	0	1 (5.0%)
M184V	3 (37.5%)	0	0	3 (15.0%)

* RPV RAMs

N=number of subjects with data, n=number of subjects with that observation
VF (≤ W48) = Virologic failures up to and including the Week 48 visit (TLOVR)

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table E6. Summary of Efficacy for trial C213

Title: A Phase II, open-label, single arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of TMC278 in antiretroviral-naïve HIV-1 infected adolescents aged 12 to <18 years			
Study identifier	Study TMC278-TiDP38-C213 (EudraCT: 2008-001696-30)		
Design	Study C213 is an ongoing Phase 2, open-label, single arm study to evaluate the pharmacokinetics, safety/tolerability and efficacy of RPV (TMC278) 25 mg qd in combination with an investigator-selected background regimen containing 2 NRTIs in ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years and weighing ≥32 kg. The study is being conducted at multiple sites in different countries. Part 1 of the study (consisting of Part 1a and Part 1b) was designed to evaluate the steady-state pharmacokinetic profile and the short-term safety/tolerability and antiviral activity of RPV 25 mg qd when administered in combination with an investigator-selected background regimen of 2 NRTIs. The allowed ARV background regimen consisted of AZT, ABC or TDF in combination with 3TC or FTC. Part 2 of the study evaluated long-term safety/tolerability, efficacy, and pharmacokinetics of RPV in combination with an investigator-selected background regimen of 2 NRTIs. Antiretroviral treatment-naïve HIV-1 infected subjects, aged ≥12 to <18 years, with a VL ≥5,000 copies/mL could be included in Part 1a of the study. However, by amendment III (29 June 2011), in Part 1b and Part 2 recruitment was limited to subjects with a VL of ≥500 copies/mL but ≤100,000 copies/mL (further to the observed effect of baseline VL on virologic outcome in adults and in line with the current approved indication in adults in most regions/countries including the EU). Subjects who experienced and were expected to continue experiencing clinical benefit from RPV and their background regimen comprising 2 NRTIs at the end of the initial 48-week treatment period, had the option to continue their ARV treatment (ie, RPV + 2 investigator-selected NRTIs) through this study for an additional 4 years in a post Week 48 treatment extension period. During this extension period, safety and efficacy of RPV will be evaluated.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks not applicable 4 years
Hypothesis	No Hypothesis		
Treatments groups	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years		36 ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years were administered RPV 25mg qd (as 1 RPV tablet) plus an investigator-selected background regimen consisting of 2 NRTIs for 48 weeks
Endpoints and definitions	Co-Primary endpoint	Safety and tolerability	To evaluate the short and long term safety and tolerability of RPV when administered as 25 mg qd in patients aged 12 to <18 years
	Co-Primary endpoint	PK	PK parameters for RPV were determined based on intensive sampling at Week 2 or Week 4 in a subset of subjects (Part 1, n=23) and sparse sampling over the 48 week treatment period in all subjects (Part 2, n=36). In Part 1, a non-compartmental PK analysis identified a RPV dose in adolescents that resulted in similar RPV exposures as in adults. In Part 2, the RPV PK was explored by means of population PK analysis.
	Co-Primary endpoint	Efficacy	Viral load <50 copies/mL by the time to loss of virologic response algorithm (TLOVR) in the ITT population at week 48.
	Secondary endpoints (main ones)	Efficacy	Proportion of virologic responders (<50 copies/mL) in the FDA Snapshot analysis for the ITT population at Week 48.

		Efficacy	Change from baseline in CD4+ cell count (NC=F: mean change)
		Resistance determinations	Changes in the viral phenotype and genotype
Database lock	12 June 2014 (cut-off date for Week 48 analysis)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat population Week 48			
Descriptive statistics and estimate variability	Treatment group	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years: Baseline Viral Load ≤100000 copies/mL	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years: Baseline Viral Load >100000 copies/mL
	Number of subject	36	28	8
	Virologic Response HIV-1 RNA <50 copies/mL, TLOVR, n (%)	26 (72.2%)	22 (78.6%)	4 (50.0%)
	95% CIs	[54.8% - 85.8%]	[59.1% - 91.7%]	[15.7% - 84.3%]
	Virologic failure never suppressed initial lack of response rebounder *Discontinued due to AE* *Discontinued due to reason other than AE*	8 (22.2%) 4 (11.1%) 1 (2.8%) 4 (11.1%) 1 (2.8%) 1 (2.8%)	5 (17.9%) 2 (7.1%) 0 3 (10.7%) 0 1 (3.6%)	3 (37.5%) 2 (25.0%) 1 (12.5%) 1 (12.5%) 1 (12.5%) 0
Notes	Rilpivirine resistance mutations were observed in 62.5% (5/8) of subjects with virological failure. In 4 of those 5 subjects, NRTI resistance was observed as well.			
Analysis population and time point description	Intent to treat population, sensitivity analyses Week 48			
Descriptive statistics	Treatment group	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years: Baseline Viral Load ≤100000 copies/mL	ARV treatment-naïve, HIV-1 infected adolescents aged 12 to <18 years: Baseline Viral Load >100000 copies/mL
	Virologic Response HIV-1 RNA <50 copies/mL, n (%)			
	Snapshot NC=F Observed	N= 36 26 (72.2) N= 36 26 (72.2) N= 29 26 (89.7)	N= 28 22 (78.6) N= 28 22 (78.6) N= 25 22 (88.0)	N= 8 4 (50.0) N= 8 4 (50.0) N= 4 4 (100)
	CD4+ cell count mean change from baseline			

	NC=F	201.2 (32.87)	214.5 (38.85)	154.5 (59.47)
	N=total number of subjects, n=number of responders.			
Analysis population and time point description	Summary Statistics of Individual Population PK Model-Derived Parameters of RPV 25 mg qd in Adolescents and Adults (Week 48 Analysis)			
PK analysis	mean±SD (range)	Adolescents (C213)	Adults (pooled Phase 3)	
	N	34	679	
	C_{0h}, ng/mL	84±39 (7 - 202)	80±37 (1.45 - 300)	
	AUC_{24h}, ng.h/mL	2391±991 (417 – 5166)	2397±1032 (482 – 8601)	
	N=number of subjects with data			

2.4.2. Discussion on clinical efficacy

Similar drug exposure was shown in adolescents as in adult, which is the main requirement for inferring antiretroviral efficacy in any paediatric population. The 48-week efficacy results demonstrate that RPV 25 mg qd, in combination with an investigator-selected background regimen of 2 NRTIs, is efficacious in adolescents, ≥12 to <18 years of age. The percentage Responder, both at Week 24 and at Week 48, is in line with results for other antiretrovirals in adolescents. Similar as in adults, the proportion of virologic responders in adolescents was clearly higher in patients with a baseline viral load ≤100,000 copies/mL (22/28 [78.6%]) than in the patients with a baseline viral load >100,000 copies/mL (4/8 [50%]). This is already incorporated in the SmPC as Edurant is currently indicated for the treatment of human-immunodeficiency-virus-type-1 (HIV-1) infection in antiretroviral-treatment- naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml. A similar restriction will be applied to adolescents.

Although efficacy in adolescents was overall acceptable, the number of youngsters having virological failure, and with resistance development to both the NNRTI and NRTI class within a year of therapy, is of concern based on available data. In 6 out of 8 patients with VF, the development of NNRTI-RAMs was observed (i.e. in 6 out of a total of 36 patients). At least 1 NRTI-RAM was observed at the same time point in 4 out of 5 patients. The proportion of patients ending up with resistance within 1 year of therapy is worrying. Adherence to treatment is of paramount importance when using a regimen of rilpivirine with 2NRTI. The PENTA paediatric HIV treatment guideline discusses well known adherence issues among adolescents, in relation to the differing barriers to resistance of different antiretroviral regimens (Bamford *et al*, HIV Medicine 2015). Based on such considerations, it is imperative that the SmPC section 4.4 emphasises the need to assess the likelihood of acceptable treatment adherence prior to prescribing rilpivirine to adolescents.

2.4.3. Conclusions on the clinical efficacy

Overall, the overall efficacy in adolescents was acceptable, with 72.2% of patients reaching viral load <50 copies/mL at week 48, and CD4+ cells increasing substantially (mean increase of 201.2 cells at week 48). However, the resistance data are worrying and the MAH was asked to propose a text for section 4.4., emphasizing the need to assess the likelihood of acceptable treatment adherence in adolescents, prior to prescribing rilpivirine.

2.5. Clinical safety

Introduction

In non-clinical studies in rats and dogs, changes in adrenal hormones and histopathology have been observed. In those studies, RPV appears to interfere with steroid biosynthesis, leading to decreases in serum cortisol and increases in serum progesterone and 17-OH-progesterone and as a result to increases in serum adrenocorticotropic hormone (ACTH). Endocrine monitoring was therefore included in the safety monitoring of all RPV studies conducted thus far. To date, no significant effects on adrenal or thyroid function were observed in any study with RPV in adults.

In theory, some concerns in adolescents could be raised by these non-clinical findings: the possibility of partial adrenal insufficiency, virilisation in girls due to 21-hydroxylase inhibition and precocious puberty due to ovarian stimulation in girls. If adolescent girls who have not reached puberty yet would sexually mature more rapidly as a result of treatment with RPV, the main effect would be the earlier occurrence of menarche. More importantly, in case significant inhibition of cortisol synthesis would occur, androgen production might increase. In adolescent girls, this could result in masculinization and blunted growth. In adolescent boys, due to increased levels of testosterone, growth might also be impaired. Therefore, in this study, growth was to be followed regularly and evaluated consistently using standardized growth charts. Sexual maturation was to be evaluated according to Tanner stages. Finally, hormone testing was to be performed, including measurements of serum testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), cortisol, progesterone, androstenedione, aldosterone, dehydroepiandrosterone sulfate (DHEAS), and 17-OH-progesterone.

Patient exposure

At the time of cut-off for the Week 48 analysis of C213, 24 (66.7%) subjects were ongoing and the mean (standard deviation [SD]) and median (range) duration of exposure to RPV 25 mg qd was 71.6 (43.09) and 63.50 (1.0-179.0) weeks, respectively. The total patient years of RPV exposure was 49.40 and half of the subjects had reached the Week 64 visit at the time of this analysis.

Adverse events / serious adverse event / deaths / other significant events

For 35 (97.2%) patients at least 1 AE was reported, for 13 (36.1%) of these patients an AE was considered treatment-related. In most patients, AEs were of grade 1-2 in severity. At least 1 grade 3-4 AE was reported in a total of 7 (19.4%) patients. One (2.8%) subject had at least 1 AE for which treatment was stopped.

There was no signal for unknown safety issues: the safety profile in adolescents was is in line with the known safety profile in adults.

Table S1. Safety profile in study C213 compared to safety in pooled Phase 3 studies

	C213	Pooled Phase 3 studies
n (%)	N=36	RPV group N=686
with at least one AE	35 (97.2%)	616 (89.8%)
with at least one SAE	6 (16.7%)	45 (6.6%)
who died due to an AE	0	1 (0.1%)
with a grade 3-4 AE	7 (19.4%)	91 (13.3%)
with at least one AE for which the study drug was permanently stopped	1 (2.8%)	23 (3.4%)

N=number of subjects with data, n=number of subjects with that observation

Depression was reported more often in adolescents (19.4%) compared to adults (4.1% in the Phase III controlled trials ECHO and THRIVE). One patient had a suicide attempt (considered not related by the investigator).

For a total of 13 (36.1%) subjects, treatment-related AEs were reported; the most frequently reported events were somnolence in 5 (13.9%) subjects and blood cortisol decreased. Although the adverse event (AE) "blood cortisol decreased", was reported in 7/36 (19.4%) adolescent subjects, analysis provided by the MAH shows that these AEs were not associated with treatment-emergent abnormal laboratory findings of basal or adrenocorticotropic hormone (ACTH)-stimulated blood cortisol. For no subjects with the AE "blood cortisol decreased", the AEs "somnolence" or "depression" were reported. Additionally, the AEs "somnolence" and "depression" were generally not associated with treatment-emergent abnormal laboratory findings of basal or ACTH-stimulated cortisol. Therefore these AEs are not considered signs and symptoms of adrenal insufficiency. Furthermore, no AE "adrenal insufficiency" was reported.

None of the SAEs reported in C213 were considered treatment-related, except for grade 2 SAE hypersensitivity ("probably related" according to the investigator).

There were no deaths in the study.

One subject discontinued study drugs due to an AE (pulmonary tuberculosis, mandatory withdrawal criterion).

Laboratory findings

There were no signals for different patterns of common lab chemistry in adolescents, as compared to in adult patients.

With regards to adrenal safety, there were no consistent mean or median changes from baseline in basal cortisol, 17-hydroxyprogesterone and aldosterone levels over the first 48 weeks of treatment. The majority of patients achieved ACTH stimulated cortisol values above the cut-off of 500 nmol/L. However, blood cortisol decreased was reported as a grade 1 AE in 7 (19.4%) patients. The AE was considered possibly related to RPV in 3 (8.3%) patients, doubtfully related to RPV in 2 (5.6%) patients and doubtfully related to ARV background regimen in 2 (5.6%) patients by the investigator (association refuted by MAH - see discussion above).

At the Week 48 analysis cut-off date, the AE had resolved in all but one of these patients, who also had an abnormal ACTH stimulation test since baseline.

Mean and median androstenedione, DHEAS, FSH, LH, progesterone and testosterone values were visually inspected for trends over time; mean and median changes from baseline were generally small and variable in direction.

2.5.1. Discussion on clinical safety

The safety profile in adolescents in general is in line with the known safety profile in adults. However, depression is reported more often in adolescents (19.4%) compared to adults (4.1% in the Phase III controlled trials ECHO and THRIVE). It is likely that this high rate of depression is due to the population under study (HIV-infected adolescents). A direct association with RPV did not emerge from additional data provided by the MAH. Hence, routine risk minimization measures ('blood cortisol decreased', 'depression' and 'insomnia' in section 4.8 of the SmPC) are considered sufficient.

RPV did not seem to have an effect on growth, as a mean increase in height of 2.6 cm was observed during the 48 weeks study period.

2.5.2. Conclusions on clinical safety

The Week 48 safety data of study C213 demonstrated that RPV, administrated at 25 mg qd, in combination with an investigator-selected background regimen of 2 NRTIs, was generally safe and well tolerated in adolescents aged ≥12 to < 18 years.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP and PRAC endorsed the Risk Management Plan version 6.1 with the following content:

Safety concerns

Table Ph 1. Safety concerns

Important Identified Risks	Development of drug resistance Depression
Important Potential Risks	QT interval prolongation Hepatotoxicity Severe skin reactions Lipodystrophy Overdose Off-label use (in adult and paediatric subjects) Bleeding disorders Blood cortisol decreased

Missing Information	Children (<12 years) Pregnancy and breast-feeding women Elderly (≥65 years) Patients with severe hepatic impairment (Child-Pugh score C) Patients with eGFRcreat <50 mL/min/1.73 m² Patients taking unstudied ARV background regimens

Pharmacovigilance plan

Table Ph 2: Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Category 3- Interventional clinical trials				
TMC114HIV3015 A single arm, open label trial to assess the pharmacokinetics of darunavir and ritonavir, darunavir and cobicistat, etravirine, and rilpivirine in HIV-1 infected pregnant women.	To assess the PK of RPV in HIV-1 infected pregnant women.	Missing Information/ -Pregnant and breast-feeding women	Started	Final planned 04Q2016 (RPV cohort)
Category 3- Non-interventional study				

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
MEA 011.1 DUS (PASS) Observational cohort study to assess RPV utilisation according to the European SmPC	To assess the use of EDURANT according to the prescribing information for EDURANT and the development of resistance in routine clinical practice.	Important Identified Risk/ -Development of drug resistance Important Potential Risk/ -Off-label use (in adult and paediatric subjects Missing Information/ -Off-label use (in adult and paediatric subjects -Patients taking unstudied ARV background regimen	Started	Final planned 02Q2019 (interim data described in PSURs/PBRERs)

Risk minimisation measures

Table Ph3. Risk Minimisation Measures

Summary Table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks:		

Summary Table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Development of Drug Resistance	Advice and guidance is provided to the treating physicians in Sections 4.1 (Therapeutic indications), 4.4 (Special warnings and precautions for use) and Section 5.1 (Pharmacodynamic properties) of the SmPC.	None
Depression	Advice and guidance is provided to the treating physicians in Section 4.8 (Undesirable effects) of the SmPC.	None
Important Potential Risks:		
QT Interval Prolongation	Advice and guidance is provided to the treating physicians in Sections 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction) and 4.9 (Overdose) of the SmPC.	None
Hepatotoxicity	Advice and guidance is provided to the treating physicians in Section 4.8 (Undesirable effects) of the SmPC.	None
Severe Skin Reactions	Advice and guidance is provided to the treating physicians in Section 4.8 (Undesirable effects) of the SmPC.	None
Lipodystrophy	Advice and guidance is provided to the treating physicians in Section 4.4 (Special warnings and precautions for use) of the SmPC.	None
Overdose	Advice and guidance is provided to the treating physicians in Sections 4.2 (Posology and method of administration) and 4.9 (Overdose) of the SmPC.	None
Off-label Use (in adult and paediatric subjects)	Advice and guidance is provided to the treating physicians in Sections 4.1 (Therapeutic indications) and 4.2 (Posology and method of administration) of the SmPC.	None
Bleeding Disorders	No information with regard to bleeding disorders is included in the SmPC.	None

Summary Table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Blood Cortisol Decreased	Advice and guidance is provided to the treating physicians in Section 4.8 (Undesirable effects) of the SmPC.	None
Missing Information:		
Children (<12years)	Advice and guidance is provided to the treating physicians in Section 4.2 (Posology and method of administration) of the SmPC.	None
Pregnancy and Breast-feeding Women	Advice and guidance is provided to the treating physicians in Section 4.6 (Fertility, pregnancy and lactation) of the SmPC.	None
Elderly (≥65 years)	Advice and guidance is provided to the treating physicians in Section 4.2 (Posology and method of administration) of the SmPC.	None
Patients with Severe Hepatic Impairment (Child-Pugh score C)	Advice and guidance is provided to the treating physicians in Section 4.2 (Posology and method of administration) of the SmPC.	None
Patients with eGFRcreat <50 mL/min/ 1.73 m²	Advise and guidance is provided to the treating physicians in Section 4.2 (Posology and method of administration) of the SmPC.	None
Patients taking unstudied ARV background regimens	Advice and guidance is provided to the treating physicians in Sections 4.5 (Interactions with other medicinal products and other forms of interactions) and 5.1 (Pharmacodynamic properties) of the SmPC.	None

This medicine has no additional risk minimisation measures.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representative in Denmark in the Package Leaflet.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

Not applicable.

3. Benefit-Risk Balance

Currently, Edurant, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve adult patients with a viral load ≤ 100,000 HIV-1 RNA copies/ml. The MAH submitted a type II variation to extend the indication to include treatment of ARV treatment-naïve paediatric patients aged 12 to <18 years of age, on the basis of a single arm, open-label study performed in 36 patients.

Benefits

Beneficial effects

The pharmacokinetic parameters analysed showed that AUC24h and Ctrough were comparable between adolescents and adults. As a consequence, no differences in efficacy are expected between adolescents and adults. An overall 72% of patients (26/36) reached viral load <50 copies/mL at week 48. As expected, patients starting treatment with a viral load ≤ 100,000 HIV-1 RNA copies/ml (approved indication for RPV) achieved better virologic responses 22/28 (78.6%).

The safety profile of RPV in adolescents was overall comparable to the known safety profile in adults, which is considered favourable. RPV did not appear to affect pubertal development or growth in the adolescents included in the study.

Uncertainty in the knowledge about the beneficial effects

Efficacy results in adolescents were slightly lower compared to those observed in adults, likely linked to sub-optimal adherence. Potential treatment adherence issues should be considered prior to start RPV antiretroviral treatment in adolescents due to the risk for development of resistance, which is adequately reflected in the product information.

Risks

Unfavourable effects

The proportion of patients with virological failure over 48 weeks is substantial (8/36), and in these cases de novo resistance to both the NNRTI- and NRTI-class was frequently observed; such class resistance was seen in 6/8 and 4/8 respectively.

AEs were frequently reported, and approximately 1/3 of the AEs observed were considered as treatment related. However, no new safety issues were identified in the adolescent patient population.

Depression was more frequently observed in adolescents (19.4%) compared to adults (4.1% in the Phase 3 controlled trials).

In non-clinical studies in rats and dogs, RPV appeared to interfere with steroid biosynthesis. In the present

study in adolescents, blood cortisol decreased was reported in 7/36 (19.4%) of patients, compared with 15/686 (2.2%) of patients in the adult pooled Phase 3 studies.

Uncertainty in the knowledge about the unfavourable effects

Depression was more frequently reported in adolescents compared to adults. This is likely linked to the population under study (HIV-1 infected adolescents) being already at higher risk.

Effects Table

Effect	*Short Description*	*Unit*	*Treatment: Rilpivirine 25mg qd*	*Uncertainties / Strength of evidence*	*References*
Favourable Effects					
Virologic response	Proportion of patients with confirmed viral load < 50 HIV-1 RNA copies/ml at week 48	n/N (%)	26/36 (72.2%)	Efficacy results in adolescents (12 to less than 18 years old) were slightly lower compared to those previously observed in adult Phase III studies Week 48 pooled analysis (C209 and C215) (i.e. virologic response was 578/686 (84.3%) and the mean increase from baseline in CD4+ cell count was 192.1 cells/uL) Relatively small sample size (n=36 patients)	Study TMC278-C213
Immuno-logical response	Mean increase from baseline in CD4+ cell count at week 48	Cells /uL (SE)	201.2 (32.87)		
Unfavourable Effects					
RAM	Incidence of RAMs	n/N (%)	6/8 patients with virologic failure (75%)	Relatively small sample size (n=36 patients)	Study TMC278-C213
Cortisol	Proportion of patients presenting blood cortisol decreased from baseline at week 48	n/N (%)	7/36 (19.4%)	In adults it was 15/686 [2.2%] of patients in Phase III studies Week 48 pooled analysis (C209 and C215)	
Depression	Proportion of patients presenting depression at week 48	n/N (%)	7/36 (19.4%)	In adults it was 40/686 [5.8%] patients in Phase III studies Week 48 pooled analysis (C209 and C215)	

Abbreviations: SE=standard error, RAM=resistance associated mutation, qd: Once daily, n= number of observations; N= number of subjects in the study (intention – to treat)

Benefit-Risk Balance

Importance of favourable and unfavourable effects

For extension of the indication to adolescents it is important to show that drug exposure in adolescents is similar to adults.

With regard to unfavourable effects, the development of resistance associated mutations are important, as these may also impact 2nd line ARV treatment options. Moreover, as the target population are adolescents, potential effects on pubertal development or growth are also of importance.

Benefit-risk balance

The pharmacokinetic parameters PK analysed showed comparable exposure in adolescents and adults, which is further supported by the efficacy data. Potential treatment adherence issues should considered prior to start RPV antiretroviral treatment due to the risk for development of resistance.

Discussion on the Benefit-Risk Balance

Rilpivirine is generally efficacious and very well tolerated. However, contrary to the case with several other modern antiretrovirals, the dose and subsequent exposure chosen for rilpivirine does not yield exposures very far above what is necessary for durable antiviral suppression, when used in combination with 2 NRTIs. This is illustrated, e.g., by the lower efficacy in patients with high viral load, which prompted a restriction of the indication to patients with <100,000 copies per mL, as well as by the fact that an exposure-response relation was seen in phase III studies (see Edurant EPAR). Furthermore, rilpivirine requires intake with food in order to achieve adequate bioavailability. Also, the clinical consequences of this relatively small margin to underexposure are aggravated by the low barrier to resistance of the regimen in question, where resistance relevant to both the NNRTI and the NRTI class is generally selected on failure.

Thus, an adequate response to rilpivirine requires a very high adherence to the regimen as such, as well as to recommendations on intake with food. Suboptimal adherence carries a high risk for loss of important future treatment options. It is generally accepted that adolescents in general, as well as HIV-infected adolescents, are challenging to treat successfully due to adherence problems. Due to the loss of important treatment options that may thus be incurred, a positive B/R for the sought, adolescent indication is not self-evident. Appropriate use in adolescents requires careful selection of patients deemed or demonstrated by treatment history to show high adherence levels. This issue has been adequately solved in response to the request for supplementary information (RSI) by including a statement in section 4.4. of the SmPC that "Only adolescents deemed likely to have good adherence to antiretroviral therapy should be treated with rilpivirine, as suboptimal adherence can lead to development of resistance and the loss of future treatment options."

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None
C.I.11.z	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	Type IB	None

Extension of Indication to include treatment of antiretroviral treatment-naïve paediatric patients aged 12 to <18 years of age based on the results of the 48-week data of study TMC278-TiDP38-C213 (PAINT), undertaken to evaluate the pharmacokinetics, safety/ tolerability, and efficacy of rilpivirine 25 mg qd in combination with an investigator-selected background regimen containing two nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs) in this adolescent population. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representative in Denmark in the Package Leaflet. A revised RMP version 6.1 was agreed during the procedure.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).