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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Edurant

rilpivirine

Procedure no: EMEA/H/C/002264/P46/029

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	26 Feb 2023	26 Feb 2023	☐
☐	CHMP Rapporteur Assessment Report	03 Apr 2023	03 Apr 2023	☐
☐	CHMP members comments	17 Apr 2023	17 Apr 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Apr 2023	n/a	☐
☐	CHMP adoption of conclusions:	26 Apr 2023	26 Apr 2023	☐
☐	Submission	23 May 2023	23 May 2023	☐
☐	Re-start	24 May 2023	24 May 2023	☐
☐	CHMP Rapporteur Assessment Report	07 Jun 2023	13 Jun 2023	☐
☐	CHMP members comments	12 Jun 2023	14 Jun 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	15 Jun 2023	n/a	☐
☒	CHMP adoption of conclusions:	22 Jun 2023	22 Jun 2023	☐

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1. Introduction

On 10 February 2023, the MAH submitted a completed paediatric study for Edurant, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that TMC278-TiDP38-C213 (Cohort 2) (Study C213), a Phase II, open-label, single-arm trial to evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of rilpivirine (TMC278) in antiretroviral-naïve HIV-1 infected adolescents and children aged ≥6 to <18 years, is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Two formulations have been used in Study C213, a 25 mg tablet and a dispersable 2.5 mg tablet. The rilpivirine (RPV) 25 mg tablet used in Study C213 is the commercial formulation, which is the same tablet formulation as used in the Phase 3 studies in adults.

For weight-adjusted dosing of rilpivirine (15 mg and 12.5 mg), an age-appropriate oral formulation was developed as tablets for dispersion containing rilpivirine hydrochloride equivalent to 2.5 mg rilpivirine. This 2.5 mg tablet (G009-001) was selected based on the results of a relative bioavailability study in healthy participants and considering manufacturability, dosing accuracy and ease of administration advantages over other formulation concepts.

The study indicated that the bioavailability of 10 x rilpivirine 2.5 mg dispersible tablets was 33% higher compared to 1 x rilpivirine 25 mg commercial tablet when administered at a dose of 25 mg after consumption of a standardised breakfast.

Food Effect

A relative bioavailability study assessed the effect of different food (standardised breakfast, fasted, or yoghurt) and dispersion (water or orange juice) conditions on the rate and extent of absorption of the 2.5 mg tablets in healthy adults. Administration of the 2.5 mg tablets dispersed in water in a fasted state or after yoghurt consumption resulted in a 31% or 28% lower bioavailability compared to administration after a standardised breakfast. These data were similar to the food effect observed for the 25 mg tablets. Participants of Study C213 were instructed to take rilpivirine with the main meal of the day.

A relative bioavailability study showed that administering the dispersible 2.5 mg tablets in orange juice after a standardised breakfast increased the bioavailability by 12% compared to administering the dispersible tablets in water after a standardised breakfast, which is not considered clinically relevant. In addition, a food compatibility study indicated that non-fizzy clean drinking water, apple/orange/cranberry juice, low-fat milk, fizzy water or fizzy drinks (Fanta, Diet Coke, Coca-cola) were appropriate vehicles for dispersion of the 2.5 mg tablets. Participants of Study C213 were allowed to disperse the 2.5 mg tablets in these vehicles.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Cohort 2 for children aged ≥6 to <12 years of the following study:

- TMC278-TiDP38-C213 (Cohort 2): "A Phase II, Open-label, Single-arm Trial to Evaluate the Pharmacokinetics, Safety, Tolerability, and Antiviral Activity of Rilpivirine (TMC278) in Antiretroviral-naïve HIV-1 Infected Adolescents and Children Aged ≥6 to <18 Years (PAINT)".

This report describes all the results for Cohort 2 when all Cohort 2 participants (children ≥6 to <12 years of age) had been treated for at least 48 weeks or had discontinued earlier. Part 1 of the study (after 4 weeks of treatment) evaluated the short-term safety, tolerability, steady-state PK, and antiviral activity of RPV. Part 2 of the study (over at least 48 weeks of treatment) evaluated the safety, tolerability, antiviral activity, immunologic changes, viral genotype, PK, PK/PD relationships (for safety and efficacy), treatment adherence, and palatability of RPV.

2.3.2. Clinical study TMC278-TiDP38-C213 (Cohort 2)

Description

The current study (TMC278-TiDP38-C213, hereafter referred to as C213) was conducted to evaluate the PK, safety, tolerability, and antiviral activity of RPV in antiretroviral treatment naïve, HIV-1 infected adolescents and children ≥6 to <18 years of age in 2 age cohorts: adolescents ≥12 to <18 years of age (Cohort 1) and children ≥6 to <12 years of age (Cohort 2).

The study consisted of a screening period of maximum 8 weeks, an initial treatment period of 48 weeks, and a post-Week 48 treatment extension period of 4 years. With Protocol Amendment 10, the post-Week 48 treatment extension period of 4 years was removed for Cohort 2, children ≥6 to <12 years of age.

When 10 participants with intensive PK data [collected at Week 2, irrespective of body weight]) were enrolled and treated for at least 4 weeks in Study C213, an analysis of RPV PK together with short-term safety and antiviral activity was performed, which was reviewed by the independent data monitoring committee (IDMC). Based on the data, the IDMC agreed with the proposed RPV dose of:

- 25 mg RPV for children with a body weight ≥25 kg;
- 15 mg RPV for children with a body weight <25 kg.

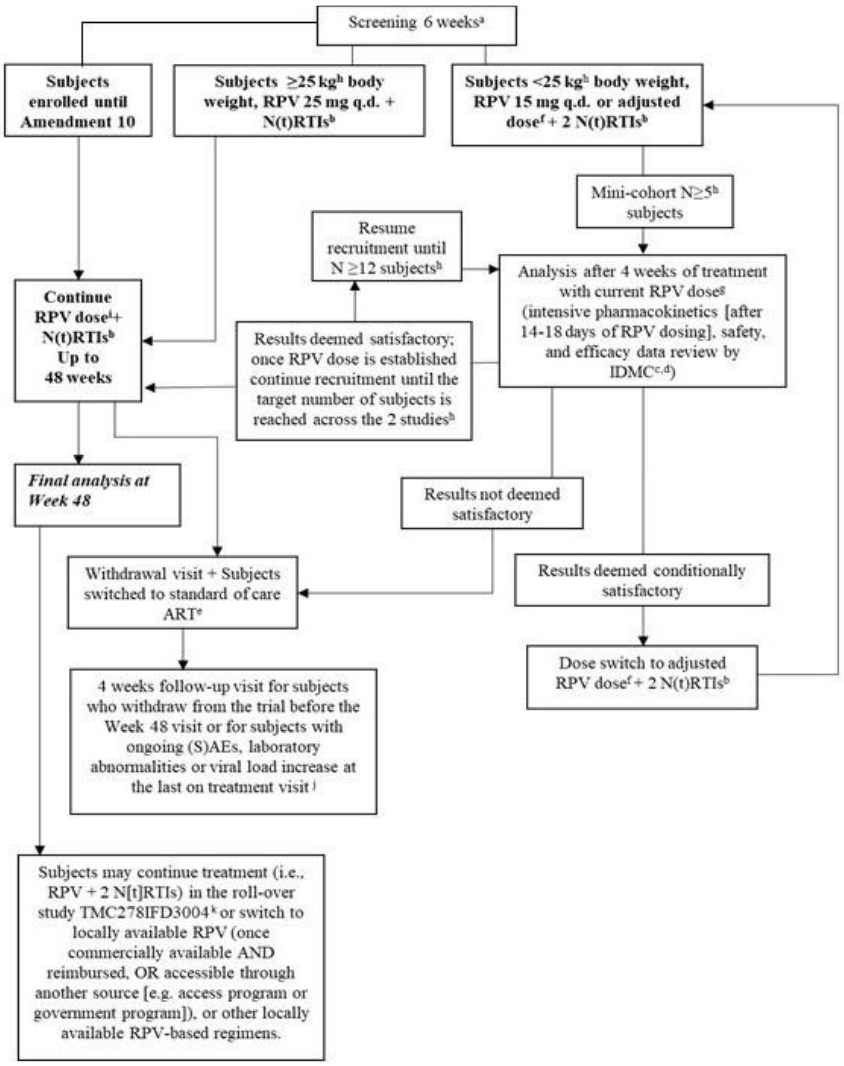
The proposed dose recommendation was included in Protocol Amendment 10 of Study C213. An additional analysis of the available PK data (intensive PK [only collected for participants <25 kg] and sparse PK [collected for all participants from week 2 to week 48 throughout the study]) and all available safety, tolerability and antiviral activity/efficacy data from both Study C213 and HTX2002 (virologically suppressed children aged ≥2 to <12 years) were reviewed by the Sponsor and the IDMC to assess the appropriateness of the dose. Based on these results, the following RPV dose recommendations were applied to any new participant recruited in the ongoing pediatric studies:

- RPV 25 mg qd with food for participants with a body weight of ≥25 kg;
- RPV 15 mg qd (6×2.5 mg tablets) with food for participants with a body weight of ≥20 to <25 kg;
- RPV 12.5 mg qd (5×2.5 mg tablets) with food for participants with a body weight of <20 kg.

Investigators in Study C213 were informed of the dosing recommendations via a Dear Investigator Letter, as allowed per protocol if an adjusted RPV dose is needed after data review by the Sponsor and IDMC.

All newly recruited participants started treatment with the weight-appropriate RPV dose stated above + 2 N(t)RTIs (investigator-selected), until they reached a total treatment duration of 48 weeks, or discontinued earlier. When participants increased in weight such that they changed weight categories, their dose was adjusted as per the dose recommendations mentioned above. The final analysis (including the 48-Week initial treatment and post-Week48 extension periods) was performed when all Cohort 2 participants had reached at least 48 weeks of treatment, rolled over to Study TMC278IFD3004, or discontinued earlier. Participants who withdrew from the study on or before the Week 48 visit or participants with ongoing (S)AEs, laboratory abnormalities, or viral load increase at the last on-treatment visit in the extension were seen for a follow-up visit 4 weeks later.

All ongoing participants in Cohort 2 who were already in the post-Week 48 treatment extension period at the time of Protocol Amendment 10 remained on the RPV 25 mg qd dose + 2 N(t)RTIs (investigator-selected), until their roll-over to Study TMC278IFD3004 had been completed (if applicable). The schematic representation of the study design is presented in Figure 1.



a During the screening period it was allowed to assess the viral load and CD4+ cell count before continuing with the other screening assessments. In such case, after obtaining informed consent, samples were to be 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 participant's clinical situation), the participant was to return within 2 weeks after availability of these results, for the remainder of the screening procedures. In case of unforeseeable circumstances, the screening period could be prolonged by 2 weeks after screening tests had been performed, resulting in a maximum screening period duration of 8 weeks.

b Investigator-selected with a choice limited to AZT, ABC, or TDF in combination with 3TC or FTC, given as a co-formulation or as separate components.

c Participants were to continue their ART during this review period.

d For details on dose evaluation criteria, see Part 1, Section 6.1 (Trial Design) of the protocol (Appendix 1).

e In case Cohort 2 was stopped, a sample was to be analysed in real time for the determination of HIV-1 genotype (as long as the viral load is sufficiently high to allow HIV-1 genotyping), in order to assist in the selection of a new ART. When determination of HIV-1 genotype on this sample was not possible due to a too low viral load, the new ART was to be based on the screening HIV-1 genotyping result.

f All participants who received an RPV dose which was deemed conditionally satisfactory (eg up to a certain body weight) were to receive an adjusted dose and undergo an intensive pharmacokinetic evaluation between 14 to 18 days after starting the adjusted dose. Those that did not need dose adjustment, were to continue their treatment.

g Analysis was to be done combined with applicable data from the HTX2002 study, when all participants had been treated for at least 4 weeks or discontinued earlier with their current RPV dose (original and/or adjusted dose[s]).

h Approximately 40 participants were to be enrolled in Cohort 2 and in paediatric study HTX2002 combined, including at least 12 participants with a body weight <25 kg, with at least 7 participants with a body weight <20 kg.

i Participants were to remain on the RPV dose established with no changes allowed in dosing except for adjustments due to body weight changes, if applicable.

j Additional unscheduled visits could be performed for safety/tolerability reasons and for confirmation of plasma viral load results.

k Any retest of abnormal laboratory results or plasma viral load/resistance testing, was to be captured in this C213 study if the participants rolled over to the TMC278IFD3004 study.

Figure 1: Schematic Overview of Study Design for Cohort 2

Treatments

RPV was formulated as an oral film-coated tablet, containing 27.5 mg of RPV as the hydrochloric acid salt, equivalent to 25 mg of RPV as the free base. The 25 mg RPV tablets were to be swallowed as a whole and could not be chewed, broken, or crushed. For weight-adjusted dosing of RPV (15 mg and 12.5 mg), an age-appropriate formulation was provided in the form of tablets containing rilpivirine hydrochloride equivalent to 2.5 mg rilpivirine. Tablets had to be dispersed prior to use.

Participants received RPV once daily in combination with an investigator-selected background regimen containing 2 N(t)RTIs: AZT, ABC, or TDF in combination with 3TC or FTC (age-appropriate formulations were to be used).

Objective(s)

The objectives for Cohort 2 are:

- To evaluate the steady-state PK (based on intensive PK analysis) of RPV 25 mg qd (for participants with a body weight of ≥25 kg), 15 mg qd (for participants with a body weight of <25 kg), or adjusted dose of RPV (qd) in participants aged ≥6 to <12 years;
- To evaluate short-term safety, tolerability and antiviral activity/efficacy of RPV in this age Group;
- To evaluate safety, tolerability and efficacy of RPV over a 48-week treatment period;

- To evaluate immunologic changes (as measured by CD4+ cell parameters) over 48 weeks of treatment with RPV;
- To assess the evolution of viral genotype and phenotype over 48 weeks of treatment with RPV;
- To evaluate PK (by means of population PK) and PK-PD relationships for safety and efficacy of RPV;
- To evaluate treatment adherence as measured by the Study Adherence Questionnaire for Children and Teenagers.

Outcomes/endpoints

For this CSR, primary endpoints are defined as follows:

- For Part 1 (Week 4):
    - PK parameters (steady-state PK parameters including Cmax, Cmin, AUC24h, Tmax, and CL/F);
- For Part 2 (Week 48):
    - Safety and tolerability of RPV;
    - PK parameters based on sparse sampling.

Secondary endpoints include the following:

- For Part 1 (Week 4): short-term safety and tolerability of RPV.
- For Part 2 (Week 48):
    - Safety parameters (AEs, laboratory parameters [including hematology, biochemistry,and endocrine parameters], vital signs, ECGs and physical examination [including assessment of growth and pubertal development]);
    - Plasma viral load at Weeks 4, 12, 24, and 48;
    - Resistance determination, including:
        - Real-time testing at screening and at any other visit in case of suspected virologic failure (ie, if HIV RNA ≥200 copies/mL after confirmed HIV RNA <50 copies /mL or in case of lack of response);
        - Plasma-based deep sequencing performed retrospectively at screening and at any other visit in case of suspected virological failure;
        - PBMC-based proviral DNA sequencing performed retrospectively at screening and at end of study (ie, upon discontinuation or at Week 48).
    - Change from baseline in CD4+ cell count (cells/µL) and percentage at Week 24 and 48;
    - PK-PD relationships for antiviral activity and safety.

Sample size

No formal sample size calculation was performed. A total of approximately 40 participants were planned to be enrolled in this Cohort 2 (children ≥6 to <12 years of age) and in Study TMC278HTX2002 (further referred to as HTX2002; which enrolled children ≥2 to <12 years of age) combined, including at least 12 participants with a body weight <25 kg, with at least 7 participants with a body weight <20 kg. The total sample size of children ≥6 to <12 years of age to be recruited in Cohort 2 of this study and combined with study HTX2002 was defined based on regulatory requirements. Therefore, the PK data from this Cohort 2 were to be combined with the data from Study HTX2002. At least 12 participants in the body weight category <25 kg with intensive PK data across the 2 studies (Study C213 Cohort 2 and Study HTX2002) was considered sufficient to allow for conclusions on the steady-state exposure of RPV in this group of children.

Randomisation and blinding (masking)

Not applicable, since this is an open-label single-arm study.

Statistical Methods

All enrolled participants (All Enrolled Analysis Set), who received at least 1 dose of RPV will be included in the full analysis set (FAS). The FAS will be used as primary and only population for all analyses; this is also referred to as the All-Participants group.
Efficacy: The efficacy parameters for this study (plasma viral load and CD4+ cell count) were tabulated, analysed descriptively (e.g., n, mean, SD, minimum, median, maximum) and presented graphically. An outcome analysis using the FDA snapshot algorithm was performed, i.e., viral load <50 and <400 HIV-1 RNA copies/mL observed, and missing = failure (M=F), whereby missing viral load (e.g., due to discontinuation) is considered non-responder. The Snapshot analysis was based on the last observed viral load data within the Week 48 window (Window 44 – 50 weeks). CD4+ cell count (absolute and %) was analysed based on observed values and on imputed values. Participants who prematurely discontinued the study had their CD4+ cell count following discontinuation imputed with the baseline value (resulting in a change of 0) and had last observation carried forward for intermediate missing values.

Resistance determinations: Relevant changes in the viral phenotype and genotype and archived resistance, as applicable, were tabulated and described, particularly for participants with (suspected) virologic failure.

Safety: Only treatment-emergent events are described. Adverse events: The AE incidence was tabulated, by dose-weight group and overall, and by SOC and PT. Adverse events were summarised by SOC and PT for SAEs, AEs leading to discontinuation, Grade 3-4 AEs, HIV-related AEs, and AEs at least possibly related to RPV. Adverse events of interest are identified as skin events, neuropsychiatric events, potential QT prolongation-related events, hepatic events, endocrinology events, AIDS-defining illnesses and Stage 3-defining opportunistic infections, and were tabulated by PT.

Treatment Adherence: Treatment adherence is defined based on drug accountability and on the Study Adherence Questionnaire for Children and Teenagers / the Study Adherence Questionnaire for Caregivers. Data were summarised descriptively by dose-weight group and overall.

Pharmacokinetics

The PK related objective of this study was to evaluate the steady state PK (based on intensive PK analysis) of RPV 25 mg qd or adjusted dose of RPV (qd) in subjects aged ≥6 to <12 years.

For this purpose, intensive PK sampling took place for participants receiving multiple qd doses of RPV at 12.5 mg (<20 kg), 15 mg (≥20 to <25 kg), and 25 mg (≥20 to <25 kg or ≥25 kg), after at least 2 weeks (between Day 14 and 18) of treatment with RPV and if a dose adjustment was required, after 14 to 18 days on the adjusted dose. Sparse PK samples were collected from all participants, but those were not described in the Clinical Pharmacology Report since these data will be used for population PK modelling which will be reported separately.

Plasma concentrations of RPV were determined using a LLOQ of 1.00 ng/mL. None of the plasma concentrations of RPV were below the LLOQ. No further information was provided on the bioanalytical method.

Results

Participant flow and recruitment

In Cohort 2 of this open-label, single-arm C213 study, 38 ART-naïve, HIV-1 infected children ≥6 to <12 years of age were screened, and 18 were enrolled and treated with RPV 25 mg qd (body weight of ≥25 kg, or <25 kg if enrolled prior to Protocol Amendment 10), RPV 15 mg qd (body weight of ≥20 to <25 kg) or RPV 12.5 mg qd (body weight of <20 kg) in combination with an investigator-selected background regimen of 2 N(t)RTIs. All participants who received the 25-mg dose took the single 25-mg tablet formulation (see Table 1). All 18 participants that were enrolled (All Enrolled Analysis Set), received at least 1 dose of RPV and were included in the FAS.

Table 1: Participants screened, enrolled, treated: All participants

	12.5 mg qd, <20kg	15 mg qd, 20-<25kg	25 mg qd, <25kg	25 mg qd, >=25kg	All RPV Recommended Dose	All Participants
Number of participants screened						38
Number of screening failures						20 (52.6%)
Reason for screening failures						
Subject did not fulfill all inclusion criteria						
Subject's weight is >= 17 kg.						1 (2.6%)
HIV-1 plasma viral load at screening >= 500 HIV-1 RNA copies/mL but =< 100,000 HIV-1 RNA copies/mL (assayed by RNA polymerase chain reaction [PCR] standard specimen procedure).						11 (28.9%)
Results from the screening HIV-1 genotype demonstrate sensitivity to the selected N(t)RTIs.						2 (5.3%)
Subject did fulfill any exclusion criteria						
Having documented genotypic evidence of NNRTI resistance at screening or from historical data available in source documents,i.e.,>= 1 NNRTI RAM from the following list (IAS-USA NNRTI RAMS and other).						8 (21.1%)
Subject has any currently active AIDS defining illness (Category C conditions according to the Centers for Disease Control and Prevention [CDC] Classification System for HIV-Infection 1993).						1 (2.6%)
Subject has active tuberculosis and/or is being treated for tuberculosis at screening.						1 (2.6%)
Number of participants enrolled	2 (5.3%)	2 (5.3%)	5 (13.2%)	9 (23.7%)	13 (34.2%)	18 (47.4%)
Number of participants enrolled but not treated	0	0	0	0	0	0
Number of participants treated with rilpivirine (FAS[a])	2 (5.3%)	2 (5.3%)	5 (13.2%)	9 (23.7%)	13 (34.2%)	18 (47.4%)

[a] Full analysis set (FAS): all participants who have taken at least 1 dose of rilpivirine, regardless of their adherence with the protocol and adherence to the dosing regimen
Note: The number of screened participants is used as a denominator
Rilpivirine dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations.
RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for >=25kg

Of the 18 participants, 17 (94.4%) participants completed the 48-week treatment period; 1 (5.6%) participant discontinued the study early during the 48-week treatment period due to reaching a virologic endpoint (see Table 2). This participant never reached plasma viral load <50 copies/mL. Of the 17 participants who completed the 48-week treatment period, 12 participants entered the post-Week 48 treatment extension of whom 4 participants discontinued the study early during the post-Week 48 treatment extension period due to reaching a virologic endpoint, and the other 8 participants rolled over to Study TMC278IFD3004 after Week 48 (see Table 3). The remaining 5 participants rolled over to Study TMC278IFD3004 at Week 48. Of the 4 participants who discontinued the study early, 1 was a virologic failure at Week 48, and 3 were virologic responders at Week 48 but reported viral load <50 copies/mL at later time points.

Table 2: Study disposition: Full Analysis Set

	Rilpivirine					
	12.5 mg qd, <20kg	15 mg qd, 20-<25kg	25 mg qd, <25kg	25 mg qd, >=25kg	All RPV Recommended Dose	All Participants
Analysis set: Full Analysis Set	2	2	5	9	13	18
Completed participation of the 48-week initial treatment period[a]	2 (100.0%)	2 (100.0%)	5 (100.0%)	8 (88.9%)	12 (92.3%)	17 (94.4%)
Terminated participation of the 48-week initial treatment period prematurely	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
Reason for termination						
Other*	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
Completed participation of the post week 48 treatment extension period (up to Week 240)	0	1 (50.0%)	3 (60.0%)	4 (44.4%)	5 (38.5%)	8 (44.4%)
Terminated participation of the post week 48 treatment extension period prematurely	0	0	2 (40.0%)	2 (22.2%)	2 (15.4%)	4 (22.2%)
Reason for termination						
Subject reached a virologic endpoint	0	0	2 (40.0%)	2 (22.2%)	2 (15.4%)	4 (22.2%)

[a] Participants who enrolled in the post week 48 treatment extension period are counted as having completed the 48-week initial treatment period
Note: As of the study protocol amendment 10, the post week 48 treatment extension period of 4 years was removed for Cohort 2 participants
Rilpivirine dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations.
*Reason was reported as reaching a virologic endpoint.
RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for >=25kg

Major protocol violations were observed in 2/18 (11.1%) participants. One of these participants (in the 25 mg qd [≥25 kg] dose-weight group) was enrolled but did not satisfy study entry criteria (participant had 1 or more risk factors for QTc prolongation). This participant had a Grade 1 AE of ventricular extrasystoles (verbatim ventricular premature complex), reported at Week 24, which resolved while continuing study treatment after Week 32. The Week 24 ECG showed frequent premature ventricular complexes. No QT abnormalities were observed at Screening and throughout the study. The other participant (in the 25 mg qd [<25 kg] dose-weight group) was listed as having received wrong treatment or incorrect dose (participant had interruptions of study intervention for 67 days [not consecutive] between baseline and Week 48). This participant had overall suboptimal adherence to RPV, was a virologic failure post-Week 48, and discontinued the study at Week 84. In addition, several minor protocol deviations occurred due to COVID-19.

Baseline data

With the exception of age and weight, demographic characteristics were comparable across dose-weight groups. The median age at screening was 9.0 years (range 6 to 11 years). Eight out of 18 (44.4%) participants were in the 6 to <9-year age group and 10/18 (55.6%) participants in the 9 to <12-year age group. The median weight at baseline was 25.0 kg (range 17 to 51 kg). Two out of 18 (11.1%) participants weighed <20 kg, 7/18 (38.9%) participants weighed ≥20 to <25 kg, and 9/18 (50.0%) participants weighed ≥25 kg. (Table 3)

Table 3: Summary of demographic data

	12.5 mg qd, <20kg	15 mg qd, 20-<25kg	25 mg qd, <25kg	25 mg qd, >=25kg	All RPV Recommended Dose	All Participants
Analysis set: Full Analysis Set	2	2	5	9	13	18
Sex, n (%)						
N	2	2	5	9	13	18
Female	1 (50.0%)	1 (50.0%)	2 (40.0%)	3 (33.3%)	5 (38.5%)	7 (38.9%)
Male	1 (50.0%)	1 (50.0%)	3 (60.0%)	6 (66.7%)	8 (61.5%)	11 (61.1%)
Age (years) at screening						
N	2	2	5	9	13	18
Mean (SD)	6.0 (0.00)	6.5 (0.71)	9.2 (0.84)	9.4(1.67)	8.5 (2.07)	8.7 (1.81)
Median	6.0	6.5	9.0	10.0	8.0	9.0
Range	(6; 6)	(6; 7)	(8; 10)	(7; 11)	(6; 11)	(6; 11)
Age (years) (categorical), n (%)						
N	2	2	5	9	13	18

6- <9 years	2 (100.0%)	2 (100.0%)	1 (20.0%)	3 (33.3%)	7 (53.8%)	8 (44.4%)
9- <12 years	0	0	4(80.0%)	6 (66.7%)	6 (46.2%)	10 (55.6%)
Race, n (%)						
N	2	2	5	9	13	18
Asian	0	0	1 (20.0%)	1 (11.1%)	1 (7.7%)	2 (11.1%)
Black or African American	2 (100.0%)	2 (100.0%)	4(80.0%)	8 (88.9%)	12 (92.3%)	16 (88.9%)
Ethnicity, n (%)						
N	2	2	5	9	13	18
Hispanic or Latino	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
Not hispanic or not Latino	2 (100.0%)	2 (100.0%)	5 (100.0%)	8 (88.9%)	12 (92.3%)	17 (94.4%)
Country, n (%)						
N	2	2	5	9	13	18
South Africa	0	0	2 (40.0%)	5 (55.6%)	5 (38.5%)	7 (38.9%)
Thailand	0	0	1 (20.0%)	1 (11.1%)	1 (7.7%)	2 (11.1%)
Uganda	2 (100.0%)	2 (100.0%)	2 (40.0%)	3 (33.3%)	7 (53.8%)	9 (50.0%)
Country/ Study site identifier, n (%)						
N	2	2	5	9	13	18
South Africa / ZA00068	0	0	2 (40.0%)	5 (55.6%)	5 (38.5%)	7 (38.9%)
Thailand / TH00089	0	0	1 (20.0%)	1 (11.1%)	1 (7.7%)	2 (11.1%)
Uganda / UG00006	2 (100.0%)	1 (50.0%)	2 (40.0%)	2 (22.2%)	5 (38.5%)	7 (38.9%)
Uganda / UG00008	0	1 (50.0%)	0	1 (11.1%)	2 (15.4%)	2 (11.1%)
Woman ofchildbearing potential*, n (%)						
N	1	1	2	3	5	7
No	1 (100.0%)	1 (100.0%)	2 (100.0%)	3 (100.0%)	5 (100.0%)	7 (100.0%)
Height (cm) at baseline						
N	2	2	5	9	13	18
Mean (SD)	107.5 (0.71)	124.0 (1.41)	125.3 (5.58)	135.6 (7.28)	129.5 (12.21)	128.3 (10.78)
Median	107.5	124.0	127.5	135.5	131.0	128.3
Range	(107; 108)	(123; 125)	(117; 131)	(126; 150)	(107; 150)	(107; 150)
Weight (kg) at baseline						
N	2	2	5	9	13	18
Mean (SD)	17.0 (0.00)	23.5 (1.06)	23.6 (0.75)	31.4(8.00)	28.0 (8.67)	26.8 (7.57)
Median	17.0	23.5	24.0	30.0	27.0	25.0
Range	(17; 17)	(23; 24)	(23; 24)	(26; 51)	(17; 51)	(17; 51)
Weight (categorical) at baseline, n (%)						
N	2	2	5	9	13	18
< 20 kg	2 (100.0%)	0	0	0	2 (15.4%)	2 (11.1%)
20 - < 25 kg	0	2 (100.0%)	5 (100.0%)	0	2 (15.4%)	7 (38.9%)
>= 25 kg	0	0	0	9 (100.0%)	9 (69.2%)	9 (50.0%)
BMI, (kg/m^2) at baseline						
N	2	2	5	9	13	18
Mean (SD)	14.7 (0.14)	15.3 (1.06)	15.1 (1.50)	16.9 (2.59)	16.3 (2.33)	16.0 (2.17)
Median	14.7	15.3	14.8	16.7	16.0	15.5
Range	(15; 15)	(15; 16)	(14; 18)	(14; 23)	(14; 23)	(14; 23)

Key: BMI= Body Mass Index; NAP= Not applicable
Note: N = number of participants with data, n = number of participants with that observation
Rilpivirine dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations.
RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for >=25kg

* Denominator based on number of females

Median duration of known HIV-1 infection was 0.1 years (range 0 to 6 years). The median baseline plasma viral load was 55,400 (range 567-149,000) copies/mL. Four out of 18 (22.2%) participants had a baseline plasma viral load of >100,000 copies/mL but were eligible to enter the study since they had

≤100,000 copies/mL at screening. Across all participants, the mean (SD) absolute baseline CD4+ cell count was 597.8 (509.37) cells/µL and the median absolute baseline CD4+ cell count was 432.5 (range 12-2,068) cells/µL (see Table 4).

Table 4: Summary of Baseline Disease Characteristics

	12.5 mg qd, <20kg	15 mg qd, 20-<25kg	25 mg qd, <25kg	25 mg qd, >=25kg	Recommended Dose	All Participants
Analysis set: Full Analysis Set	2	2	5	9	13	18
HIV-1 Subtype, n (%) N	2	2	5	9	13	18
A	1 (50.0%)	0	0	0	1 (7.7%)	1 (5.6%)
A/D	1 (50.0%)	0	0	0	1 (7.7%)	1 (5.6%)
A1	0	2 (100.0%)	0	1 (11.1%)	3 (23.1%)	3 (16.7%)
AE	0	0	1 (20.0%)	1 (11.1%)	1 (7.7%)	2 (11.1%)
C	0	0	2 (40.0%)	5 (55.6%)	5 (38.5%)	7 (38.9%)
Complex	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
D	0	0	2 (40.0%)	1 (11.1%)	1 (7.7%)	3 (16.7%)
Mode of HIV infection, n (%)						
N	2	2	5	9	13	18
Mother to child transmission	2 (100.0%)	2 (100.0%)	5 (100.0%)	8 (88.9%)	12 (92.3%)	17 (94.4%)
Other	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
Clinical stage of HIV-infection at screening based on age-specific CD4+ count OR percentage of total lymphocytes, n (%)						
N	2	2	5	9	13	18
Category A (mild symptomatic)	0	1 (50.0%)	2 (40.0%)	3 (33.3%)	4(30.8%)	6 (33.3%)
Category B (moderately symptomatic)	1 (50.0%)	0	0	2 (22.2%)	3 (23.1%)	3 (16.7%)
Category N (not symptomatic)	1 (50.0%)	1 (50.0%)	3 (60.0%)	4(44.4%)	6 (46.2%)	9 (50.0%)
ARV PMTCT during pregnancy, n (%)						
N	2	2	5	8	12	17
No	1 (50.0%)	2 (100.0%)	5 (100.0%)	7 (87.5%)	10 (83.3%)	15 (88.2%)
Not available	1 (50.0%)	0	0	1 (12.5%)	2 (16.7%)	2 (11.8%)
ARV PMTCT at time ofbirth, n (%)						
N	2	2	5	8	12	17
No	2 (100.0%)	2 (100.0%)	5 (100.0%)	7 (87.5%)	11 (91.7%)	16 (94.1%)
Not available	0	0	0	1 (12.5%)	1 (8.3%)	1 (5.9%)
Hepatitis B virus surface antigen, n (%)						
N	2	1	5	9	12	17
Negative	2 (100.0%)	1 (100.0%)	5 (100.0%)	9 (100.0%)	12 (100.0%)	17 (100.0%)
Hepatitis C virus antibody, n (%)						
N	2	1	5	9	12	17
Negative	2 (100.0%)	1 (100.0%)	5 (100.0%)	9 (100.0%)	12 (100.0%)	17 (100.0%)
HIV-1 viral load (copies/mL) at baseline						
N	2	2	5	9	13	18
Mean (SD)	116650.0 (45749.81)	30770.0 (31437.97)	45071.4 (54615.65)	65475.1 (46492.01)	68008.9 (48249.88)	61637.4 (49567.54)
Median	116650.0	30770.0	32500.0	65100.0	65100.0	55400.0
Range	(84300; 149000)	(8540; 53000)	(567; 133000)	(876; 142000)	(876; 149000)	(567; 149000)

HIV-1 viral load (log10 copies/mL) at baseline						
N	2	2	5	9	13	18
Mean (SD)	5.0 (0.17)	4.3 (0.56)	4.1 (1.04)	4.6 (0.67)	4.6 (0.61)	4.5 (0.76)
Median	5.0	4.3	4.5	4.8	4.8	4.7
HIV-1 viral load (categorical) at baseline, n (%)						
N	2	2	5	9	13	18
≤ 100,000 copies/ml	1 (50.0%)	2 (100.0%)	4(80.0%)	7 (77.8%)	10 (76.9%)	14(77.8%)
> 100,000 copies/ml	1 (50.0%)	0	1 (20.0%)	2 (22.2%)	3 (23.1%)	4(22.2%)
CD4+ count (cells/mm^3) at baseline						
N	2	2	5	9	13	18
Mean (SD)	704.5 (218.50)	599.5 (200.11)	612.0 (561.01)	565.8 (615.54)	592.3 (512.39)	597.8 (509.37)
Median	704.5	599.5	407.0	338.0	458.0	432.5
Range	(550; 859)	(458; 741)	(12; 1441)	(107; 2068)	(107; 2068)	(12; 2068)
CD4+ (%) at baseline						
N	2	2	5	9	13	18
Mean (SD)	28.6 (4.10)	24.0 (3.89)	21.6 (16.19)	23.3 (12.11)	24.2 (10.21)	23.5 (11.69)
Median	28.6	24.0	19.1	19.1	25.7	23.5
Range	(26; 32)	(21; 27)	(2; 45)	(8; 40)	(8; 40)	(2; 45)
CD4+ count (binary) at baseline, n (%)						
N	2	2	5	9	13	18
< 350 cells/mm^3	0	0	2 (40.0%)	5 (55.6%)	5 (38.5%)	7 (38.9%)
350 - < 500 cells/mm^3	0	1 (50.0%)	1 (20.0%)	1 (11.1%)	2 (15.4%)	3 (16.7%)
500 - < 750 cells/mm^3	1 (50.0%)	1 (50.0%)	0	1 (11.1%)	3 (23.1%)	3 (16.7%)
≥ 750 cells/mm^3	1 (50.0%)	0	2 (40.0%)	2 (22.2%)	3 (23.1%)	5 (27.8%)
Duration of known HIV infection (years)						
N	2	2	5	9	13	18
Mean (SD)	0.1 (0.06)	0.4(0.56)	0.1 (0.09)	1.4(2.54)	1.0 (2.16)	0.8 (1.87)
Median	0.1	0.4	0.0	0.1	0.1	0.1
Range	(0; 0)	(0; 1)	(0; 0)	(0; 6)	(0; 6)	(0; 6)

Key: ARV= antiretroviral therapy; DAIDS= Division of AIDS; HIV= Human immunodeficiency virus; PMTCT= Prevention Mother to Child Transmission

Note: N = number of participants with data, n = number of participants with that observation

Rilpivirine dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations.

RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for >=25kg

At baseline, all participants used 3TC and 10/18 (55.6%) participants (40-100% per dose-weight group) used 3TC in combination with ABC. Other combinations of ARVs were less frequently used.

The overall mean (SD) duration of exposure to RPV was 100.2 (63.26) weeks. Based on pill count, the mean (SD) RPV treatment adherence for all participants through Week 48 was 98.34% (6.868) and through the end of the study was 98.41% (6.018). All participants had an adherence of at least 65%. The majority of participants (14/18 [77.8%]) had an adherence to RPV treatment >95%. Four out of 18 (22.2%) participants had adherence to RPV treatment ≤95% during the 48-week treatment period: 1 in the 25 mg (≥25 kg) group, 2 in the 25 mg (<25 kg) group (1 of whom had adherence >65% to ≤ 80%), and 1 in the 12.5 mg (<20 kg) group. Of these 4 participants with adherence ≤95%, 3 participants showed a virologic response (viral load <50 copies/mL) at Week 48 (although they reported a viral load >50 copies/mL as of Week 60, Week 72, and Week 120, respectively) and 1 participant was a virologic failure at Week 48 (lack of virologic response).

Number analysed

All 18 participants that were enrolled (All Enrolled Analysis Set), received at least 1 dose of RPV and were included in the FAS. The FAS was used as primary and only population for all analyses.

Pharmacokinetic results

Intensive PK data of Cohort 2 of the C213 study were available for 14 participants receiving multiple qd doses of RPV at 12.5 mg (<20 kg, n=2), 15 mg (≥20 to <25 kg, n=2), and 25 mg (≥20 to <25 kg, n=4 or ≥25 kg, n=6). Moreover, the taste acceptability and palatability of the 2.5 mg RPV tablet dispersed in water was assessed.

A summary list of key PK parameters of RPV per dose-weight category is presented in Table 5. A visual comparison of C_{max} and AUC_{24h} is shown in Figure 2. After multiple oral dose administrations of RPV at 12.5 mg qd, 15 mg qd or 25 mg qd, individual t_{max} ranged from 0 to 9 hours. The mean C_{0h}, C_{min}, C_{max} and AUC_{24h} after multiple oral dosing of RPV at a recommended dose of 25 mg qd (≥25 kg) were 121 ng/mL, 73.2 ng/mL, 154 ng/mL and 2,610 ng.h/mL, respectively.

Individual values after multiple dosing of RPV at recommended doses of 12.5 mg qd (≥10 to <20 kg) and 15 mg qd (≥20 to <25 kg) were similar to these mean values considering the SD observed at 25 mg qd ≥25 kg), while mean C_{max} and AUC_{24h} were slightly higher at a higher dose of 25 mg qd in the ≥ 20 to <25 kg weight group.

Table 5: Pharmacokinetic results of RPV after multiple oral administration of RPV at 12.5, 15, and 25 mg once daily (Study TMC278-TiDP38-C213: Pharmacokinetics Data Analysis Set)

Pharmacokinetics of RPV (mean [SD][a], t_{max}: median [range][a])	**RPV 12.5 mg qd ≥10 to <20 kg**	**RPV 15 mg qd ≥20 to <25 kg**	**RPV 25 mg qd ≥20 to <25 kg**	**RPV 25 mg qd ≥25 kg**
n	2[b]	2	4[c]	6[d]
C_{0h} (ng/mL)	66.5; 93.8	39.8; 122	115 (63.6)	121 (66.1)
C_{24h} (ng/mL)	123; -	43.3; 90.7	52.8; 160	85.5 (33.5)
C_{min} (ng/mL)	55.5; 77.9	39.8; 90.7	82.5 (56.3)	73.2 (26.7)
C_{max} (ng/mL)	81.9; 156	138; 184	238 (160)	154 (52.2)
$C_{ss,av}$ (ng/mL)	71.1; 123	80.6; 119	138 (91.1)	111 (35.0)
t_{max} (h)	4.07; 6.00	2.00; 6.00	4.50 (3.95 - 5.00)	2.98 (0.00 - 9.03)
AUC_{24h} (ng.h/mL)	1710; 2958	1933; 2877	3339 (2233)	2610 (776)
CL/F (L/h)	4.23; 7.31	5.21; 7.76	11.6 (8.84)	10.3 (3.20)
V_{ss}/F (L)	-	139; 307	53.3; 605	300 (142)
FI (%)	37.1; 63.5	78.1; 122	113 (57.9)	72.0 (22.8)

[a] Individual values are shown for n<3; [b] n=1 for C_{24h} and n=0 for V_{ss}/F; [c] n=2 for C_{24h} and V_{ss}/F; [d] n=3 for V_{ss}/F.
Cross reference: Clinical Pharmacology Report

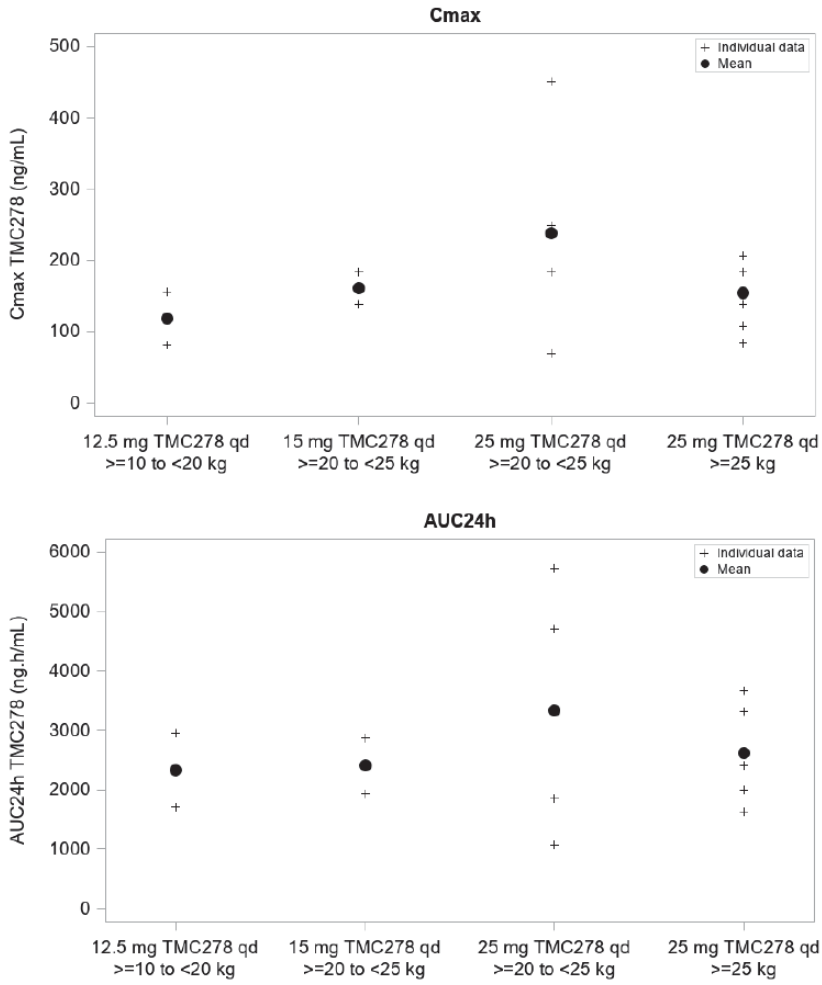


Figure 2: Pharmacokinetic parameters of RPV after multiple oral administration of RPV at 12.5, 15, and 25 mg once daily (Study TMC278-TiDP38-C213: Pharmacokinetics Data Analysis Set)

According to the Applicant, RPV PK data derived from the population PK model developed based on pediatric data (studies C213 and HTX2002) and adult data (intensive PK substudies C209 and C215) and a comparison between paediatric and adult exposures are described in a separate population PK report. The population report was however indicated to be in preparation and was not provided in this procedure.

Efficacy results

Based on the FDA Snapshot algorithm, virologic response (defined as plasma viral load <50 copies/mL) in the All-Participants group at Week 48 was achieved in 13/18 (72.2%) participants, while virologic failure was observed in 3/18 (16.7%) participants. When considering virologic response as plasma viral load <400 copies/mL, 15/18 (83.3%) participants were virologic responders, while 1/18 (5.6%) participant was a virologic failure at Week 48. Two out of 18 (11.1%) participants in the 15 mg qd (20 to ≤25 kg) dose group had missing viral load data at Week 48 but remained on study. The latest available viral load for these 2 participants was <50 copies/mL, ie, <20 copies/mL (target not detected) post-Week 48 and 22 copies/mL prior to Week 48, respectively (see Table 6).

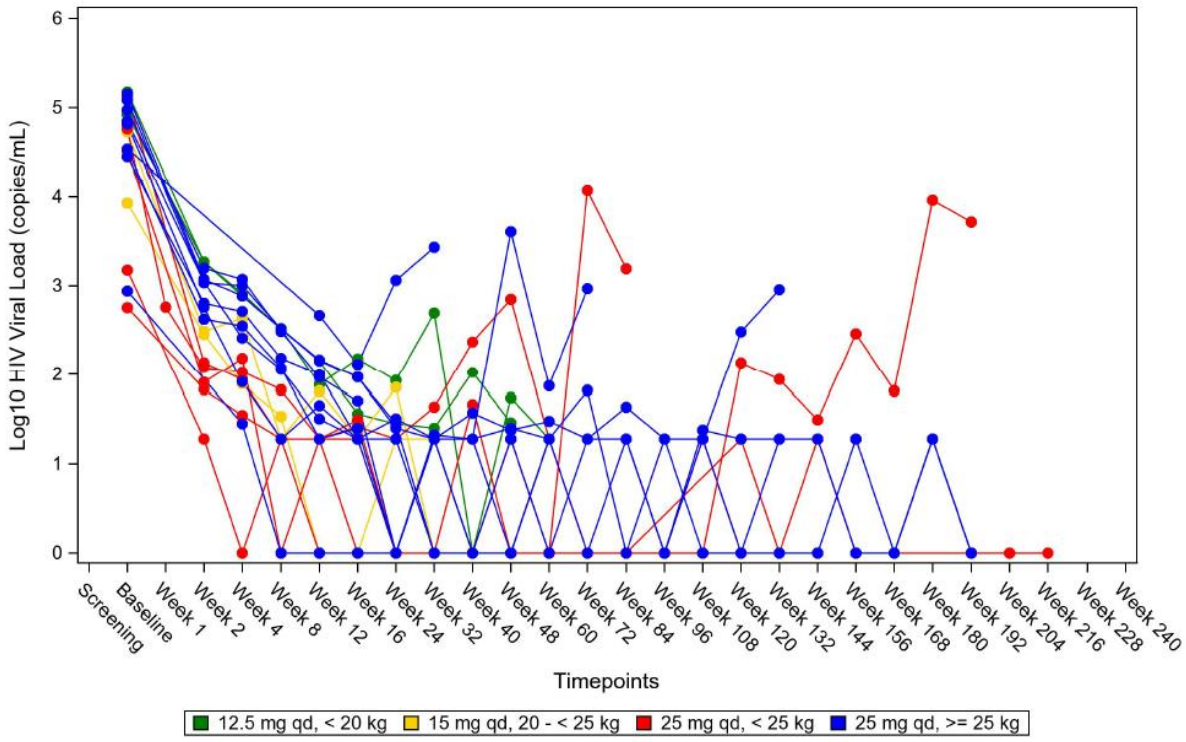
Table 6: Virologic Outcome for the 48-week initial treatment period (snapshot approach) by Dose-Weight group

	rilpivirine					
Analysis set: Full Analysis Set	12.5 mg qd, <20kg 2	15 mg qd, 20-<25kg 2	25 mg qd, <25kg 5	25 mg qd, >=25kg 9	All RPV Recommended Dose 13	All Participants 18
Snapshot Outcome (<50 copies/ml) 48-week initial treatment period, n(%) (95% CI)						
N	2	2	5	9	13	18
Virologic Response (< 50 copies/mL)	1 (50.0%) (1.26;98.74)	0	4 (80.0%) (28.36;99.49)	8 (88.9%) (51.75;99.72)	9 (69.2%) (38.57;90.91)	13 (72.2%) (46.52;90.31)
Virologic Failure	1 (50.0%) (1.26;98.74)	0	1 (20.0%) (0.51;71.64)	1 (11.1%) (0.28;48.25)	2 (15.4%) (1.92;45.45)	3 (16.7%) (3.58;41.42)
HIV RNA ≥ 50 copies/mL	1 (50.0%) (1.26;98.74)	0	1 (20.0%) (0.51;71.64)	0	1 (7.7%) (0.19;36.03)	2 (11.1%) (1.38;34.71)
Virologic failure - leading to discontinuation	0	0	0	0	0	0
Virologic failure – discontinued due to other reason[a] and last available HIV RNA ≥ 50 copies/mL	0	0	0	1 (11.1%) (0.28;48.25)	1 (7.7%) (0.19;36.03)	1 (5.6%) (0.14;27.29)
Virologic failure - switch in background regimen not permitted by the protocol	0	0	0	0	0	0
No viral load data in time window	0	2 (100.0%) (15.81;100)	0	0	2 (15.4%) (1.92;45.45)	2 (11.1%) (1.38;34.71)
Missing data during window but on study	0	2 (100.0%) (15.81;100)	0	0	2 (15.4%) (1.92;45.45)	2 (11.1%) (1.38;34.71)
Discontinued due to other reason and last available HIV RNA < 50 copies/mL	0	0	0	0	0	0
Discontinued due to AE/death	0	0	0	0	0	0
Snapshot Outcome (<400 copies/ml) 48-week initial treatment period, n(%) (95% CI)						
N	2	2	5	9	13	18
Virologic Response (< 400 copies/mL)	2 (100.0%) (15.81;100)	0	5 (100.0%) (47.82;100)	8 (88.9%) (51.75;99.72)	10 (76.9%) (46.19;94.96)	15 (83.3%) (58.58;96.42)
Virologic Failure	0	0	0	1 (11.1%) (0.28;48.25)	1 (7.7%) (0.19;36.03)	1 (5.6%) (0.14;27.29)
HIV RNA ≥ 400 copies/mL	0	0	0	0	0	0
Virologic failure - leading to discontinuation	0	0	0	0	0	0
Virologic failure – discontinued due to other reason[a] and last available HIV RNA ≥ 400 copies/mL	0	0	0	1 (11.1%) (0.28;48.25)	1 (7.7%) (0.19;36.03)	1 (5.6%) (0.14;27.29)
Virologic failure - switch in background regimen not permitted by the protocol	0	0	0	0	0	0
No viral load data in time window	0	2 (100.0%) (15.81;100)	0	0	2 (15.4%) (1.92;45.45)	2 (11.1%) (1.38;34.71)
Missing data during window but on study	0	2 (100.0%) (15.81;100)	0	0	2 (15.4%) (1.92;45.45)	2 (11.1%) (1.38;34.71)
Discontinued due to other reason and last available HIV RNA < 400 copies/mL	0	0	0	0	0	0
Discontinued due to AE/death	0	0	0	0	0	0

Key: CI = Clopper-Pearson confidence interval
Note: N = number of participants with data, n = number of participants with that observation
Rilpivirine dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations.
RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for >=25kg

a Other reason specified as reaching a virologic endpoint.

Virologic response rate increased until Week 32, with 16/18 (88.9%) participants considered to be virologic responder at that time point, and decreased thereafter. When considering virologic response as plasma viral load <400 copies/mL, peak virologic response occurred at Week 16 (18/18; 100% participants) and remained stable through Week 40 (ranging from 16 [88.9%] to 17 [94.4%] participants), before declining at Week 48. The mean (SE) change from baseline in plasma viral load was -2.2 (0.13) log10 at Week 4, -3.0 (0.14) log10 at Week 12, -3.6 (0.21) log10 at Week 24, and -3.5 (0.32) log10 at Week 48. A graphical representation of the individual viral load profiles is provided in Figure 3.



Note: Values <20 copies/mL with HIV-1 RNA detected are scored as log10(19)=1.279; no HIV-1 RNA detected as log10(1)=0

Note: log10(50)=1.7 and log10(400)=2.6

Figure 3: Graphical representation of Individual Viral load (log 10 copies/ML) profiles by Dose-Weight group

The mean increase (SE) in CD4+ cell count from baseline was 163.9 (49.16) cells/µL,304.7 (113.01) cells/µL, and 215.9 (62.42) cells/µL at Weeks 24, 32, and 48, respectively. The mean change from baseline (SE) in CD4% was 6.6 (0.89) at Week 24 and 8.2 (1.44) at Week 48.

For all 18 enrolled participants, standard (PhenoSense) genotypic and phenotypic data were available at screening and baseline. According to the phenotypic analysis at screening and baseline, all 18 participants were susceptible to RPV and all were susceptible to their NRTI backbone regimen. For 8 participants PBMC-based proviral DNA sequencing results were available at screening. One participant with archived NNRTI RAM K101K/Q did not reach undetectable plasma viral load (<50 copies/mL) and withdrew from the study at Week 32. The participant with archived M184I/M at screening had undetectable HIV-1 viral load from Week 12 onwards.

Of the 6 participants with post-baseline standard genotypic data, 2 participants were reported with virologic failure (i.e., lack or loss of virologic response), 3 participants met suspected virologic failure criteria only, and 1 participant did not meet (suspected) virologic failure criteria. Five of these participants had available viral load data at baseline: 2 of these participants had a baseline viral load ≥ 100,000 copies/mL of whom 1 also had overall suboptimal adherence; 1 other participant only had overall suboptimal adherence. The 2 participants with suboptimal adherence and post-baseline genotypic data experienced SVF at Week 60 and Week 72, respectively.

Five out of the 6 participants mentioned above had treatment-emergent RPV RAMs (1/2 VFs, 3/3 SVFs, and 1 non-[S]VF) and 4 carried treatment-emergent NRTI RAMs (3/3 SVFs and 1 non-[S]VF). The vast majority of NNRTI and NRTI RAMs observed at screening, Week 48 or early withdrawal, by plasma-based standard sequencing were confirmed using plasma-based deep sequencing. Data obtained

retrospectively at Screening and post-Baseline using plasma-based deep sequencing were generally consistent with the results obtained through standard plasma-based or PBMC-based proviral DNA sequencing.

Safety results

No Grade 3 or 4 adverse events (AEs), no serious AEs (SAEs), no AEs leading to study drug discontinuation, and no deaths were reported during this study in the 48-week treatment period and in the post-Week 48 treatment extension period. A summary of AEs by dose-weight group and by study phase is presented in Table 7.

Table 7: Overall Summary of Treatment Emergent Adverse Event by Dose-Weight Group

	12.5 mg qd, <20kg	15 mg qd, 20-<25kg	25 mg qd, <25kg	25 mg qd, >=25kg	All RPV Recommended Dose	All Participants
Analysis set: Full Analysis Set	2	2	5	9	13	18
48-week initial treatment period:						
Participants, n (%)	2	2	5	9	13	18
with at least one AE	2 (100.0%)	2 (100.0%)	5 (100.0%)	8 (88.9%)	12 (92.3%)	17 (94.4%)
with a DAIDS grade 1 AE or mild AE	2 (100.0%)	2 (100.0%)	5 (100.0%)	6 (66.7%)	10 (76.9%)	15 (83.3%)
with a DAIDS grade 2 AE or moderate AE	0	0	2 (40.0%)	6 (66.7%)	6 (46.2%)	8 (44.4%)
with an AE which is related[a] to RPV	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
with an AE which is possibly related to background regimen	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
with an AE which is related[a] to background regimen	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
Post Week 48 treatment extension period:						
Participants, n (%)	0	1	5	6	7	12
with at least one AE	0	1 (100.0%)	2 (40.0%)	4 (66.7%)	5 (71.4%)	7 (58.3%)
with a DAIDS grade 1 AE or mild AE	0	1 (100.0%)	2 (40.0%)	2 (33.3%)	3 (42.9%)	5 (41.7%)
with a DAIDS grade 2 AE or moderate AE	0	0	1 (20.0%)	3 (50.0%)	3 (42.9%)	4 (33.3%)
with a DAIDS grade 2, 3 or 4 AE	0	0	1 (20.0%)	3 (50.0%)	3 (42.9%)	4 (33.3%)
Treatment phase:						
Participants, n (%)	2	2	5	9	13	18
with at least one AE	2 (100.0%)	2 (100.0%)	5 (100.0%)	8 (88.9%)	12 (92.3%)	17 (94.4%)
with a DAIDS grade 1 AE or mild AE	2 (100.0%)	2 (100.0%)	5 (100.0%)	7 (77.8%)	11 (84.6%)	16 (88.9%)
with a DAIDS grade 2 AE or moderate AE	0	0	2 (40.0%)	6 (66.7%)	6 (46.2%)	8 (44.4%)
with a DAIDS grade 2, 3 or 4 AE	0	0	2 (40.0%)	6 (66.7%)	6 (46.2%)	8 (44.4%)
with an AE which is possibly related to RPV	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
with an AE which is related[a] to RPV	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
with an AE which is possibly related to background regimen	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)
with an AE which is related[a] to background regimen	0	0	0	1 (11.1%)	1 (7.7%)	1 (5.6%)

Key: AE= adverse event; DAIDS = Division of AIDS; RPV = rilpivirine; SAE= serious adverse event. Rilpivirine dose group is determined by the initial administered dose, irrespective of subsequent dose-alterations. RPV Recommended dose: 12.5mg qd for <20kg, 15mg qd for 20-<25kg, 25mg qd for >=25kg

a An AE is categorised as related if assessed by the investigator as possibly, probably, or very likely related to study treatment OR background regimen.

Note: n = number of participants with that particular AE; % = percentage of participants with that particular AE against the total number of participants.

Note: Denominator for post-Week 48 treatment extension period is the number of participants who enrolled in this treatment period.

In the 48-week treatment period, 17/18 (94.4%) participants were reported with AEs. The most commonly reported AEs (in ≥2 participants overall) were upper respiratory tract infection (12/18 [66.7%] participants), and otitis media, decreased appetite, anaemia, diarrhoea, vomiting, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, cough, and rash (2/18 [11.1%] participants). In the post-Week 48 extension period, 7/12 (58.3%) participants were reported with AEs. Upper respiratory tract infection was the only AE reported in more than 1 participant (5/12 [41.7%] participants).

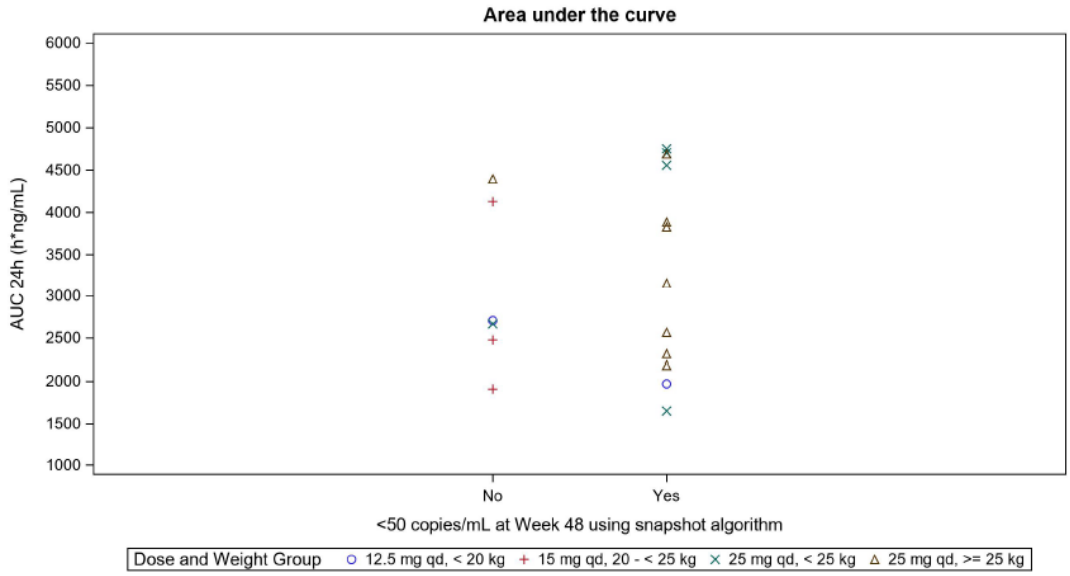
AEs that were considered by the investigator as possibly related to RPV included non-serious Grade 1 ALT increased and Grade 1 AST increased, both reported in the same participant, in the 25 mg qd (≥25 kg) dose-weight group in the 48-week treatment period. No action was taken as a result of the events, which resolved spontaneously during the 48-week treatment period. The participant continued receiving RPV and rolled over to Study TMC278IFD3004. No other AEs were considered by the investigator to be at least possibly related to RPV during the study. One AE of upper respiratory tract infection was documented as HIV-related event in the eCRF in a participant in the 25 mg qd, <25 kg dose-weight group in the 48-week treatment period. No other AEs were considered to be HIV-related during the study.

No clinically relevant changes from baseline were identified for any of the laboratory parameters examined in the study.

No increases from baseline in QTcF or QTcB by >60 msec or increases >480 msec were reported at any time point during the study. Three (16.7%) participants each had a worst increase in QTcB and QTcF from baseline of 30 to ≤60 msec, but these increases did not lead to QTcF intervals out of range. In one participant, the QTcB increase was reported as a Grade 2 AE. No clinically relevant abnormalities were reported for other ECG parameters (HR, PR, QRS, and RR interval).

Pharmacokinetic/Pharmacodynamic Relationships

Scatter plots of individual RPV AUC_{24h} by virological response, defined as achieving a plasma viral load <50 copies/mL or <400 copies/mL are shown in Figure 4. Overall virologic response rate at Week 48, defined as achieving a plasma viral load <50 copies/mL, was high and there was no clear relationship between RPV PK and this efficacy parameter of interest within the observed RPV exposure range.



Note: Includes all PK parameter values (1 per dose) for participants who switched dose during the study (due to weight-changes or otherwise). For 1 participant, no PK parameters could be derived due to missing PK concentrations throughout the study.

Figure 4. Scatterplot of individual AUC24h by virologic response HIV RNA < 50 copies/mL at week 48; Full Analysis Set (Study TMC278-TiDP38-C213)

Within the observed RPV exposure range, no clear relationship was observed between RPV PK and safety parameters of interest, including occurrence of adverse events of interest or QTcF abnormalities, changes in laboratory parameters of interest, and changes in QTcF interval.

2.3.3. Discussion on clinical aspects

The results of Study C213 (Cohort 2) presented in this submission indicate that RPV, combined with an investigator-selected background regimen, is efficacious in HIV-1 infected treatment-naïve children ≥6 to <12 years of age. The study population represents a treatment-naïve HIV-1 infected population of children ≥6 to <12 years of age eligible for ART. RPV was evaluated in this single-arm open-label trial in combination with varying background regimens of 2 N(t)RTIs, which is representative for standard of care.

Based on the data for the subpopulation for which intensive PK sampling was applied, the applied weight-dependent qd dose of 12.5 mg, 15 mg, 25 mg or 25 mg for children ≥6 to <12 years of age weighing <20 kg, ≥20 to <25 kg, ≥20 to <25 kg or ≥25 kg, respectively, yielded similar C_{max} and AUC_{24h} across all weight groups at the recommended doses.

With respect to exposure-effect, the overall virologic response rate at Week 48, defined as achieving a plasma viral load <50 copies/mL, was high and there was no clear relationship between RPV PK and this efficacy parameter of interest within the observed RPV exposure range. The observed efficacy (virologic response: VL <50 copies/mL, 72.2%) is comparable to what has been observed in this study as part of cohort 1 (12-18-year-olds, 72.2%). Three (16.7%) participants showed virologic failure within the 48-week time frame (>50 copies/mL), and only one of these participants had a viral load of>400 copies/mL.

The MAH indicated that one participant discontinued the study early during the 48-week treatment period due to reaching a virologic endpoint, however Table 10 of the CSR indicates "other reason specified as reaching a virologic endpoint". The MAH indicates this participant never reached plasma viral load <50 copies/mL.

The safety data indicate that RPV was generally safe and well tolerated when administered in combination with an investigator-selected background regimen of 2 NRTIs in HIV-1 infected treatment-naïve children ≥6 to <12 years of age. There were no new relevant safety findings compared with the known RPV safety profile in HIV-1 infected adults and adolescents. There was a non-serious Grade 1 ALT increased and Grade 1 AST increased, both reported in the same participant, which was considered by the investigator as possibly related to RPV. "Increased transaminases" is a known ADR listed in section 4.8 of the SmPC. Within the observed RPV exposure range, no clear relationship was observed between RPV PK and safety parameters of interest, including the occurrence of adverse events (AEs) of interest or QTcF abnormalities, changes in laboratory parameters of interest, and changes in QTcF interval.

PK information provided so far was only based on the limited number of subjects for which intensive sampling was applied. A more elaborate comparison of RPV exposure in children ≥6 to <12 years of age using popPK analysis will be provided in the future Type II variation. In this popPK analysis, the potential consequences of the 33% higher bioavailability of the dispersible 2.5 mg tablets (10x) as compared to the 25 mg tablet should be included as a potential covariate.

Information on the analytical method used for quantification of plasma levels of RPV was already provided in a previous procedure.

3. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The timetable is a 30 day response timetable with clock stop.

1. PK information provided so far from Study TMC278-TiDP38-C213- Cohort2 was only based on the limited number of subjects for which intensive sampling was applied. A more elaborate comparison of RPV exposure in children ≥6 to <12 years of age and other populations using popPK analysis, as announced by the Applicant, should be provided. In this popPK analysis, the potential consequences of the 33% higher bioavailability of the dispersible 2.5 mg tablets (10x) as compared to the 25 mg tablet should be included as a potential covariate.
2. Information on the validation of the analytical method used for the quantification of plasma levels of RPV and the bioanalytical report for Study TMC278-TiDP38-C213- Cohort2 should be provided.
3. The protocol and CSR provides different definitions concerning loss of response (<400 copies/mL and <50 copies/mL). The MAH is asked to clarify the used definition for the provided analyses and to specify if deviations were made from the original protocol.
4. The MAH is requested to commit to filing a Type II variation to include relevant efficacy and PK data of this paediatric study in the SmPC.

MAH responses to Request for supplementary information

QUESTION 1

PK information provided so far from Study TMC278-TiDP38-C213- Cohort2 was only based on the limited number of subjects for which intensive sampling was applied. A more elaborate comparison of RPV exposure in children ≥6 to <12 years of age and other populations using popPK analysis, as announced by the Applicant, should be provided. In this popPK analysis, the potential consequences of

the 33% higher bioavailability of the dispersible 2.5 mg tablets (10x) as compared to the 25 mg tablet should be included as a potential covariate.

Applicant's response

The MAH intends to provide a more elaborate comparison of paediatric versus adult PK data in the Grouped Line Extension / Type 2 variation (T2V) submission for use of RPV in paediatrics, planned to be submitted by the end of July 2023. This comparison is supported by a population PK model built with intensive and sparse PK data obtained in paediatric patients who participated in studies TMC278-C213 (Cohort 1 and 2) and TMC278HTX2002, and with intensive PK data from adult patients who participated in the PK substudies TMC278-C209 and TMC278-C215. The population PK model addresses the evaluation of potential covariates, including the higher bioavailability of the dispersible tablet (2.5 mg x10) as compared to the 25 mg tablet.

Assessment of response

The applicant indicates that a more elaborate comparison of paediatric versus adult PK data will be provided in the future Type II variation. This is agreed, issue resolved.

QUESTION 2

Information on the validation of the analytical method used for the quantification of plasma levels of RPV and the bioanalytical report for Study TMC278-TiDP38-C213- Cohort2 should be provided.

Applicant's response

The validation report of the analytical method used for the quantification of plasma levels of RPV has previously been submitted in procedure EMEA/H/C/00264/II/024 in December 2016 (Mod5.3.1.4/TMC278-C213-Cohort2-W48 Method Validation Report BA1674). The bioanalytical report for TMC278-C213 (Cohort 2) is submitted as part of this response in Mod5.3.5.2/TMC278-C213-Cohort2-W48 CSR/Bioanalytical Study Summary.

Assessment of response

The validation report of the analytical method was previously provided. It is advised to include the validation report in the eCTD for the future type II variation. Issue resolved.

QUESTION 3

The protocol and CSR provides different definitions concerning loss of response (<400 copies/mL and <50 copies/mL). The MAH is asked to clarify the used definition for the provided analyses and to specify if deviations were made from the original protocol.

Applicant's response

Rationale

Indeed, different thresholds were applied, ie. 400 copies/mL HIV-RNA in the CTP and 400 or 50 copies/mL HIV-RNA in the CSR. 'Loss of response' in the protocol was used for the purpose of participant monitoring, more specifically in Section 6.2.5 pertaining to (potential) withdrawal of participant from treatment and the study. For the analysis, the following more stringent definition was used in the context of resistance analysis (cfr. SAP section 6.2.1):

Loss of response:

- Two consecutive measurements of ≥400 HIV-1 RNA copies/mL after having been confirmed virologic responder.
- Confirmed responder is defined as two consecutive measurements of <50 copies/mL.

No protocol deviations were made in terms of participant management (Section 6.2.5 of the CTP) or efficacy statistical analyses (Section 6.6.2.2.).

Assessment of response

The applicant confirms the use of different thresholds for loss of response for patient monitoring and statistical analyses. For the analysis loss of response was defined as two consecutive measurements of ≥400 HIV-1 RNA copies/mL after having been confirmed virologic responder (two consecutive measurements of <50 copies/mL). The clarification is considered acceptable; hence this issue is resolved.

QUESTION 4

The MAH is requested to commit to filing a Type II variation to include relevant efficacy and PK data of this paediatric study in the SmPC.

Applicant's response

The MAH commits to filing a Grouped Line Extension / Type II variation (including the popPK model) to include relevant efficacy and PK data of both paediatric studies TMC278-TiDP-C213 Cohort 2 and TMC278HTX2002 in the SmPC and plans to submit by the end of July 2023.

Assessment of response

The applicant confirms to submit a Type II variation to update the SmPC with the relevant data from this p46 procedure. The issue is considered resolved.

4. Rapporteur's overall conclusion and recommendation

The paediatric development to support the use of oral RPV in HIV-1 infected children aged ≥2 to <12 years consists of the completed Study C213 in ARV treatment-naïve children aged ≥6 to <12 years (Cohort 2), and ongoing Study TMC278HTX2002 in virologically suppressed children aged ≥2 to <12 years. The MAH states that results from both studies will be combined to accommodate regulatory requirements.

Information on the RPV PK in the subset of children ≥6 to <12 years of age for which intensive sampling was applied was provided. Similar C_{max} and AUC_{24h} were observed across all weight groups at the recommended doses of 12.5 mg, 15 mg, 25 mg or 25 mg qd for children weighing <20 kg, ≥20 to <25 kg, ≥20 to <25 kg or ≥25 kg, respectively. There was no clear relationship between RPV PK and the plasma viral load <50 copies/mL efficacy parameter, nor between RPV PK and safety parameters.

PK information provided so far was only based on the limited number of subjects for which intensive sampling was applied. A more elaborate comparison of the RPV exposure in children ≥6 to <12 years of age by means of popPK analysis will be provided in a future Type II variation.

Information on the analytical method used for the quantification of plasma levels of RPV was provided in a previous procedure. It is advised to include the validation report in the eCTD for the future type II variation.

Although this is a single-arm open-label trial, based on the provided safety data, RPV seems generally safe and well tolerated when administered in combination with an investigator-selected background regimen of 2 NRTIs in HIV-1 infected treatment-naïve children ≥6 to <12 years of age, especially in relation to available safety data in older age groups. In addition, virologic response rates above <50 copies/mL and <400 copies/mL were respectively 72.2% and 83.3%, which is in line with expectations.

☒ Fulfilled:

In view of the available data regarding the efficacy and PK data of this paediatric study, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.