Rilpivirine pharmacokinetics in HIV-1-infected adolescents: a substudy of PAINT (Phase II trial)

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Introduction

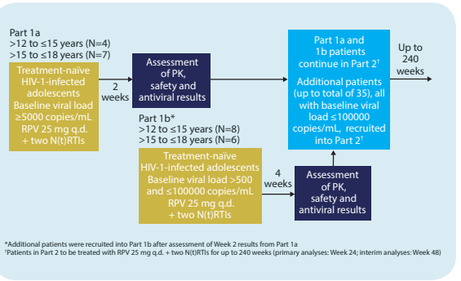
- The NNRTI rilpivirine (RPV, TMC278) combined with other antiretrovirals (ARVs) is approved for use in treatment-naïve, HIV-1-infected adults with a viral load ≤100000 copies/mL and is available as a single-agent tablet (EDURANT®)[1–5] and as a single-tablet regimen (i.e. emtricitabine plus RPV plus tenofovir disoproxil fumarate; COMPLERA®; EVIPLERA®).[6,7]
- As for adults, a combination of three ARVs, from at least two ARV classes, is recommended for ARV treatment-naïve HIV-1-infected children and adolescents[8,9]
  - However, management of HIV-1-infected pediatric patients is clinically challenging for several reasons, such as:
    - Medication nonadherence (particularly in adolescents)[10,11] due to pill burden, lack of support, substance abuse etc[12]
    - Availability of age-appropriate formulations to ensure appropriate drug exposure[8,13,14]
    - Differences in pharmacokinetics between children and adults,[15] which can impact efficacy and safety[16]
  - The NNRTIs, efavirenz and nevirapine, combined with other ARVs, are approved for use in ARV treatment-naïve, HIV-1-infected pediatric patients (i.e. ≥3 months/≥3.5 kg and ≥15 days, respectively), although these NNRTIs are associated with certain adverse events (AEs).[8,9]
- RPV dosing for ARV treatment-naïve, HIV-1-infected pediatric patients has not been established.
  PAINT (**P**ediatric study in **A**dolescents **I**nvestigating a new **N**NRTI **T**MC278) is an ongoing, 48-week, 2-part, Phase II trial investigating the pharmacokinetics, efficacy, safety and tolerability of RPV in ARV treatment-naïve, HIV-1-infected adolescents (≥12 to ≤18 years old) (NCT00799864)
  - Part 1 of this trial aimed to establish, in a subset of adolescents, a well-tolerated RPV dose providing RPV exposure comparable to that in adults
  - We present the steady-state RPV pharmacokinetics at 25 mg q.d. in adolescents and preliminary efficacy and safety data up to Week 4 from Part 1 of PAINT
  - Part 2 of this trial is evaluating the long-term safety and efficacy of RPV over 24 and 48 weeks, with an extension phase up to 240 weeks, and data will be presented at a later date.

Methods

Study design and treatment

- PAINT is an ongoing Phase II, open-label, single arm trial (**Figure 1**).
- The eligible treatment population is ARV treatment-naïve, HIV-1-infected male or female adolescents aged ≥12 to ≤18 years and weighing ≥32 kg
  - In Part 1a, patients with a plasma viral load ≥5000 copies/mL were recruited
  - Following review of Part 1a, 2-week results by an independent data monitoring committee, Part 1a was extended to Part 1b to collect more RPV intensive pharmacokinetic (PK) data and, in line with the adult indication, further enrollment was limited to patients with a viral load of ≥500 to ≤100000 copies/mL
  - Data are presented for Part 1 overall (Part 1a plus 1b); relevant differences are highlighted.
- Key exclusion criteria were: ≥1 NNRTI resistance-associated mutation (RAM) from the IAS-USA list;[17] HIV-2 infection; life expectancy <6 months; any active clinically significant disease.
- Patients were treated with RPV 25 mg q.d. in combination with an investigator-selected background regimen of two N(t)RTIs
  - The N(t)RTIs were restricted to zidovudine, abacavir, or tenofovir disoproxil fumarate with either lamivudine or emtricitabine and based on marketing approval, or local standards of care for adolescents in a particular country
  - RPV was taken once daily with a meal and the background regimen was administered according to the prescribing information.

Figure 1. Study design.



*Additional patients were recruited into Part 1b after assessment of Week 2 results from Part 1a
†Patients in Part 2 to be treated with RPV 25 mg q.d. + two N(t)RTIs for up to 240 weeks (primary analyses: Week 24; interim analyses: Week 48)

- Assent to participate in the trial was obtained from all patients and informed consent was provided by their parent/caregiver, as appropriate. The trial protocol, amendments and other documents were reviewed and approved by an independent ethics committee. The study was conducted in accordance with the Declaration of Helsinki and consistent with Good Clinical Practices and applicable regulatory requirements.

PK evaluations

- For the evaluation of RPV plasma concentrations at steady-state, 2 mL venous blood samples were collected at 0 (predose), 2, 4, 5, 6, 9, 12 and 24 hours after an observed intake of RPV at the Week 2 (Part 1a) or Week 4 (Part 1b) visit.
- Plasma concentrations of RPV were assayed using a validated liquid chromatography-mass spectrometry/mass spectrometry method, with a lower limit of quantification of 1.00 ng/mL.[18]
- RPV plasma PK parameters were calculated using a non-compartmental model with extravascular input (WinNonlin® version 6.3, Pharsight Corporation, CA, USA).
- Descriptive statistics were calculated for RPV PK parameters (Microsoft Excel®; Microsoft Redmond, Washington, USA)
  - RPV PK parameters (geometric mean) in adolescents were compared with those in HIV-1-infected adults treated with RPV 25 mg q.d. in the pooled Phase III ECHO/THRIVE PK substudy.[19]

Antiviral activity and safety evaluations

- Blood samples for plasma viral load (Roche HIV-1 viral load assay) and CD4+ cell count evaluations were collected at screening, baseline and in Weeks 2 and 4
  - Efficacy endpoints for this early stage of the trial included the change in viral load and CD4+ cell count from baseline (observed).
- Safety and tolerability assessments included AE monitoring, physical examination, vital signs, height and weight, clinical laboratory evaluations (clinical biochemistry, hematology, urinalysis) and electrocardiograms
  - Safety data were summarized using descriptive statistics and frequency tabulations.

Results

Study population

- Forty-nine patients were screened in Part 1; 24 were not eligible and the main reasons for screening failures included: baseline viral load levels, presence of NNRTI RAMs and low body weight.
- In Part 1, 25 patients were enrolled from one site in India (N=3), one site in Thailand (N=1), one site in Uganda (N=7) and three sites in South Africa (N=14), and all of them received the study drugs
  - Two patients discontinued the trial before having the Week 4 visit; one patient was diagnosed with pulmonary tuberculosis (mandatory withdrawal criterion) and the other patient had an NNRTI RAM at screening (an exclusion criterion) and should not have been treated.
  - Therefore, intensive RPV PK data were available for 23 patients.
- Baseline demographics and disease characteristics are shown in **Table 1**
  - The majority of patients were Black or African-American
  - Demographics and disease characteristics were well balanced between age categories (>12 to ≤15 and >15 to ≤18 years) and between genders
  - Most patients had a baseline viral load of ≤100000 copies/mL (as screening viral load ≤100000 copies/mL was an inclusion criterion for Part 1b patients); there were seven Part 1a patients with a baseline viral load >100000 copies/mL, one of whom had a viral load of ≤100000 copies/mL at screening and just above this value at baseline.

RPV pharmacokinetics

- Mean RPV plasma concentration over time profiles were comparable between adolescents and adults (**Figure 2**)
  - The reason for the apparent lower observed mean maximum plasma concentration (C_{max}) in adolescents is not clear. This difference may be due, at least partly, to small differences in the PK sampling time points in adults (i.e. 1, 2, 3, 4, 6, 9, 12 and 24 hours) and adolescents.
- The geometric mean PK parameters for adolescents treated with RPV 25 mg q.d. are presented in **Table 2**
  - The mean RPV PK parameters in Part 1b were higher than in Part 1a: geometric mean area under the plasma concentration–time curve from time of administration up to 24 hours (AUC_{24h}), plasma concentrations predose (C_{0h}) and 24 hours post dosing (C_{24h}), and C_{max} were 2032 vs 1488 ng•h/mL, 80.5 vs 61.1 ng/mL, 72.2 vs 55.3 ng/mL and 121.2 vs 85.0 ng/mL, respectively
  - Potential factors contributing to these differences were: suspected and/or reported non adherence for several adolescents in Part 1a prior to the intensive PK visit and not having achieved steady-state RPV PK in some Part 1a patients at the time of their Week 2 visit.
  - Individual RPV C_{0h} and AUC_{24h} values for adolescents in Parts 1a and 1b and for adults are shown in **Figure 3**

Table 1. Baseline demographics and disease characteristics.

	Overall (Part 1a + 1b) (N=25)
Demographics	
Female sex, N (%)	14 (56)
Age, years, median (range)	15 (13–17)
Age categories, years, N (%) >12 to ≤15 >15 to ≤18	 12 (48) 13 (52)
Height, cm, median (range)	153 (139–166)
Weight, kg, median (range)	44 (35–58)
Race, N (%) Asian Black or African-American	 4 (16) 21 (84)
Disease characteristics	
Viral load, log_{10} copies/mL, median (range)	4.9 (3.3–5.8)
Viral load categories, copies/mL, N (%) ≤100000 100000 to ≤500000 ≥500000	 18 (72) 5 (20) 2 (8)
Absolute CD4+ count, cells/mm³, median (range)	375 (25–983)
Duration of known HIV infection, years, mean (SD)	2.97 (3.39)

SD = standard deviation

Figure 2. Mean (SD) plasma concentration-time curves of RPV 25 mg q.d. in adolescents (Part 1, PAINT) and adults (pooled Phase III ECHO/THRIVE PK substudy).

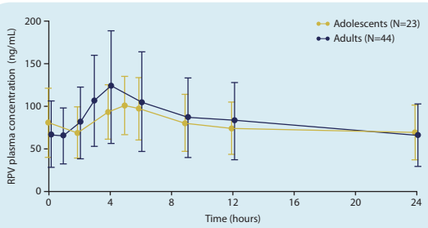


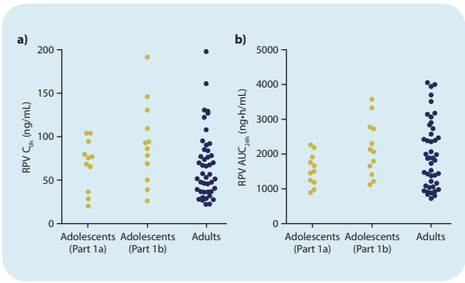
Table 2. Steady-state RPV PK parameters in adolescents (Part 1 PAINT) and comparison with RPV PK parameters in adults (pooled Phase III ECHO/THRIVE PK substudy).

	Overall (Part 1a + 1b) (N=23)	
PK parameter, geometric mean (range); t_{max}: median (range)		
t_{max}, hours	5 (2–9)	
C_{max}, ng/mL	102.3 (48.5–182.0)	
C_{min}, ng/mL	51.3 (48.5–182.0)	
C_{0h}, ng/mL	70.6 (20.3–191.0)	
C_{24h}, ng/mL	63.6 (32.8–162.0)	
AUC_{24h}, ng•h/mL	1750 (887–3573)	
Adolescent/adult ratio*	**Ratio†**	**95% CI**
C_{max}, ng/mL	0.88	0.68–1.14
C_{0h}, ng/mL	1.21	0.91–1.61
C_{24h}, ng/mL	1.10	0.85–1.41
AUC_{24h}, ng•h/mL	0.98	0.78–1.25

*Ratio of geometric mean RPV PK parameters in adolescents (PAINT, Part 1)/adults (pooled Phase III ECHO/THRIVE PK substudy)
†Ratio (adolescents/adults) of >0.80 and <1.25 was prespecified to demonstrate comparability in RPV PK parameters between adults and adolescents
C_{min} = minimum plasma concentration; t_{max} = time to reach the maximum plasma concentration

- The ratios of the geometric mean PK parameters for adolescents (PAINT Part 1)/adults (pooled Phase III ECHO/THRIVE PK substudy) for C_{max}, C_{0h}, C_{24h} and AUC_{24h} were all >0.80 and <1.25 (**Table 2**)
  - An AUC_{24h} ratio (adolescents/adults) >0.80 and <1.25 was prespecified in the PAINT protocol to demonstrate comparability in RPV PK between adults and adolescents
  - The AUC_{24h} and C_{0h} ratios were 0.83 and 1.05, respectively, for Part 1a and 1.14 and 1.38, respectively, for Part 1b.

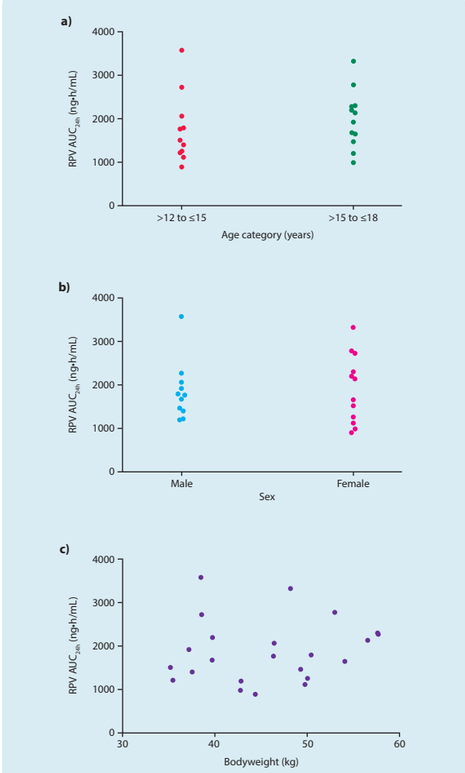
Figure 3. Individual RPV a) C_{0h} and b) AUC_{24h} values in adolescents (PAINT) and adults (pooled Phase III ECHO/THRIVE PK substudy).



RPV pharmacokinetics by subgroups

- There was no apparent relationship between RPV AUC_{24h} and age category (>12 to ≤15 and >15 to ≤18 years) (**Figure 4a**), sex (**Figure 4b**) or bodyweight (**Figure 4c**).
- Also, there were no apparent relationships between RPV C_{max} or RPV C_{0h} and age, sex or bodyweight (data not shown).

Figure 4. Individual RPV AUC_{24h} values in adolescents (PAINT Part 1), by a) age category b) sex and c) bodyweight.



Antiviral activity at Week 4

- All but two patients (92%) had at least a 1 log_{10} drop in viral load from baseline. The mean standard error (SE) decrease in viral load from baseline was 2.3 (0.17) (N=24) log_{10} copies/mL
  - For patients with a baseline viral load ≤100000 copies/mL or >100000 copies/mL, the mean (SE) decrease in viral load was 2.6 (0.11) (N=17) and 2.2 (0.52) (N=7) log_{10} copies/mL, respectively.
- The mean (SE) increase in CD4+ cell count from baseline was 105 (27) (N=21) cells/mm³.

Safety and tolerability up to Week 4 visit

- Overall, in the first 4 weeks of treatment, no patients discontinued study drugs due to AEs.
- Sixteen of the 25 patients (64%) had ≥1 AE by Week 4
  - The majority of AEs were grade 1 or 2 in severity; only two patients had a grade 3 AE (malaria, a serious AE [n=1], pancreatitis [n=1] considered not RPV-related) and none had a grade 4 AE.
- The most frequently reported treatment-emergent AEs were somnolence (4/25, 16%) and nausea (3/25, 12%)
  - Eight AEs at least possibly related to RPV were reported in five patients by Week 4: somnolence (n=2), nausea (n=2), upper abdominal pain (n=1), pyrexia (n=1), dizziness (n=1) and headache (n=1); all were grade 1 in severity
  - The observed AEs were similar (type and severity) to those reported in adults (53% up to Week 4).
- No clinically significant changes in laboratory parameters were observed up to Week 4.

Conclusions

- RPV 25 mg q.d., taken with a meal, resulted in an RPV exposure in adolescents that was comparable to that in adults.
- These first data in adolescents indicated that this dosing regimen of RPV 25 mg q.d. in combination with two N(t)RTIs reduced viral load, increased CD4+ cell count and was well tolerated in this patient population.
- Long-term safety/tolerability, efficacy and PK of RPV 25 mg q.d. taken with a meal are being evaluated in a larger group of HIV-1-infected adolescents in Part 2 of PAINT.

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