Week 48 safety and efficacy of a rilpivirine (TMC278)-based regimen in HIV-infected treatment-naïve adolescents: PAINT phase II trial

Johan Lombaard,[1] Torsak Bunupuradah,[2] Patricia M. Flynn,[3] John Ramapuram,[4] Francis Ssali,[5] Herta Crauwels,[6] Annemie Hoogstoel,[6] Veerle Van Eygen,[6] Marita Stevens[6] and Katia Boven[7]

[1]Josha Research, Bloemfontein, South Africa; [2]HIV-NAT, Thai Red Cross AIDS Research Centre, Bangkok, Thailand; [3]St. Jude Children's Research Hospital, Memphis, TN, USA; [4]Kasturba Medical College Hospital, Mangalore, India; [5]Joint Clinical Research Centre, Kampala, Uganda; [6]Janssen Infectious Diseases BVBA, Beerse, Belgium; [7]Janssen Research & Development LLC, Titusville, NJ, USA

Background to RPV and the PAINT trial

- The NNRTI, rilpivirine (RPV, TMC278) 25 mg qd is approved in combination with other ARVs, for use in ART-naïve adults.[1,2] In most countries this is limited to patients with VL ≤100,000 copies/mL
  - A single-tablet regimen (FTC/RPV/TDF) is also available
- **PAINT** is an ongoing, two-part, phase II trial evaluating RPV 25 mg qd in ART-naïve adolescents (≥12 to <18 years)
  - Part 1 of the study showed that RPV exposure was comparable between adolescents and adults[3]
  - Virologic response (<50 copies/mL) at 24 weeks was 75% overall and 86% in patients with baseline VL ≤100,000 copies/mL[4]
  - RPV resistance and safety over 24 weeks were consistent with data in adults[4]

[1]Molina JM, et al. AIDS 2013;27:889–97
[2]EDURANT® (rilpivirine) tablets prescribing information, 2011; revised 2014
[3]Crauwels H, et al. 21st CROI 2014. Abstract 900
[4]Lombaard J, et al. 6th HIV Pediatrics Workshop 2014. Abstract O_05

PAINT = Pediatric study in Adolescents Investigating a new NNRTI TMC278 (NCT00799864)
ART = antiretroviral (ARV) treatment; VL = viral load

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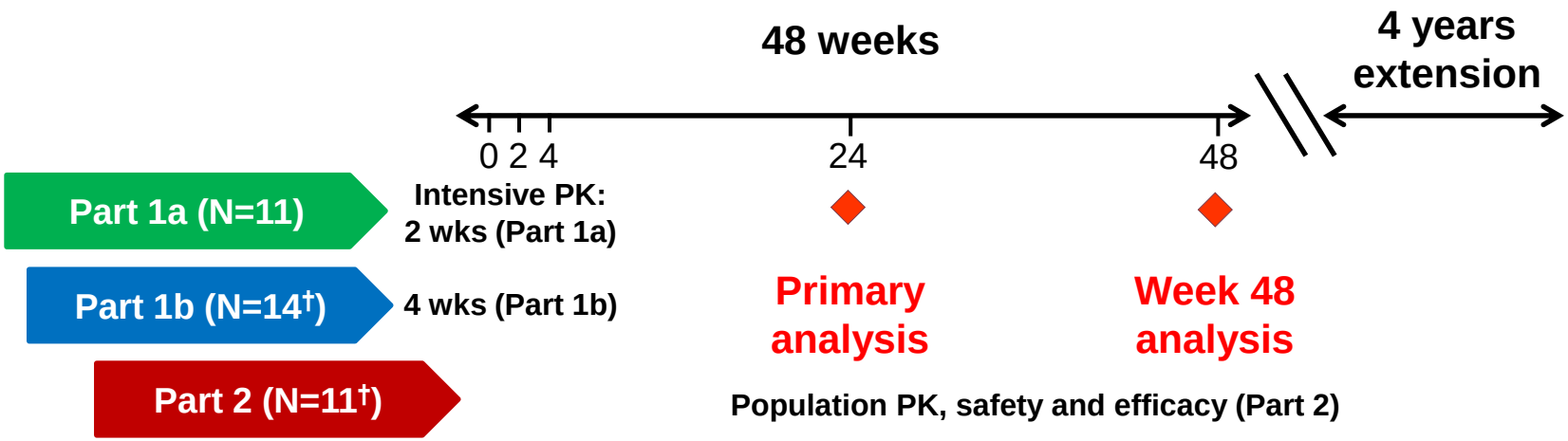
PAINT: Phase II, open-label trial design



RPV 25 mg qd + background regimen* (N=36)
*Investigator's choice: TDF/FTC (67%); TDF/3TC (22%); AZT/3TC (11%)

- Male or female aged ≥12 to <18 years
- Weight ≥32kg
- VL ≥5000 copies/mL (Part 1a)
- VL ≥500 but ≤100,000 copies/mL (Parts 1b and 2)‡
- ART-naive, sensitive to N(t)RTIs and no NNRTI RAMs§ (genotypic analysis)

†Additional patients recruited; ‡Amendment after Part 1a, in line with the adult indication in most countries; §From a predefined list of 41 NNRTI resistance-associated mutations (RAMs)

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PAINT: Demographics

	N=36
Female, n (%)	20 (56)
Median age, years (range)*	14.5 (12–17)
≥12 to <15 years, n (%)	18 (50)
≥15 to <18 years, n (%)	18 (50)
Median weight, kg (range)*	45 (33–93)
Race, n (%)	
Black or African-American	32 (89)
Asian	4 (11)
Country, n (%)	
South Africa	20 (56)
Site 1	15 (42)
Site 2	4 (11)
Site 3	1 (3)
Uganda (1 site)	11 (31)
India (1 site)	3 (8)
Thailand (1 site)	1 (3)
USA (1 site)	1 (3)

*At screening

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PAINT: Baseline characteristics

	N=36
Median log_{10} BL VL, copies/mL (range)	4.76 (3.31–5.83)
BL VL ≤100,000 copies/mL, n (%)	28 (78)
BL VL >100,000 copies/mL, n (%)	8* (22)
Median $CD4^+$ count, cells/mm^3 (range)	414 (25–983)
Mode of HIV infection, n (%)	
Mother-to-child transmission	30 (83)
Heterosexual contact	4 (11)
Other or unknown	2 (6)
Median duration of infection, years (range)	1.3 (0–11)
Clinical stage of HIV infection, CDC Category C, n/N (%)	
Patients ≥13 years	6/31 (19)
Patients <13 years	1†/5 (20)
Clade, n (%)	
C	23 (64)
A1	9 (25)
D	2 (6)
B	1 (3)
CRF01_AE	1 (3)

*Six patients with baseline (BL) VL >100,000 copies/mL were from Part 1a with one each from Parts 1b and 2 (both had screening VL ≤100,000 copies/mL); †For one of the five patients aged <13 years, the sponsor-defined category was equivalent to CDC category C

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PAINT: Adverse event summary at Week 48

	RPV 25 mg (N=36)
Mean treatment duration, weeks (SD)	71.6 (43.1)
Incidence, n (%)	
Any AE	35 (97)
Any AE with grade 3–4	7* (19)
Any serious AE†	6 (17)
Discontinuations due to AEs	1‡ (3)
Any AEs at least possibly related to RPV (any grade)	13 (36)
Most common possibly related AEs§	
Somnolence	5 (14)
Nausea	2 (6)

*Mostly malaria and depression (each n=2 and not related to RPV); †Only one serious AE was considered possibly related to RPV (drug hypersensitivity – hospitalization for rash); ‡Pulmonary tuberculosis; §Occurring in >5% of patients and not including investigations or laboratory abnormalities categorised as AEs

- Most adverse events (AEs) occurred in the first 24 weeks of the study
- No deaths were reported

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PAINT: Week 48 laboratory and ECG results

Incidence of grade 3 or 4 treatment-emergent lab abnormalities, n (%)*	RPV 25 mg (N=36)
Grade 3	
Decreased neutrophils	2 (6)
Increased amylase	2 (6)
Hypophosphatemia	1 (3)
Grade 4	
Increased creatinine	1 (3)
Decreased neutrophils, precursors and segmented	1 (3)

*In most, but not all cases, reported lab abnormalities were confirmed on more than one visit

- No consistent or clinically relevant changes in laboratory parameters or QTcF interval over time

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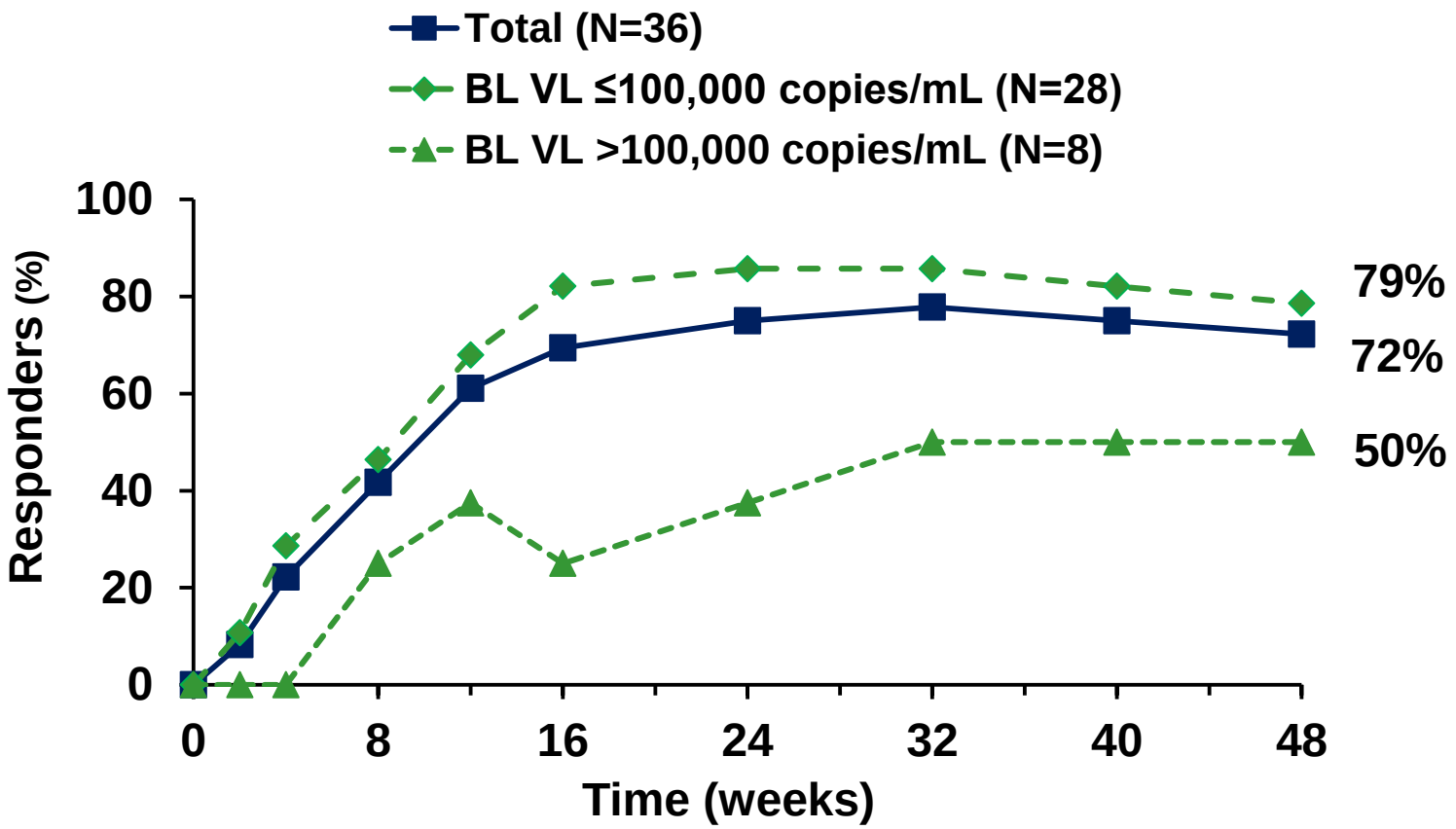
PAINT: Response (<50 copies/mL) over 48 weeks (ITT-TLOVR)



- Median $CD4^+$ increase from baseline at Week 48 = 184 cells/mm^3 (NC=F)

ITT-TLOVR: intent-to-treat-time-to-loss-of-virologic response algorithm; NC=F: non-completer=failure

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PAINT: ITT-TLOVR outcome (<50 copies/mL) at Week 24 and 48

Outcome, n (%)	Week 24			Week 48		
	BL VL ≤100,000 copies/mL (N=28)	BL VL >100,000 copies/mL (N=8)	Total (N=36)	BL VL ≤100,000 copies/mL (N=28)	BL VL >100,000 copies/mL (N=8)	Total (N=36)
Responders (VL <50 copies/mL)	**24 (86)**	**3 (38)**	**27 (75)***	**22 (79)**	**4 (50)**	**26 (72)**
Virologic failure	**3 (11)**	**4 (50)**	**7 (19)**	**5 (18)**	**3 (38)**	**8 (22)**
– Rebounder	0	1 (13)	1 (3)	3 (11)	1 (13)	4 (11)
– Never suppressed	3 (11)	3 (38)	6 (17)	2 (7)†	2 (25)†	4 (11)
Discontinued due to adverse event	**0**	**1 (13)‡**	**1 (3)‡**	0	**1 (13)‡**	**1 (3)‡**
Discontinued for other reasons	**1 (4)¶**	**0**	**1 (3)¶**	**1 (4)¶**	0	**1 (3)¶**

*Primary efficacy endpoint; †One patient demonstrated an initial lack of response; ‡Pulmonary tuberculosis; ¶Patient dosed in error (protocol deviation: NNRTI RAM at screening); Rebounder: confirmed virologic response before Week 24 or 48 with confirmed rebound at or before Week 24 or 48; Never suppressed: no confirmed virologic response before Week 24 or 48

- The Snapshot responses were in line with the TLOVR responses

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PAINT: Summary of resistance findings[1]

- Of the 8 VFs (3 BL VL>100k) in the Week 48 TLOVR analysis, 5 had treatment-emergent RPV RAMs
  - E138K (n=4), K101E (n=2), M230L (n=2), and E138G, E138R, Y181I and H221Y (n=1 for each)
  - In 4/5 of these VFs, emergence of RPV RAMs was associated with emergence of N(t)RTI RAMs, usually M184V
- Of the 3 VFs who had no RPV RAMs at Week 48, one transiently carried E138E/K at Week 16
- Resistance pattern consistent with that in adults[2–4]

[1]Van Eygen V, et al. XXIVth IHDRW 2015. Poster 34; [2]Rimsky L, et al. JAIDS 2012;59:39–46; [3]Rimsky L, et al. Antivir Ther 2013;18:967–77; [4]Vingerhoets J, et al. Antivir Ther 2013;18:253–6

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PAINT: Adherence over 48 weeks of study

Adherence by pill count	To Week 48* (N=36)
Mean (SD) adherence, %	**97.5 (4.8)**
Adherence level, n (%)	
>95%	**28 (78)**
≤95%	**8 (22)**

*Or last intake for discontinued patients

- Of the 8 patients with VF, 2 had adherence <95% (pill count)
- Adherence by self-report questionnaire was high with only 3/34 (9%) missing at most 1 dose during 3 days preceding a visit not more than once

VF = virologic failure in the Week 48 TLOVR analysis

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PAINT: Pharmacokinetic results (Population pharmacokinetic modelling)[1]

Parameter	PAINT (adolescents)		Week 48 values in adults (ECHO/THRIVE pooled analysis)[2] (N=679)
	Week 24 (n=34)	Week 48 (n=34)	
AUC_{24h}, ng•h/mL			
Mean (SD)	2378 (1003)	2391 (991)	2397 (1032)
Median (range)	2200 (417–5280)	2264 (417–5166)	2204 (482–8601)
C_{trough}, ng/mL			
Mean (SD)	82.9 (39.9)	83.5 (38.7)	80.0 (36.5)
Median (range)	76.1 (7–209)	78.7 (7–202)	74.2 (1–300)

AUC_{24h} = area-under-the-concentration-time curve from 0 to 24 hours; C_{trough}= plasma concentration at 0 hours

- No impact of age, gender or body weight on RPV pharmacokinetics
- Median RPV exposure was lower in VFs than in responders but exposure ranges overlapped

[1]Brochot A et al, 16th IWCPHIV. Poster 33
[2]Crauwels H et al, HIV 10 Congress 2010. Poster P186

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PAINT conclusions at Week 48

- RPV 25 mg qd safety, efficacy, resistance and pharmacokinetic profiles in HIV-infected treatment-naïve adolescents were similar to those observed in adults
  - Low rates of discontinuations due to AEs and laboratory abnormalities
  - Virologic response (<50 copies/mL): 79% in patients with BL VL ≤100,000 copies/mL and 72% overall
  - VF occurred in 8/36 patients (of these, 3 had BL VL >100,000 copies/mL)
  - Most frequently emerging RPV RAM was E138K, usually in combination with M184V
  - PK similar to adults and no impact of age, gender or body weight on RPV pharmacokinetics
- The findings support the use of RPV 25 mg qd, taken with a meal and in combination with other ARVs, in treatment-naïve adolescents (≥12 to <18 years) with VL ≤100,000 copies/mL

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