Safety and efficacy of a rilpivirine-based regimen in HIV-infected treatment-naïve adolescents: Week 24 primary analysis of the PAINT phase II trial

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Background: RPV in pediatric patients

- The NNRTI, rilpivirine (RPV, TMC278) 25 mg qd in combination with other ARVs is approved for ART-naïve, HIV-1-infected 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
- In pediatric patients, ARVs with age-appropriate doses and formulations are needed[3,4]
- PAINT is an ongoing, 2-part, phase II trial investigating RPV in ART-naïve, HIV-1-infected adolescents
  - Part 1 confirmed comparability of exposure for RPV 25 mg qd dose between adolescents and adults, as well as short-term antiviral activity and safety[5]
  - **Week 24 safety and efficacy (primary analysis; Part 2) are presented**

[1]Molina JM, et al. AIDS 2013;27:889–97; [2]EDURANT® (rilpivirine) tablets prescribing information, 2011; revised 2014
[3]DHHS guidelines for use of antiretroviral agents in pediatric HIV infection (November 2012)
[4]Phelps BR, Rakhmanina N. Paediatr Drugs 2011;13:175–92; [5]Crauwels H, et al. 21st CROI 2014. Abstract 900

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

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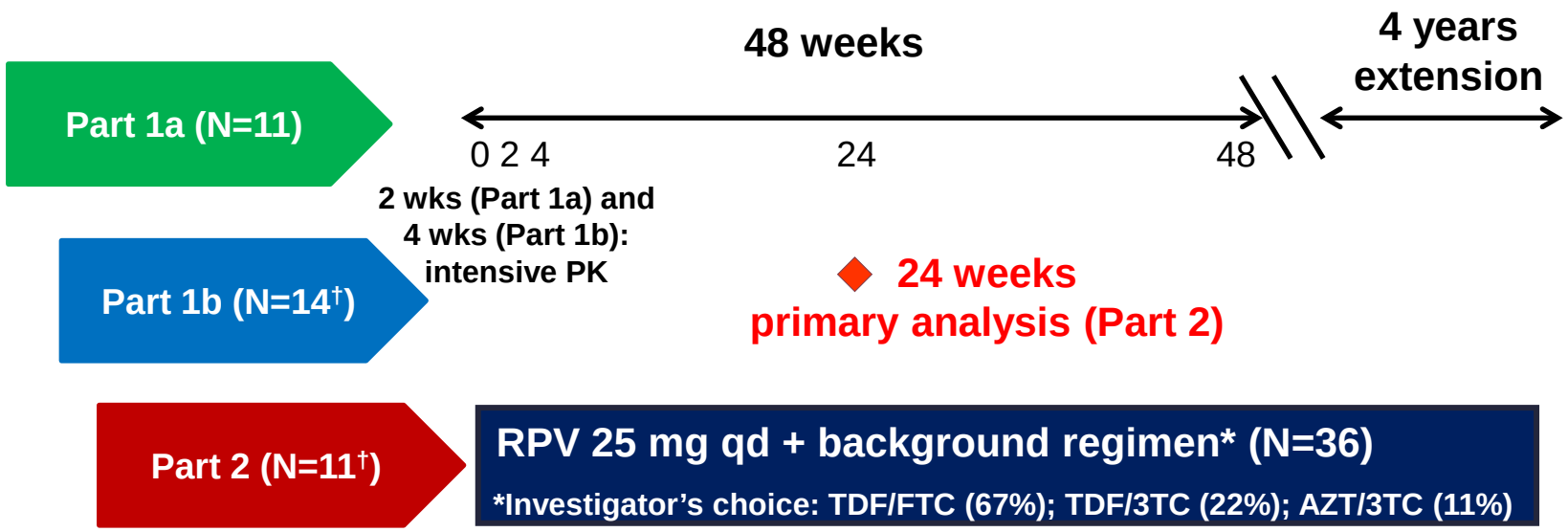
PAINT: Phase II, open-label trial design



- Male or female
- Aged ≥12 to <18 years
- Weight >32 kg
- VL ≥5000 copies/mL (Part 1a)
- VL ≥500 but ≤100,000 copies/mL (Parts 1b and 2)‡
- 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
RAM = resistance-associated mutation

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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 (%)	
Asian	4 (11)
Black or African-American	32 (89)
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)

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PAINT: Baseline (BL) characteristics

	N=36
Median log_{10} BL VL, copies/mL (range)	**4.757 (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)	**415 (30–980)**
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)	**1.30 (0.0–11.2)**
Clinical stage of HIV infection, n (%)	
Category A	**23 (64)**
Category B	**2 (6)**
Category C	**6 (17)**
Missing	**5 (14)**
Clade, n (%)	
A1	**9 (25)**
B	**1 (3)**
C	**23 (64)**
CRF01_AE	**1 (3)**
D	**2 (6)**

*All patients with BL VL >100,000 copies/mL were from Part 1A and all but one were from the same site

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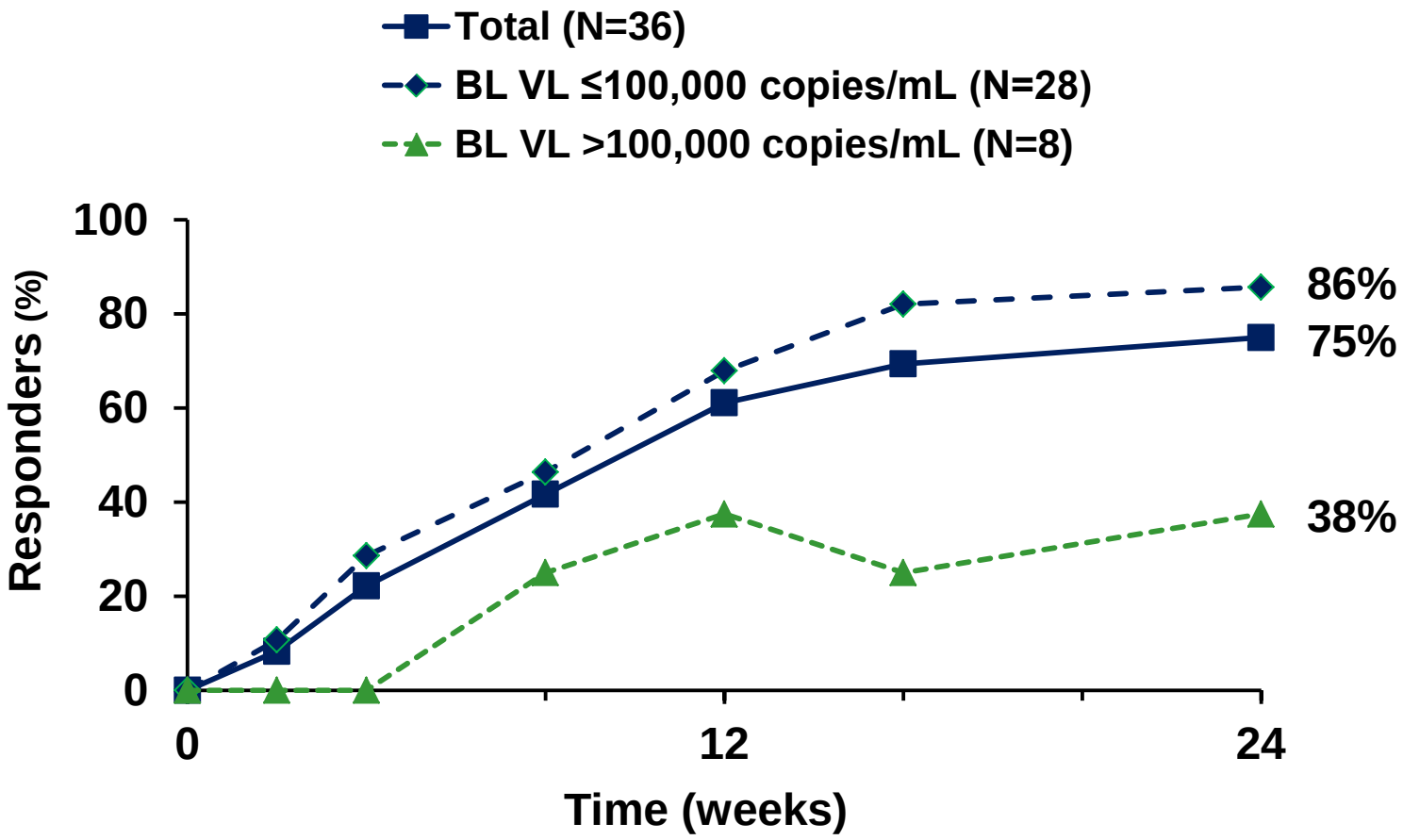
PAINT: Response (<50 copies/mL) over 24 weeks (ITT-TLOVR)



ITT-TLOVR = intent-to-treat-time-to-loss-of-virologic-response algorithm

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

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

*Primary efficacy endpoint
†Pulmonary tuberculosis
‡Patient dosed in error (protocol deviation: NNRTI RAM at screening)

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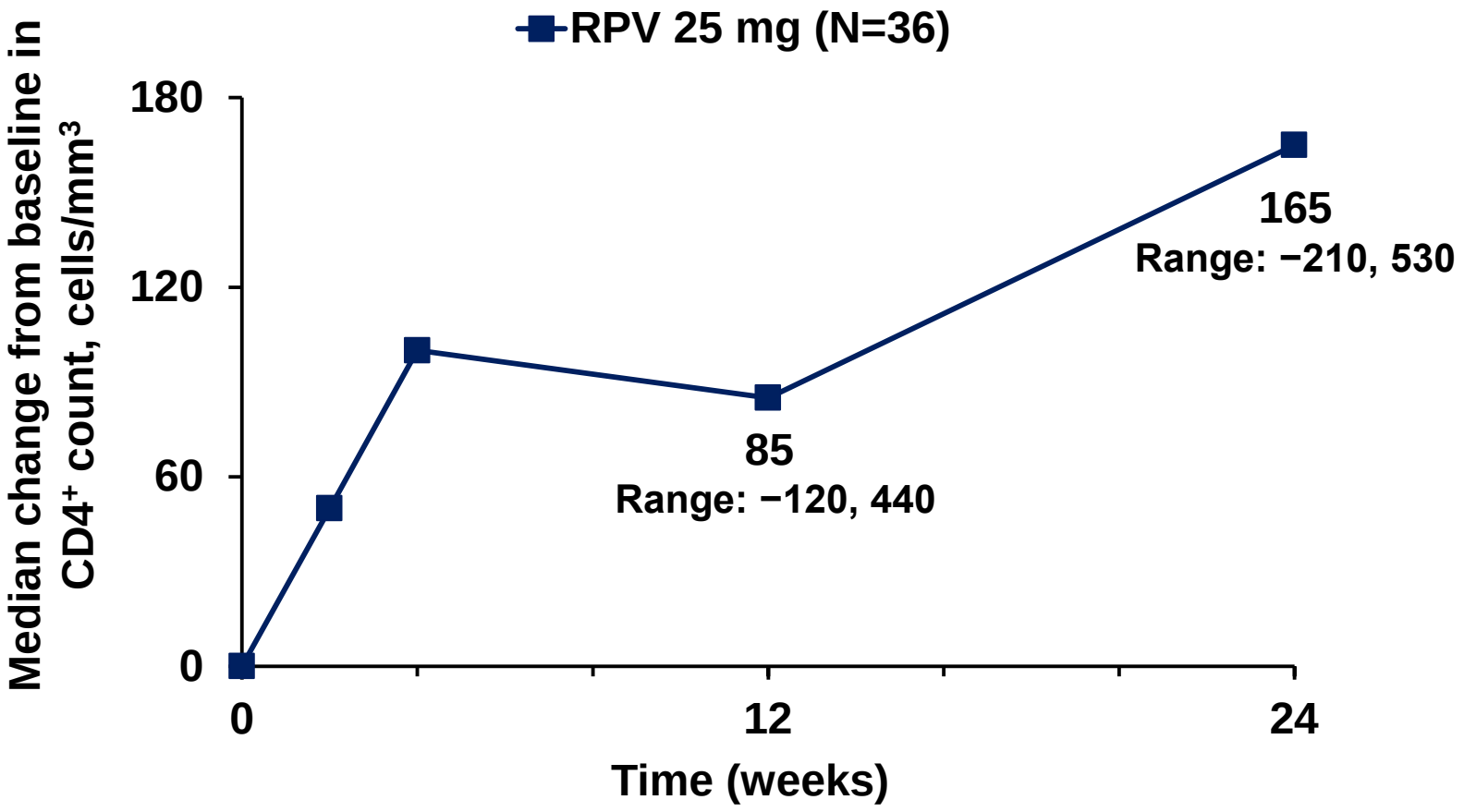
PAINT: Change in CD4⁺ cell count (Non-completer=failure*)



- Median (range) change in CD4⁺ % from BL to Week 24: 5.95 (–3.0, 19.3)%

* Missing values imputed as a change of 0

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PAINT: Adherence based on pill count over 24 weeks of study

	To Week 24* (N=36)
Mean (SD) adherence, %	**97.7 (4.56)**
Adherence level, n (%)	
>95%	**30 (83)**
≤95%	**6 (17)**

*Or last intake for discontinued patients; SD = standard deviation

- Of the patients with adherence <95%, three were VFs, of whom two had baseline viral load >100,000 copies/mL

VF = virologic failure in the Week 24 TLOVR analysis

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PAINT: Summary of resistance findings

- Resistance pattern similar to that in adults
  - Of the 7 VFs in the Week 24 TLOVR analysis, 5 had treatment-emergent RPV RAMs, most commonly E138K (4 VFs)
  - In 4/5 VFs, emergence of RPV RAMs was associated with N(t)RTI RAMs, usually M184V
- Two VFs without RAMs are ongoing (responders after Week 24)

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PAINT: Adverse event summary

	RPV 25 mg (N=36)
Median treatment duration, weeks (range)	48.2 (1–154)
Incidence, n (%)	
Any AE	34 (94)
Any AE with grade 2–4	26 (72)
Any AE with grade 3–4	4 (11)
Any serious AE*	5 (14)
Discontinuations due to AEs	1 (3)†
Most common AEs at least possibly related to RPV (any grade)‡	13 (36)
Somnolence	5 (14)
Rash	2 (6)
Nausea	2 (6)

*Of the serious AEs, only one (drug hypersensitivity – hospitalization for rash) was considered possibly related to RPV
†Pulmonary tuberculosis; ‡Occurring in >5% of patients and not including investigations

- No deaths were reported

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PAINT: Laboratory and ECG results

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

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

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PAINT conclusions at Week 24

- RPV 25 mg once daily demonstrated a high response (<50 copies/mL) in HIV-infected treatment-naïve adolescents
  - 75% overall
  - 86% in patients with BL VL ≤100,000 copies/mL
- VF occurred in 7/36 patients (3/28 vs 4/8 with BL VL ≤100,000 vs >100,000 copies/mL)
- Resistance and safety profiles consistent with the known profiles of RPV
  - Most frequently emerging RPV RAM was E138K usually in combination with M184V
  - Low rates of discontinuations due to AEs and laboratory abnormalities
- RPV 25 mg qd in combination with 2 N[t]RTIs was effective and generally well tolerated for the treatment of HIV-1-infected, ART-naïve adolescents (with VL ≤100,000 copies/mL)

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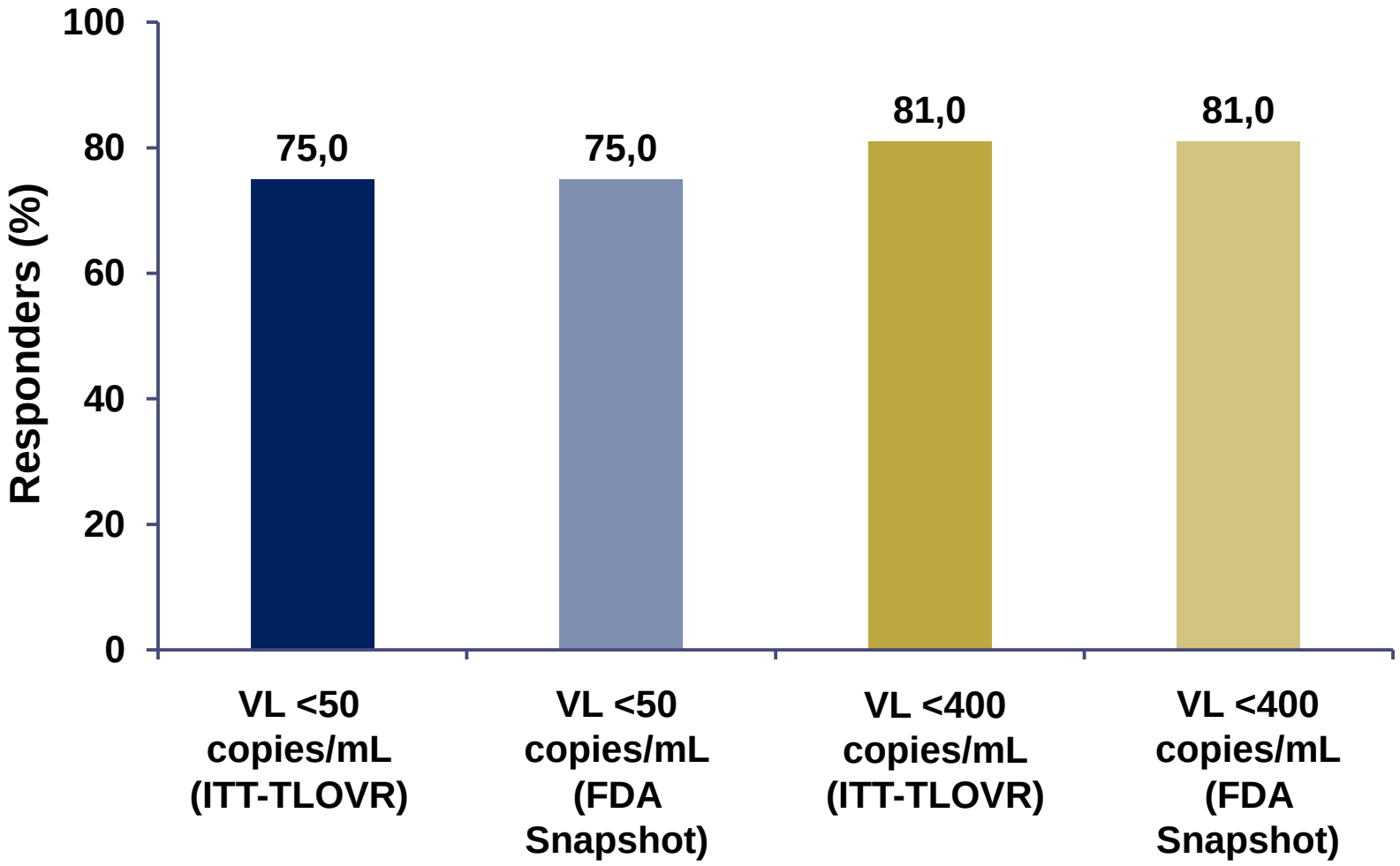
Backup

PAINT: ITT-TLOVR and Snapshot responses at Week 24, (N=36)



ITT-TLOVR = intent-to-treat-time-to-loss-of-virologic-response algorithm
FDA = Food and Drug Administration

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PAINT: Summary of resistance findings*

Response (<50 copies/mL at Week 24)	N(t)RTIs	Adherent	HIV-1 subtype	Last visit with data (week)	RPV FC	Emerging NNRTI RAMs	Emerging N(t)RTI RAMs
BL VL ≤100,000 copies/mL							
NS/VE	AZT/3TC	Yes	D	24	6.0	K101E	M184V
NS/VE	AZT/3TC	No	A1	24	29.4‡	E138G/K/R, H221Y, M230L	M184V
NS/ongoing†	TDF/FTC	Yes	C	16	4.9	None	None
BL VL >100,000 copies/mL							
NS/VE	TDF/3TC	No	A1	12	468.8	E138K, Y181I	K65R, Y155F
NS/VE	AZT/3TC	Yes	A1	16	10.3	E138K, M230L	M184V
RB/VE	TDF/3TC	Yes	A1	24	0.4	(V179I), E138K¶	None
NS/ongoing†	TDF/FTC	No	C	24	NA	None	None

*Virologic failure patients (TLOVR) with post-baseline resistance data in the first 24 weeks;
†Ongoing patients are responders after Week 24; ‡Week 12; ¶Week 16
NS = never suppressed; RB = rebound; VE = virologic endpoint; NA = not available;
RPV RAMs are underlined; BL RAMs are between brackets

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PAINT: Grade 3 or 4 and serious AEs

	RPV 25 mg N=36
Grade 3 or 4 AEs*, n (%)	**4 (11)**
Grade 3 *malaria*	1 (3)
Grade 3 *severe malaria* and decreased blood phosphorus (in the same patient)	1 (3)
Grade 3 pancreatitis	1 (3)
Grade 4 depression, *suicidal ideation and suicide attempt* (in the same patient).	1 (3)
Serious AEs, n (%)	**5 (14)**
Malaria	2 (6)
Lobar pneumonia	1 (3)
Drug hypersensitivity	1 (3)†
Suicidal ideation and attempt (in the same patient)	1 (3)

*Regardless of causality – serious AEs are italicised; †Possibly related to RPV (hospitalization for rash)

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