Julius Caesar Bustamante – *Pajaros*
Artwork from Healing Arts Initiative, a nonprofit organization that inspires healing, growth and learning through access to the arts for the culturally underserved.

16th HIV-HEPPK, Washington, May 2015

Herta Crauwels[1], on behalf of the Janssen RPV LA team[2]

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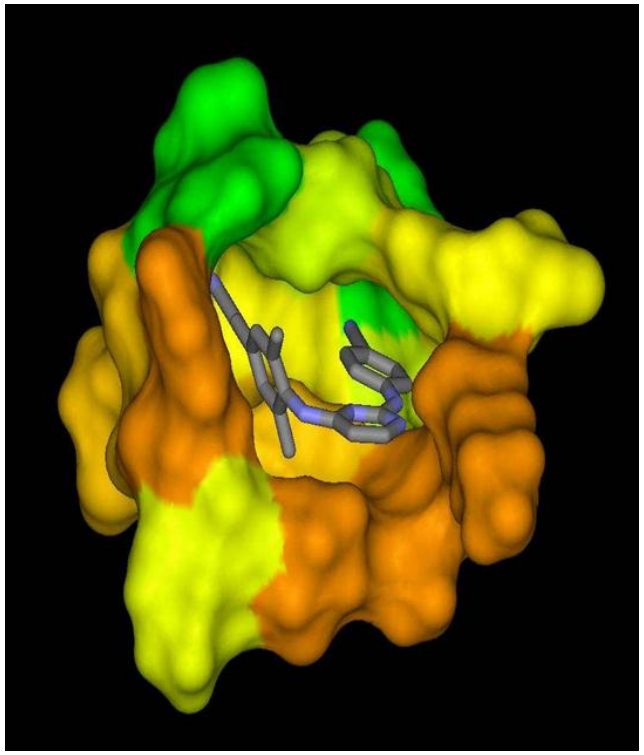
janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Rilpivirine (TMC278), a Potent NNRTI



- 0.26 nM median EC_{50} against HIV-1 primary clinical isolates[1]
- $t_{1/2}$ ~45 hours[2]
- CYP3A substrate
- no clinically relevant impact on metabolism other drugs[2]
- therapeutic oral dose 25 mg once a day
- approved* as single agent (EDURANT®), for treatment of HIV-1 in combination with other ARVs and as once-daily full regimen FDC (Complera/Eviplera®, GSI)
- other (co-)developments ongoing

*In most countries, including US and EU the use is restricted to ARV treatment-naïve patients with a viral load ≤100,000 c/mL

1. Azijn H, et al. AAC 2010;54:718–27
2. Crauwels H et al. AIDS Rev. 2013;15:87-101
3. Cohen CJ, et al. AIDS 2013;27:939–50.

The advantages of a long-acting injectable

LA Injectable Formulations and Therapeutic Applications

- Use of LA injectable formulations
  - Schizophrenia (e.g. paliperidone palmitate)[1]
  - Contraceptives (e.g. medroxyprogesterone acetate)[2]
- Application of NanoCrystal® technology led to the development of various LA formulations for intramuscular (IM) or subcutaneous (SC) injection
- NanoCrystal® Technology is a registered trademark owned by Elan Pharma International Limited, Ireland, resulting in improved bioavailability and absorption of sparingly soluble/insoluble drugs
  - Elan has licensed this technology to companies including Janssen (October 2003)

1. Spanarello S, La Ferla T. Curr Clin Pharmacol 2014;9:310–17
2. Draper BH, et al. Cochrane Database Syst Rev 2006;CD005214

LA ARV Formulations: a New Paradigm and Potential Advantages

Infrequent parenteral dosing offers potential advantages over daily (oral) treatment

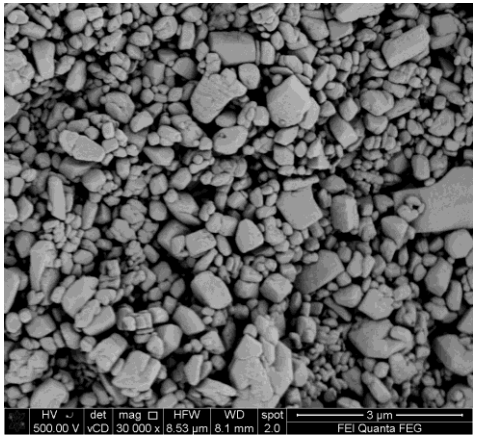
- Sustained concentrations of drugs in plasma
- May improve adherence to therapy/prophylaxis
- May avoid gastrointestinal AEs
- May avoid certain DDIs

Potential future uses of such formulations could include

- Injectable HAART
  - Maintenance of undetectable viral load
  - Need for other LA (preferably injectable) ARV(s)
- Pre-exposure prophylaxis

AEs, adverse events; DDI, drug-drug interaction; HAART, highly-active ARV therapy

Development of Optimized Rilpivirine Long-Acting Formulation

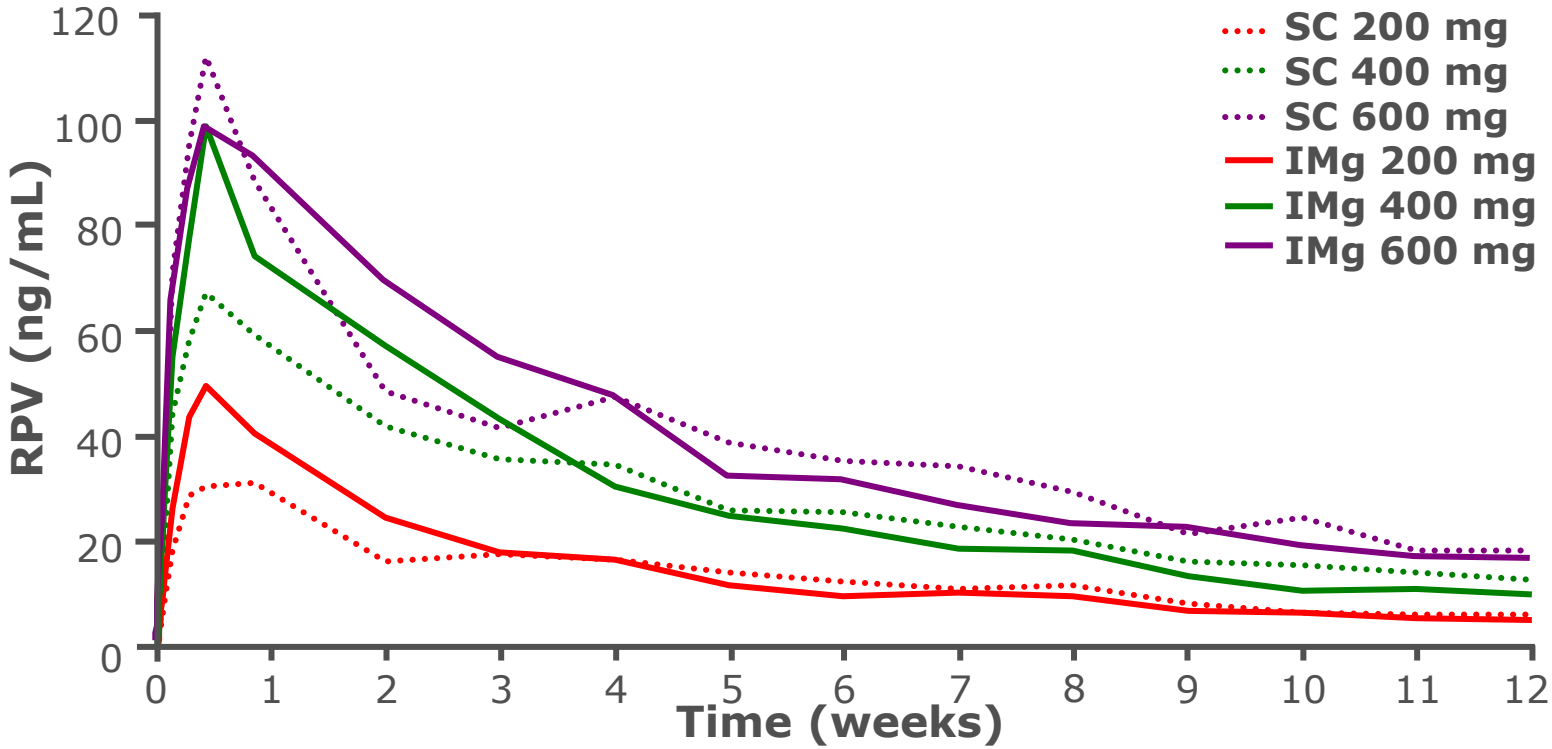


Wet bead milling
particles of pure RPV
average size of 200 nm

Sterile aquous formulation
(sterile manufacturing proces)
with neutral pH

Baert, L et al. Eur J Pharm Biopharm 2009;72:502–8
van 't Klooster G, et al. AAC 2010;54:2042–50

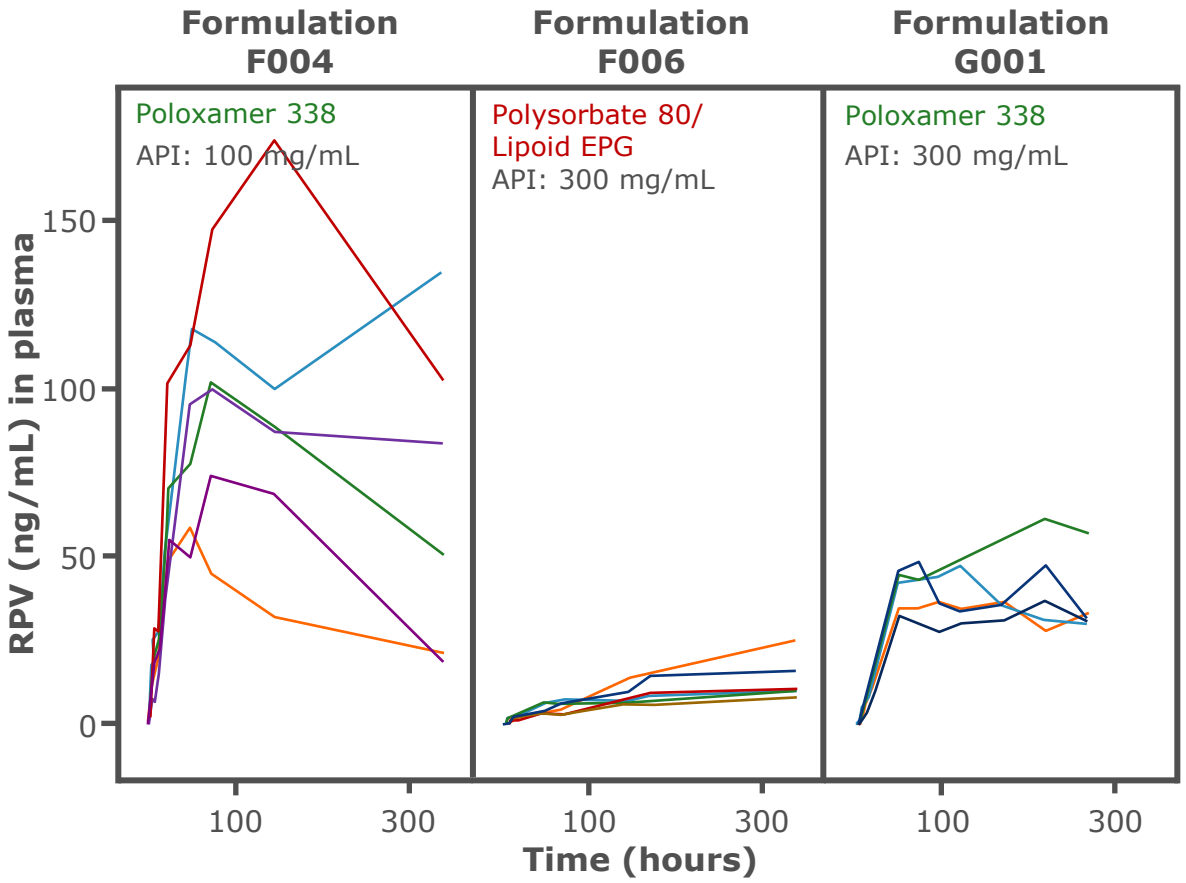
Single-dose RPV LA (F004, 100mg/mL) in Humans: Sustained Mean Plasma Concentrations up to 12 Weeks

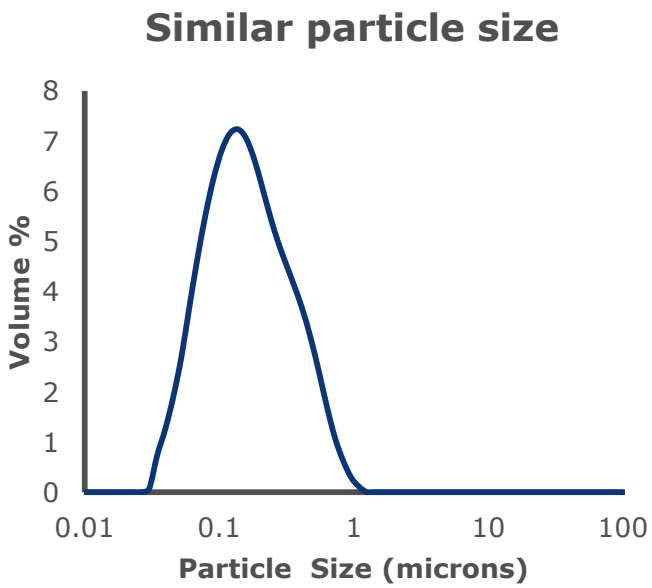


- Good systemic safety and tolerability
- Reasonable local tolerability, mild ISR (IM better tolerated than SC)
- Large volume and imperfect particle size stability –> formulation optimisation

van 't Klooster G, et al. CROI 2008; Abstract 134

Influence of Formulation/Stabilizer on In Vivo PK Profiles in Human Studies (600 mg dose)

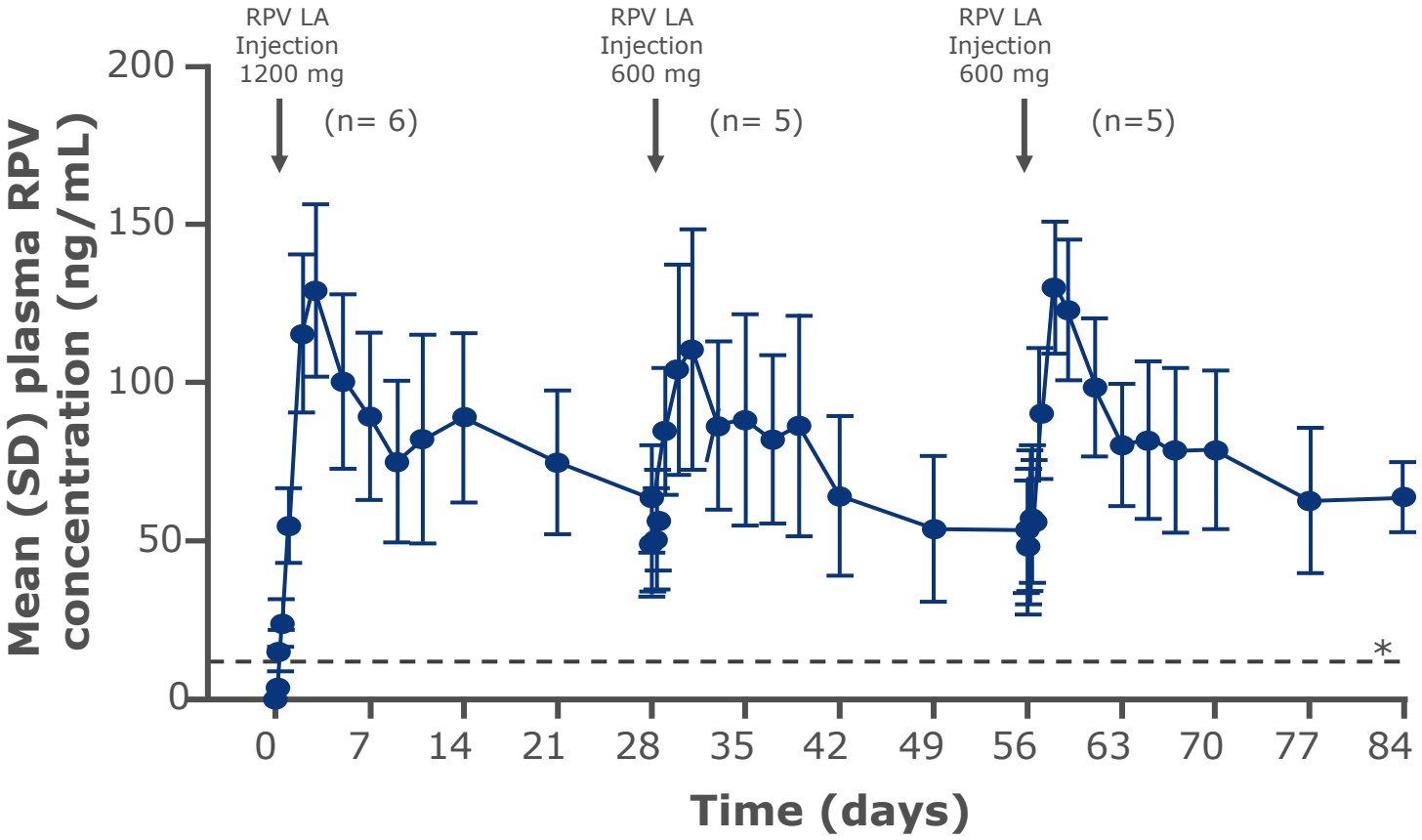




- Different formulations with similar particle size exhibit different human PK profiles
- G001 has an adequate PK profile and drug loading and was selected for further development

EPG, egg phosphatidyl glycerol

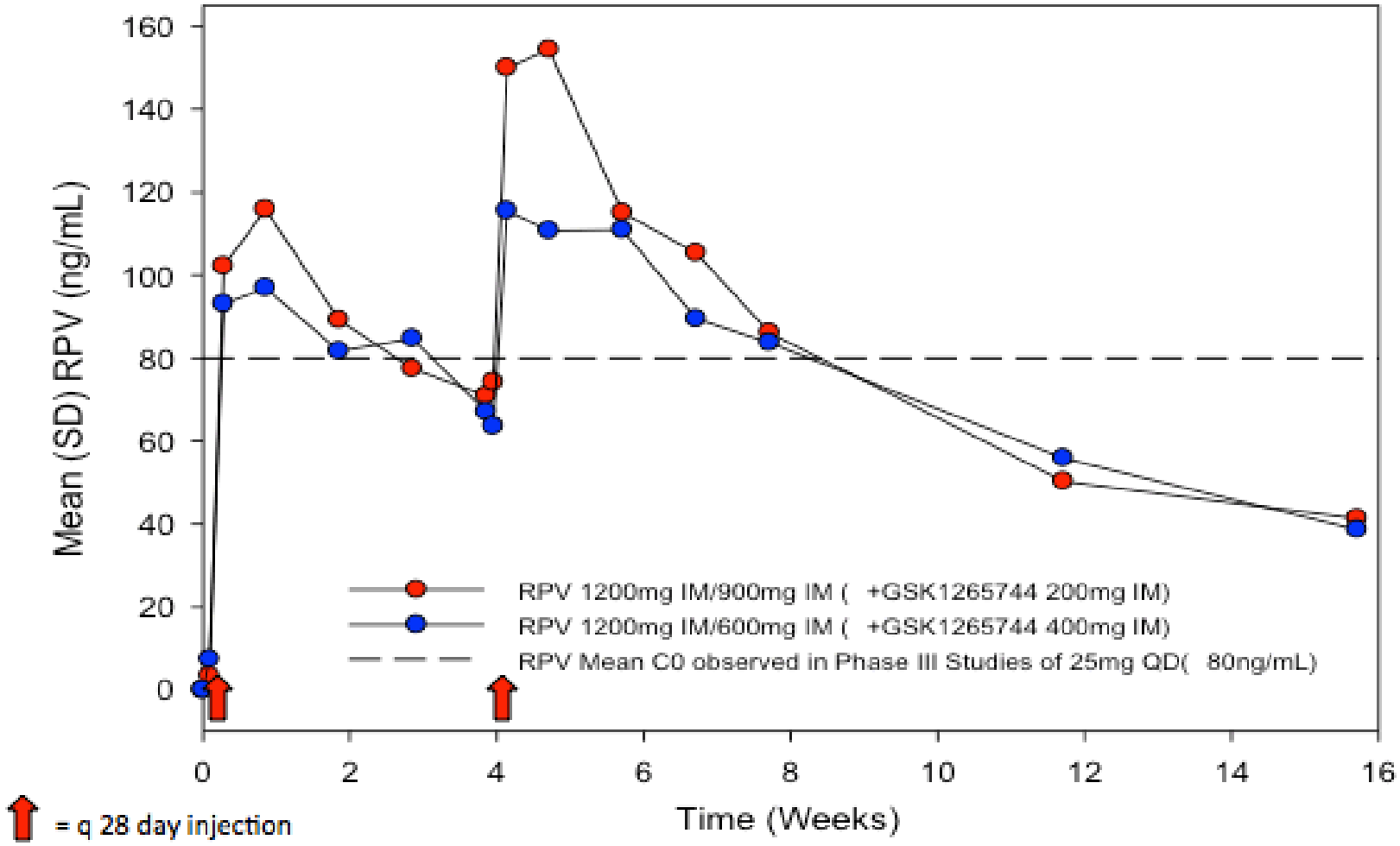
Plasma RPV Exposure after Multiple 4-weekly IMg Injections of RPV LA G001



*RPV EC_{90} value (12 ng/mL) corrected for protein binding

Verloes R, et al. HIV Medicine; In press

Plasma RPV Exposure after IM Injections of RPV LA G001(*in combination with cabotegravir LA*)



Spreen W et al. JAIDS 2014; 67(5):487-92

G001 Tolerability Summary Across Clinical Phase 1

- 168 doses of G001 given to 138 different healthy volunteers, as IMg injections
  - 300 mg (1 mL), 600 mg (2 mL), 900 mg (3 mL), 1200 mg (2 x 2 mL)
- ISRs limited to DAIDS Grade 1 or 2
  - Pain (upon touch) lasting 1–5 days
  - Occasional bruise or redness
  - Infrequent nodules
- One treatment discontinuation (recurrent rash, later found to be a fungal infection)
- No new systemic AEs associated with RPV
  - Infrequent transient Grade 1 rash
  - No relevant prolongations of corrected QT interval

RPV LA for Pre-Exposure Prophylaxis (PrEP)

RPV LA as Potential Pre-exposure Prophylaxis (PrEP)

No vaccine yet, hence a substantial need for PrEP

Adherence has driven efficacy in PrEP trials so far

Preclinical study of RPV LA for HIV Prevention in BLT Mice

(Snyder O, et al. HIVR4P 2014. Abstract OA3.01)

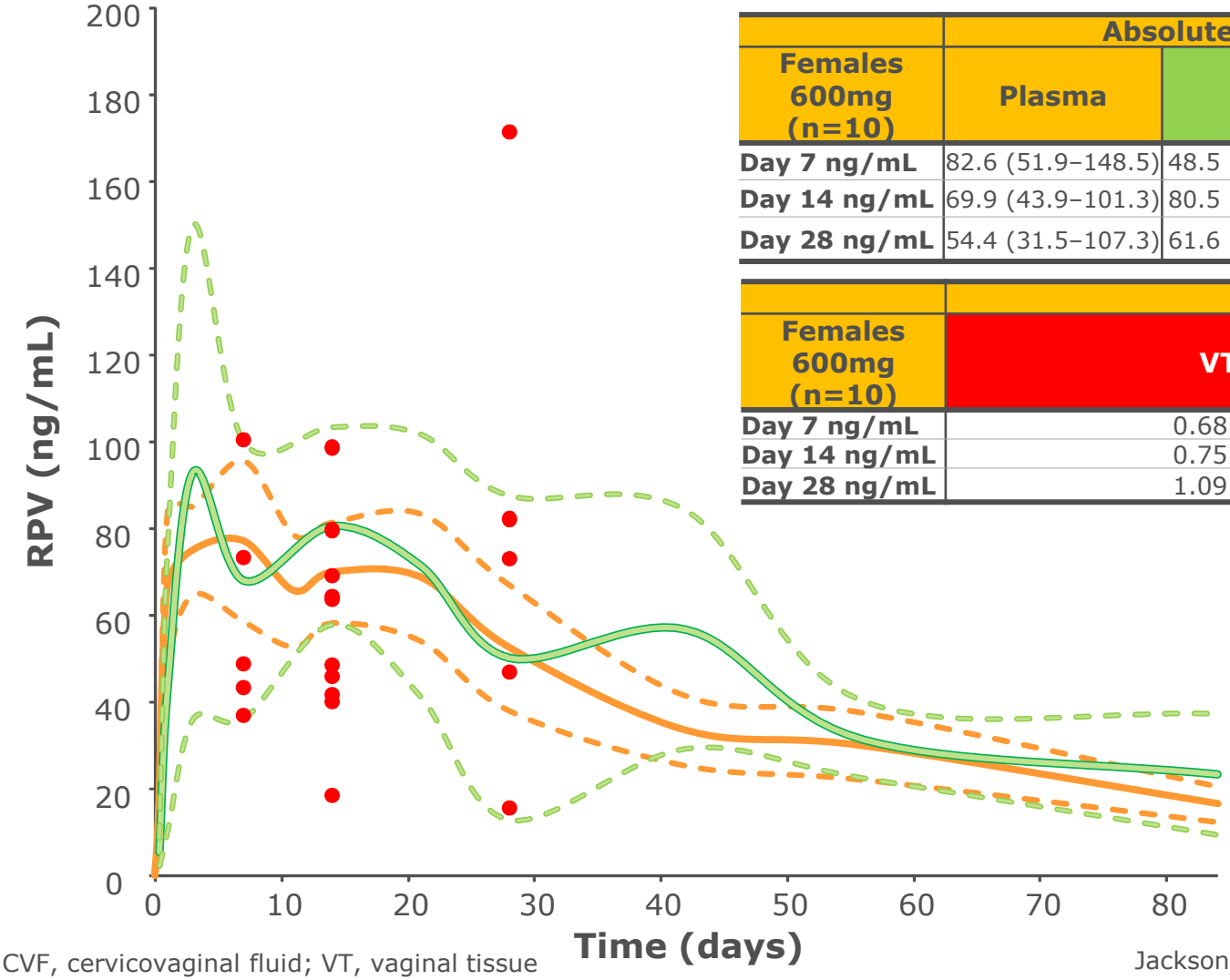
Phase 1 studies (SSAT040, MWRI-01) sponsored by Gates Foundation

Collaboration with PATH (also sponsored by Gates Foundation) and HPTN to develop RPV LA as a prevention measure, in addition to counselling, condoms, etc (HPTN 076)

Aiming for an 8-weekly regimen for women and men at high risk of acquiring HIV infection

PATH, Program for Appropriate Technology in Health; HPTN, HIV Prevention Trials Network

SSAT040: Plasma, CVF and VT RPV 600 mg PK in Females (Geometric Mean; 90% CI)



Females 600mg (n=10)	Absolute concentration		
	Plasma	CVF	VT
Day 7 ng/mL	82.6 (51.9–148.5)	48.5 (18.2–100.9)	56.5 (36.9–100.5)
Day 14 ng/mL	69.9 (43.9–101.3)	80.5 (18.7–166.7)	52.3 (18.6–98.7)
Day 28 ng/mL	54.4 (31.5–107.3)	61.6 (11.9–240.8)	59.6 (15.6–171.4)

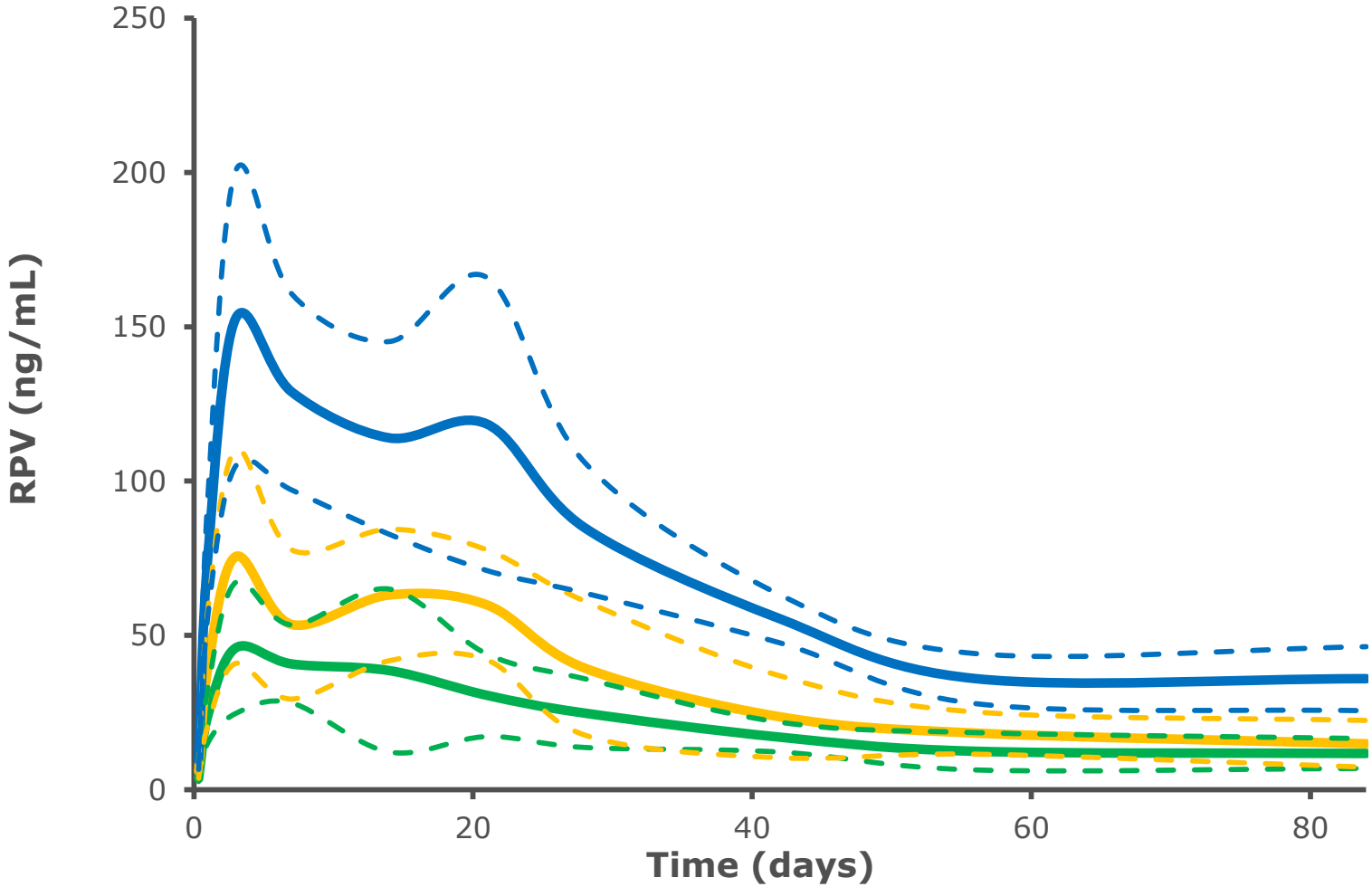
Females 600mg (n=10)	Ratio
	VT:Plasma
Day 7 ng/mL	0.68 (0.43–0.97)
Day 14 ng/mL	0.75 (0.41–1.18)
Day 28 ng/mL	1.09 (0.29–1.60)

CVF, cervicovaginal fluid; VT, vaginal tissue

Jackson et al. CROI 2012 Abstract 35

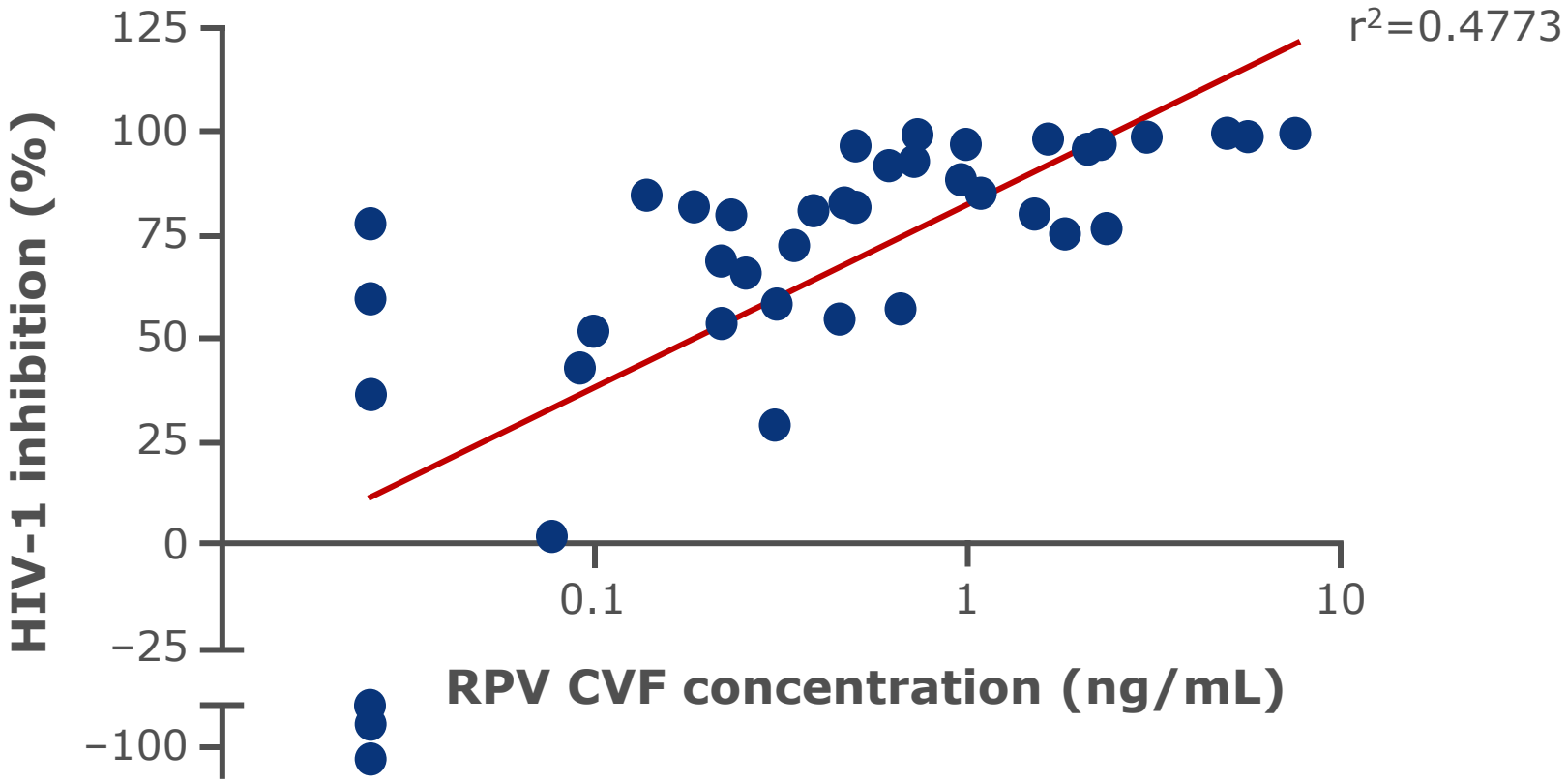
SSAT040: 300, 600 and 1200 mg Doses

Mean (90% CI) RPV Levels in Cervicovaginal Fluid



Jackson AG, et al. Clin Pharmacol Ther 2014;96:314–23

SSAT040: PK/PD in Cervicovaginal Lavage



Lavage samples 28 and 56 days after 300 mg (n=10) and 1200 mg (n=10) doses

Jackson AG, et al. Clin Pharmacol Ther 2014;96:314–23

MWRI-01*: Overall Summary

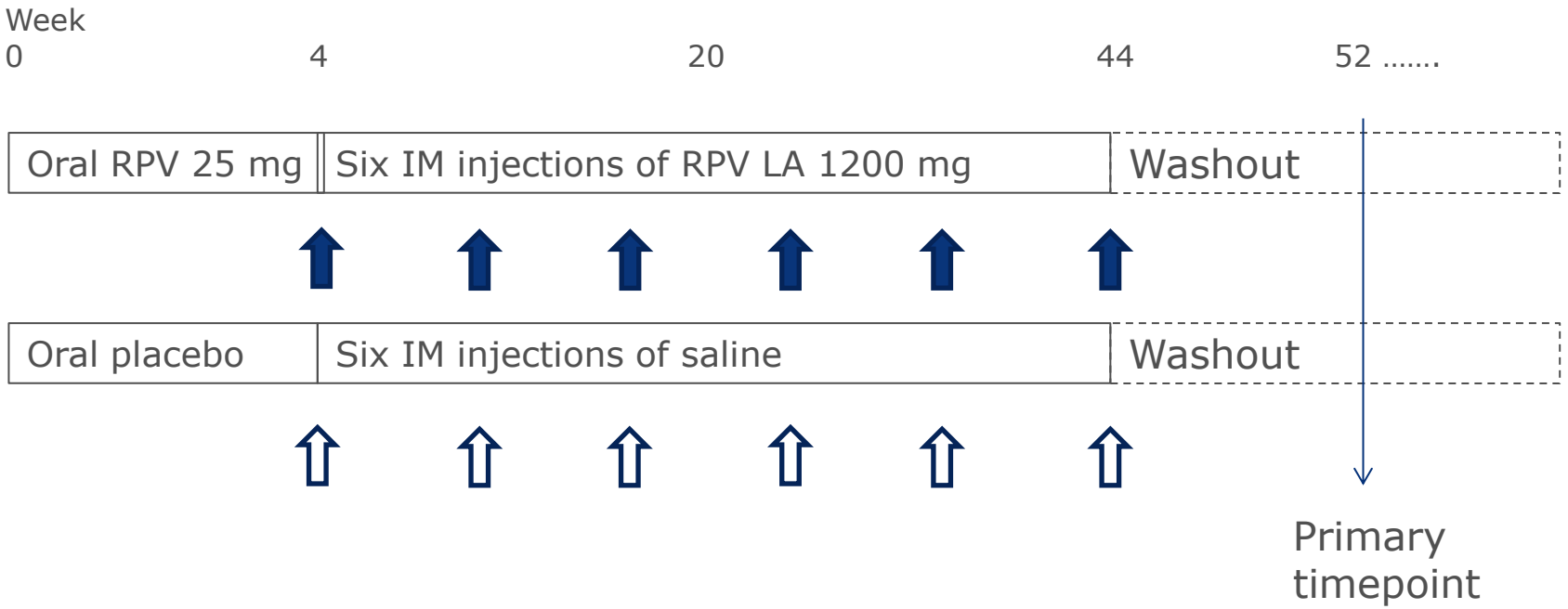
- Single dose RPV LA injectable is safe and acceptable at 1200 mg and 600 mg doses
- Dose dependent compartmental pharmacokinetics was seen following IM injection of RPV LA
  - Levels in rectal tissue were approximately two-fold higher than in cervical or vaginal tissue
- Dose dependent viral inhibition was seen in rectal tissue that persisted out to Day 112 (+4 months)
- Cervicovaginal explant data did not demonstrate significant viral suppression

*NCT01656018

McGowan I, et al. HIVR4P 2014. Abstract OA27.06LB

HPTN 076*: Phase 2 Safety and Acceptability of an Investigational Injectable Product for PrEP

Randomize (2:1) a total of 132 seronegative female volunteers



Primary endpoints: safety/acceptability of 'maximum feasible dose'

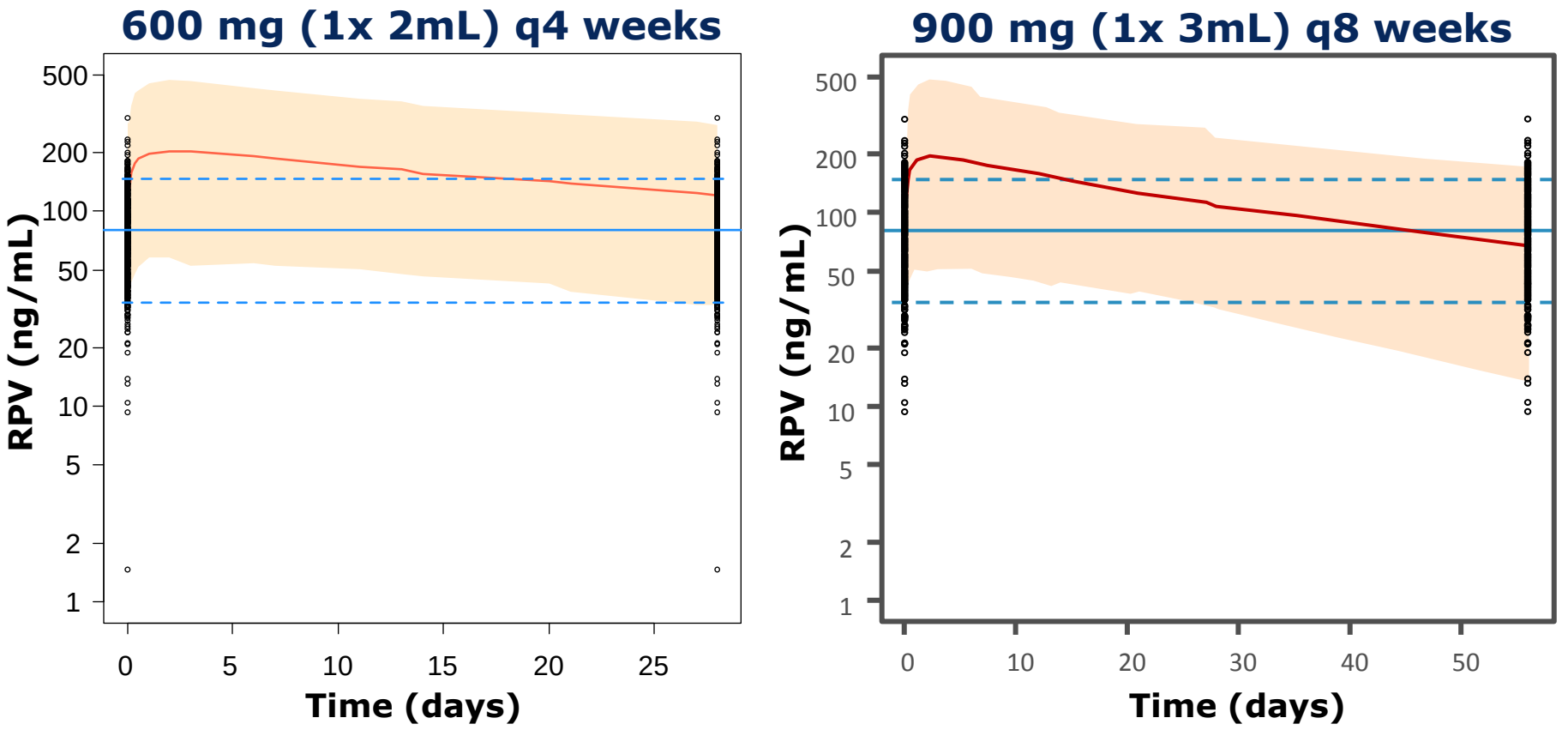
*NCT02165202

RPV LA as Part of First All-injectable ARV Treatment Regimen

ViiV/GSK – Janssen: Partners in development

For details, refer to W. Spreen, 16th HIV-HEPPK

Simulation of injectable RPV LA at steady-state: dose regimens under evaluation (LATTE-2)



Red line is mean profile and shaded area the 5th–95th prediction interval of injectable RPV LA

Open black circles are individual observed C_{0h} in TMC278-C209 and C215

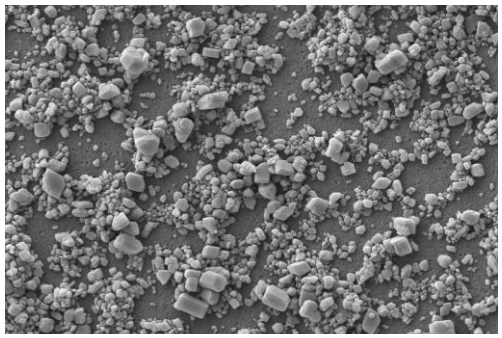
Blue solid line is the mean $C_{0h;}$ Blue dotted lines are the 90% confidence intervals around the mean C_{0h}

RPV LA: Where we are and Future Perspective

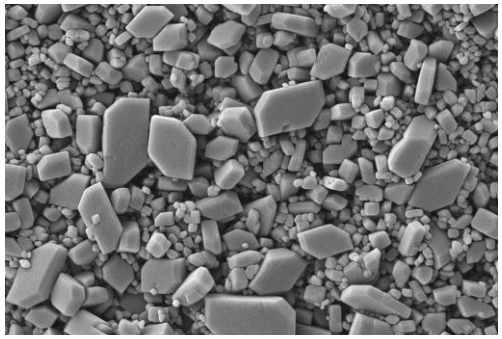
RPV LA: G001 formulation

- Sustained release, apparent terminal half-life 30–90 days
- Plasma RPV levels in range with those for oral RPV in Phase 3
- Substantial distribution into genital and rectal tract
- Generally safe and well tolerated in Phase 1
- Cold chain storage (2 – 8 °C) - Or not?

Target G001



‘Aged’ G001



- Storage room temperature
  - Impact on particle size
  - Impact in vitro dissolution profile
  - In vivo relevance unknown
- Phase 1 relative BA study to evaluate the in vivo impact

RPV LA: Conclusion and Future Perspective

From the results obtained in development so far, RPV LA may have a substantial role to play as

- intermittent PrEP intervention
  - supportive Phase 1/2 trials ongoing
- half of the first all-injectable ARV maintenance regimen
  - currently in Phase 2 of development
  - innovative therapeutic paradigm for patients who find adherence to oral ARV therapy challenging

THANK YOU

- work presented was supported by Janssen R&D, the Bill & Melinda Gates Foundation and ViiV Healthcare
- RPV LA team members Global Public Health and Janssen R&D
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  - Marta Boffito, Akil Jackson, Laura Else and team (SSAT)
  - Olivia Snyder, J. Victor Garcia and team (UNC Chapel Hill)
  - Ian McGowan and team (Univ. Pittsburgh)
  - Bill Spreen, David Margolis, Steve Piscitelli, Susan Ford and team (GSK-ViiV)