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.

17th HIV-HEPPK, Washington, June 2016

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

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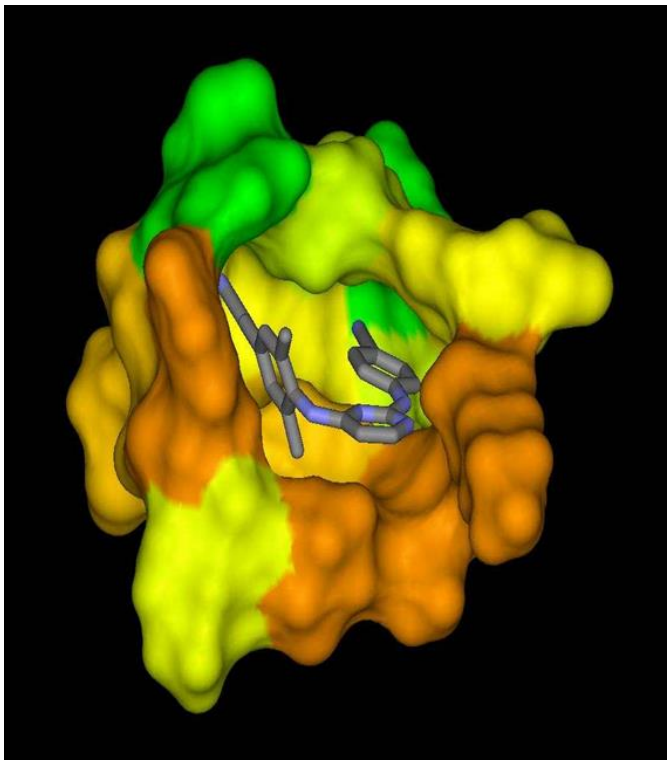
janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

RPV
CAB

TMC
CAB
RPV

Rilpivirine, a potent NNRTI

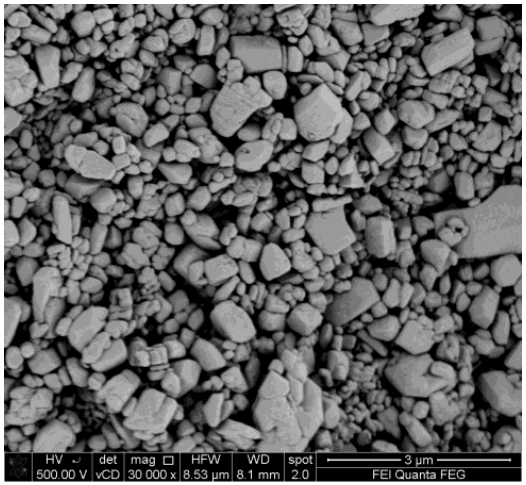


- 0.26 nM median EC_{50} against HIV-1 primary clinical isolates[1]
- $t_{1/2}$ ~45 hours[2]
- CYP3A substrate
- no clinically relevant impact on metabolism of other drugs[2]
- therapeutic oral dose 25 mg qd[3]
- Approved as single agent (EDURANT®) for treatment of HIV-1 combined with other ARVs, and as part of once-daily full regimen FDC (COMPLERA/EVIPLERA/ODEFSEY®, GSI)*
- other (co-)developments ongoing

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

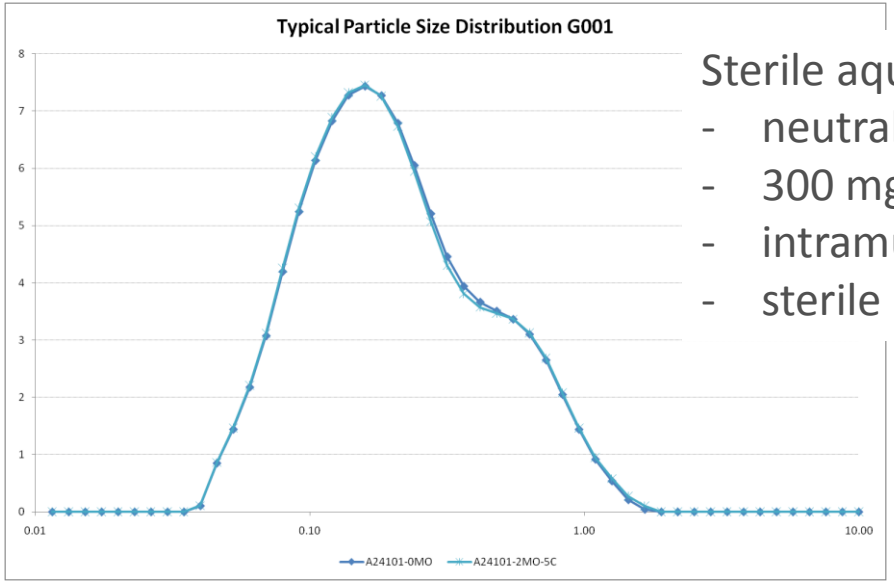
1. Azijn H, et al. AAC 2010;54:718–27
2. Crauwels H et al. AIDS Rev. 2013;15:87-101
3. Cohen CJ, et al. AIDS 2013;27:939–50.

Rilpivirine Long-Acting Nanosuspension



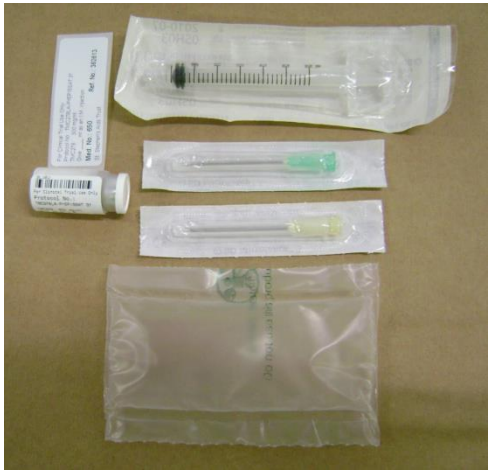
NanoCrystal® technology*

- improved bioavailability and absorption of sparingly soluble/insoluble drugs
- wet bead milling (Netzsch)
- particles of pure RPV, average size of 200 nm
  (D10 ~ 75 nm; D50 ~200 nm; D90 ~600-700 nm)



Sterile aqueous formulation G001

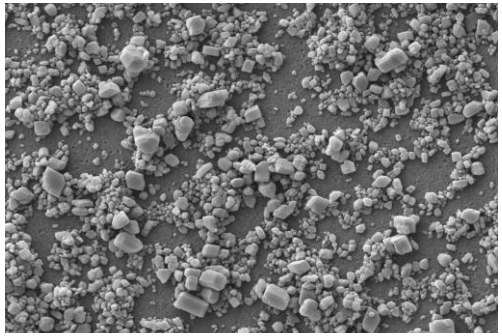
- neutral pH
- 300 mg/mL
- intramuscular injection
- sterile manufacturing process



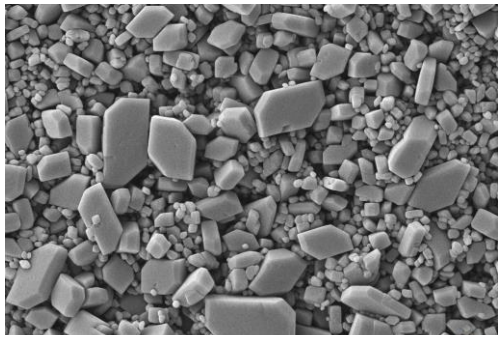
RPV LA: G001 formulation

- apparent terminal half-life 30–90 days
- substantial distribution into genital and rectal tract
- generally well tolerated
- cold chain storage (2 – 8 °C) - Or not?

Refrigerated product



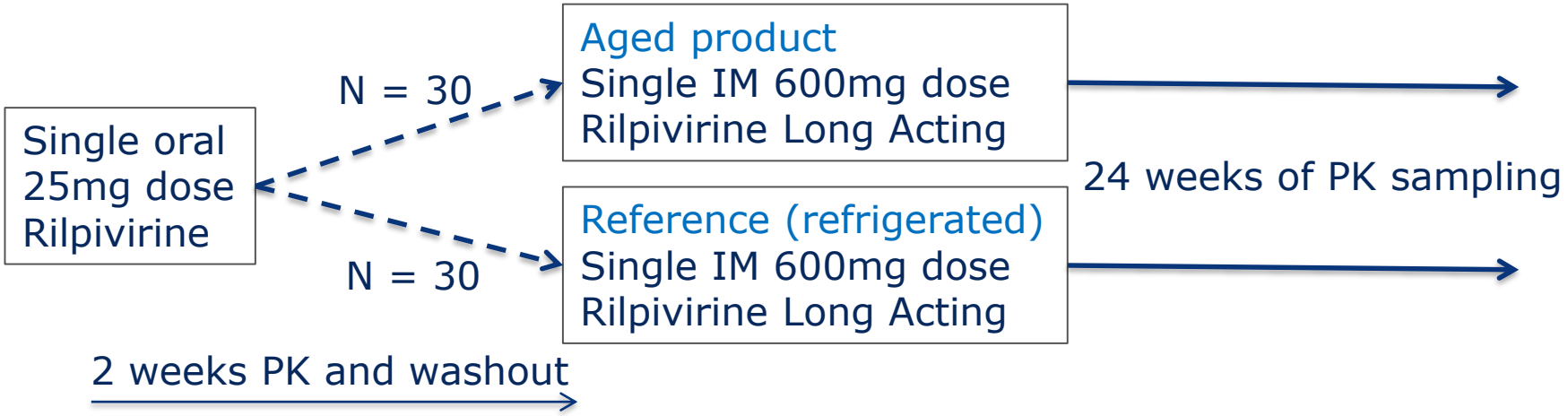
'Aged' product



- Storage at room temperature
  - Impact on particle size/morphology
  - Impact on *in vitro* dissolution profile
  - In vivo relevance unknown
- Phase 1 relative bioavailability study (TMC278LAHTX1001)

Parallel group PK study, NCT02547870

- N=60 HIV-negative volunteers, randomisation stratified for gender and BMI



May lead to further study and evaluation of **IVIVC**

- **IVIVC = I**n **V**itro (dissolution) **I**n **V**ivo (PK) **C**orrelation
- Objectives
  - Evaluate the in vivo impact of particle size differences:
    - different milling times
    - stability sample (1-2M at 40 °C)
  - Support clinically relevant specifications for particle size and in vitro release

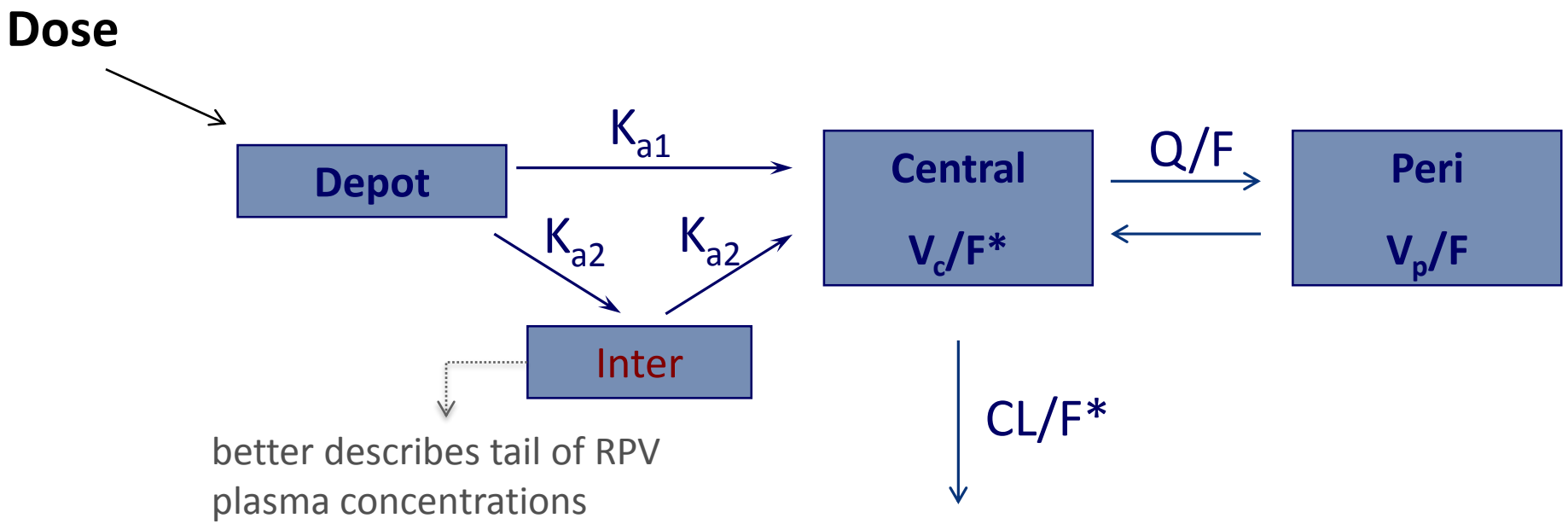
RPV LA (G001) Clinical development

- Study SSAT040 (NCT01275443)[1]
  - Single dose (300, 600, 1200 mg), mainly in female healthy volunteers (HV), n=66
- Study C158 (NCT01031589)[2]
  - Single (300, 600 mg) and multiple dose (1200/600/600 mg) in HV, n=17
- Study LAI115428 (NCT01593046)[3]
  - Multiple dose (1200/600 or 1200/900 mg) in HV, n=20
- PK/PD study TMC278-MWRI-01 (NCT01656018)[4]
  - Single dose (300, 600, 1200 mg) in HV, n=36
  - Multiple dose (1200/1200/1200 mg) in HV, n=12 (ongoing)
- Study TMC278LAHTX1001 (NCT02547870)
  - Single dose (600 mg) of fresh or aged G001, in HV, n=60 (ongoing)
- HPTN076 (NCT02165202)
  - Phase 2 Safety and Acceptability Study of RPV LA for PrEP (ongoing)
  - 6 injections (Q8W) of (2:1) RPV LA 1200 mg or placebo, n=132 seronegative women
- CAB LA + RPV LA Phase 2b study - LATTE-2 (NCT02120352)[5]
  - Q4wks (n=115), Q8wks (n=115) versus oral ART (n=56) (ongoing)
- CAB LA + RPV LA Phase 3 studies – ATLAS and FLAIR (planned)[6]

1. Jackson AG et al. ClinPharmTher 2014;96:314–323
2. Verloes R et al. HIV med 2015;16:477–484
3. Spreen W et al. JAIDS 2014;67:487–492
4. McGowan I et al. Abstract OA27.06 LB. HIVR4P, 2014
5. Margolis D et al. Abstract 31LB. CROI, 2016
6. Spreen W et al. 17th HIVHEPPK, 2016

Population Pharmacokinetic model (POPPK) Structural model

2-compartment model with
first order absorption, linear pharmacokinetics
first order elimination from the central compartment



* fixed to oral RPV PK model[1] parameters

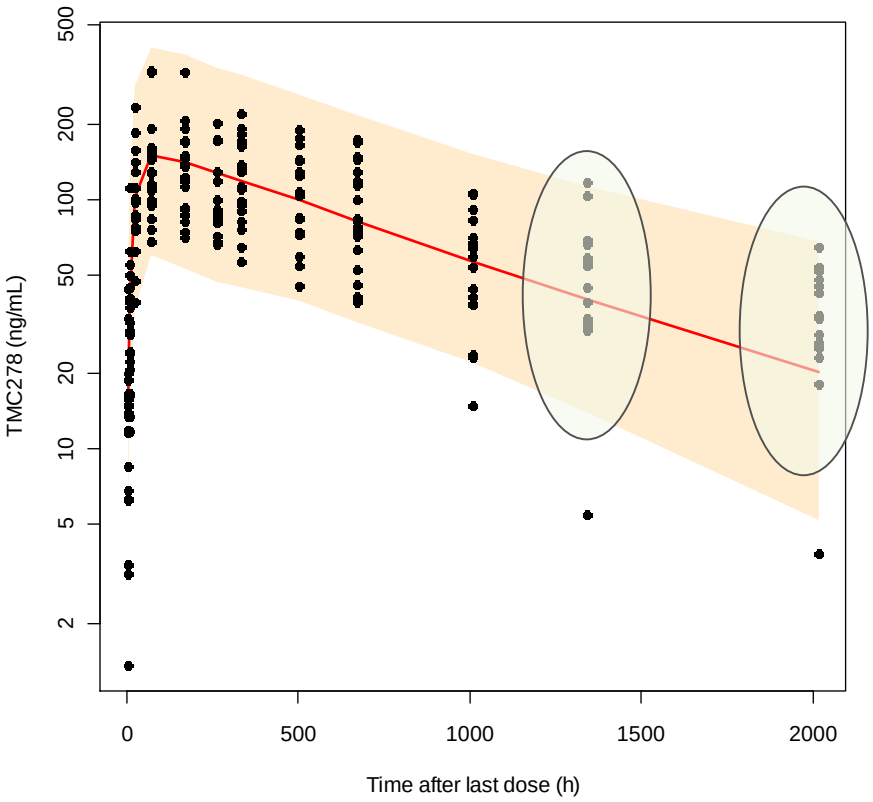
Modelling performed within NONMEM VII

[1]Crauwels et al (2010) HIV10. P186

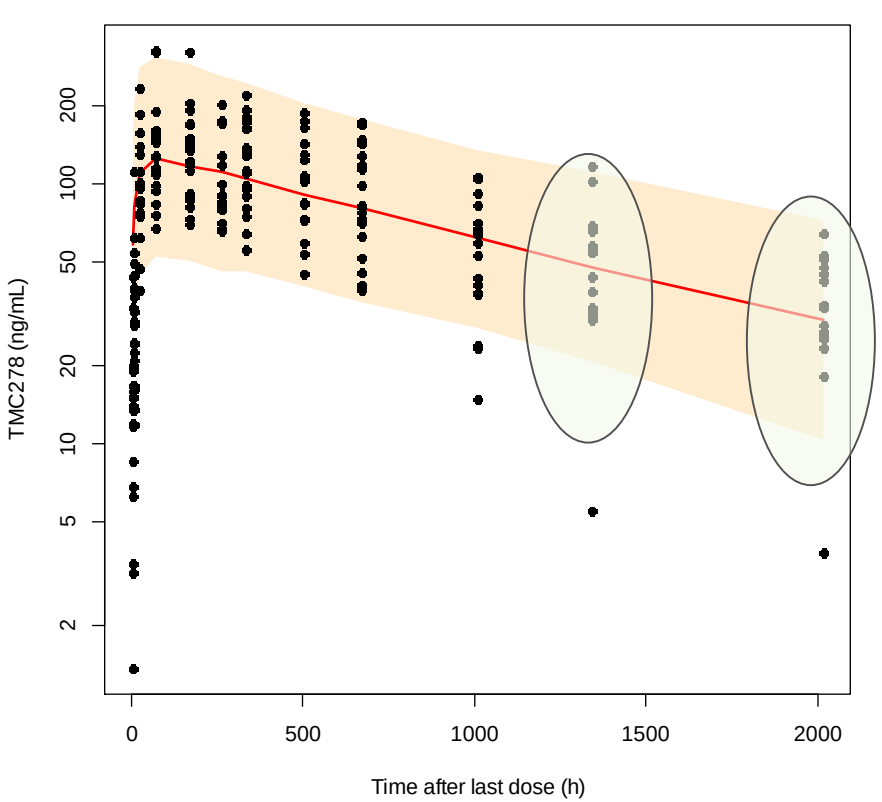
Visual Predictive Check (VPC) model with and w/o intermediate compartment

- Before using the model for simulation purposes, a VPC was performed to evaluate the model predictiveness

No intermediate compartment



With intermediate compartment

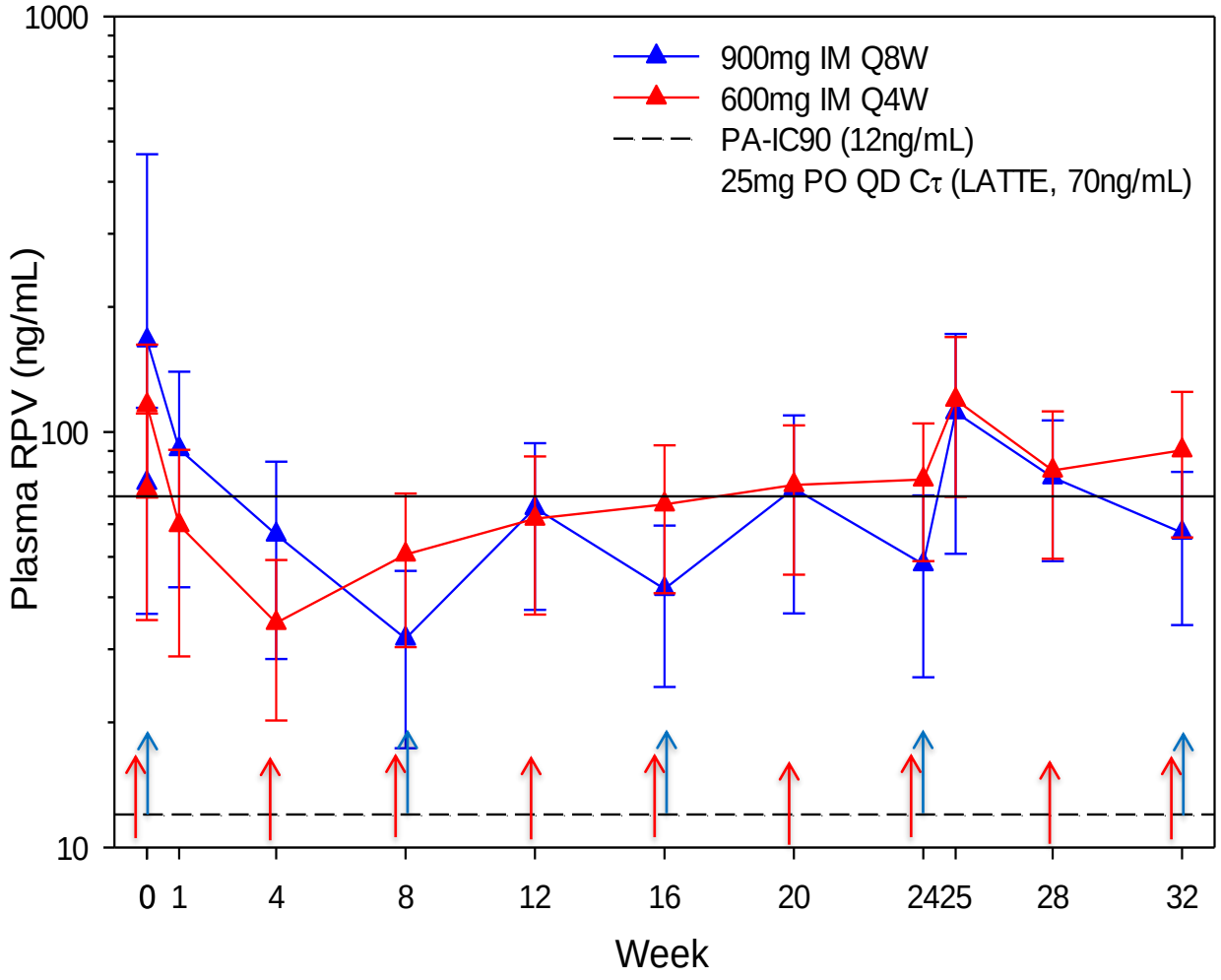


Optimisation LA Dosing Regimens

- Design CAB LA + RPV LA dosing regimen that
  - achieves steady-state as soon as possible
  - avoids lower ARV plasma concentrations early on
  - is an aligned regimen for both compounds
  - is practically feasible regimen (also beyond clinical trial)

- Several strategies evaluated, e.g.
  - different timings (interval) in between 1st and 2nd dose
  - higher 1st dose
  - evaluate impact oral lead-in for PK after LA

Mean (SD) RPV Observed Plasma Concentrations Over Time, Q4Wk and Q8Wk (LATTE-2, W32)



mean C_{0h} oral RPV Phase 3 (range: 1.5 – 300 ng/mL)

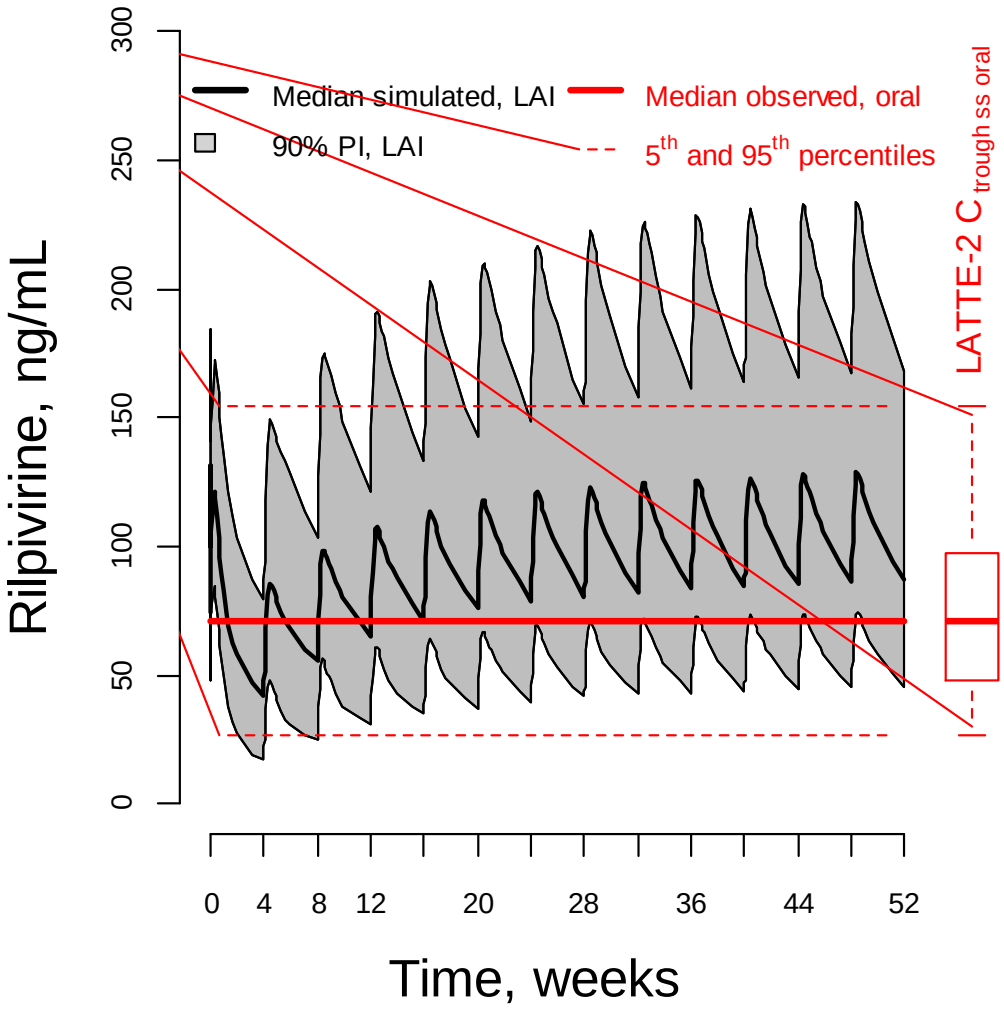
- similar in LATTE
- similar at start of injections LATTE-2

↑ Injection Q4Wk

↑ Injection Q8Wk

5. Margolis D et al. Abstract 31LB. CROI, 2016

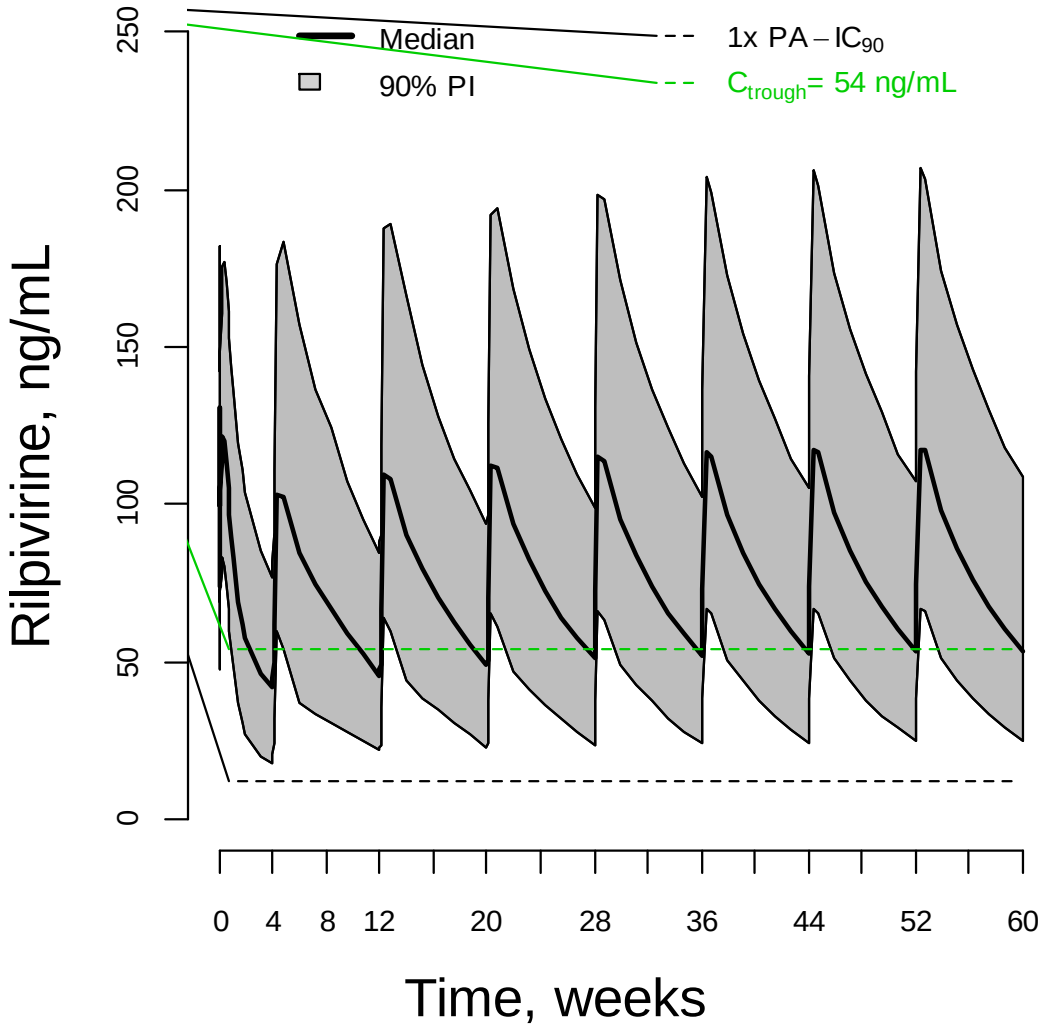
Revised Q4W dosing regimen RPV LA



- Loading dose Day 1: 900mg (3mL)
- Week 4 and onwards:
  - 600mg (2mL)
  - every 4 weeks

- Median C_{trough} ~86ng/mL
- ~99.5% subjects with C_{trough} above 5th percentile LATTE-2 C_{trough} at steady state (2x PA IC90)

Revised Q8W dosing regimen RPV LA



- 900mg on Day 1 and Week 4
- Week 12 and onwards:
  - 900mg
  - every 8 weeks

- Median C_{trough} ~54ng/mL
- ~93% subjects with C_{trough} above 5th percentile LATTE-2 C_{trough} at steady state (2x PA IC90)

Oral lead-in of rilpivirine (EDURANT) 25mg q.d.?

- 4 weeks dosing before the first LA injection during which any serious adverse drug reaction could be detected
- apparent half-life of RPV LA means RPV may be detectable in plasma (LLOQ = 1ng/mL) more than a year after an LA injection

Included oral lead-in

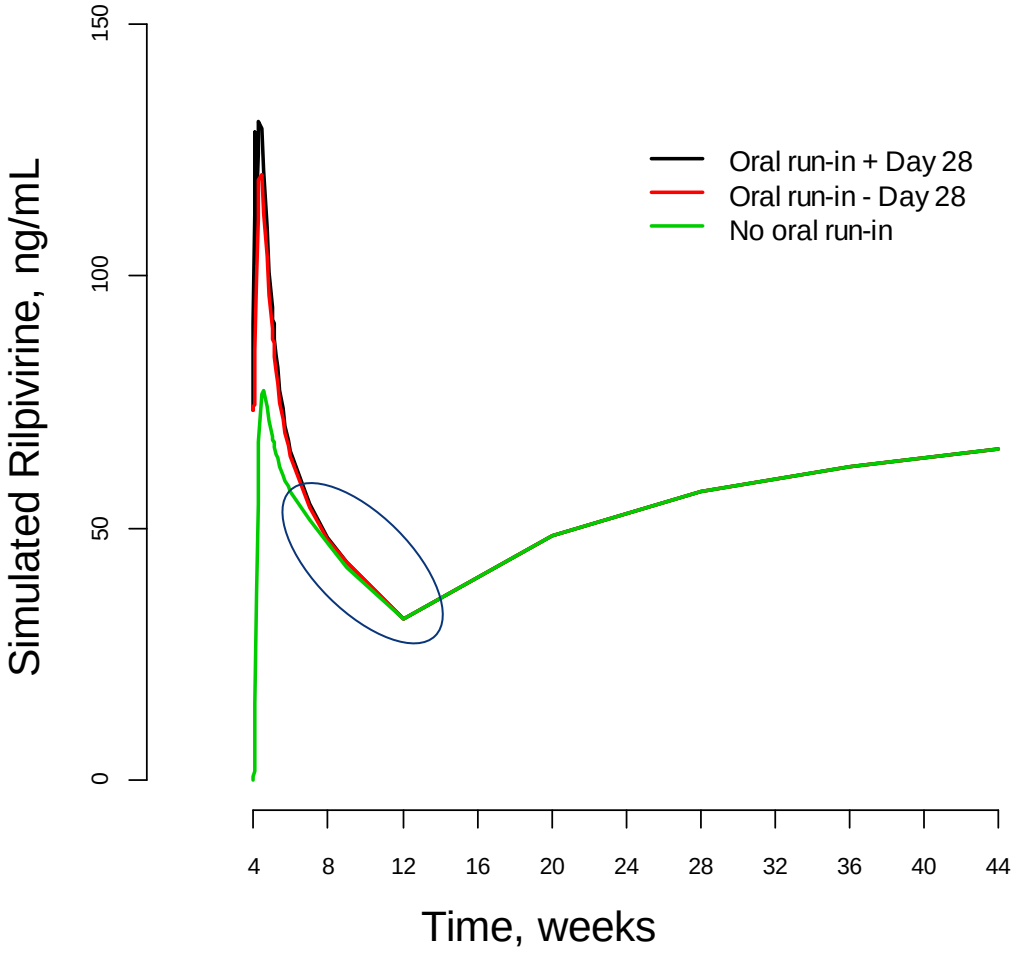
LATTE-2 (n= 230 patients)
HPTN 076 (n= 80 HV)

Not included

C158 (n= 17 HV)
SSAT040 (n = 60 HV)
MWRI-01 (n = 36 +12 HV)
LAI115428 (n = 20 HV)
HTX1001 (n = 60 HV)

Supported by safety in RPV clinical Phase 3, n= 686 patients
Pharmacovigilance since approvals of oral formulations in 2011

Oral lead-in has no significant impact for RPV LA PK profile



- Higher concentrations on day of injection (peak oral)
- No significant impact on RPV LA PK profile from ~2 weeks postdose onwards
- Inclusion of oral lead-in based on safety considerations only

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
- half of the first all-injectable ARV maintenance regimen
  - innovative therapeutic paradigm for patients, who find adherence to oral ARV therapy challenging
  - currently in Phase 2 of development[1]
  - Phase 3 in preparation[2]

1. Margolis D et al. Abstract 31LB. CROI, 2016
2. Spreen W et al. 17th HIVHEPPK, 2016

THANK YOU

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- Clinical Study Participants and Investigative Staff

- RPV (LA) team members Global Public Health and Janssen R&D

- CAB (LA) team (GlaxoSmithKline R&D and ViiV Healthcare)

- Our collaborators
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  - Ian McGowan and team (MWRI-01/Univ. Pittsburgh)
  - HPTN