AVAC

Global Advocacy for HIV Prevention

The Future of PrEP Shots and Potent Treatment: An Advocate's Guide to Long-Acting Injectables

Research & Reality dialogue series
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www.avac.org/advocacy2014

GSK 744 LA: A Next Generation PrEP Candidate

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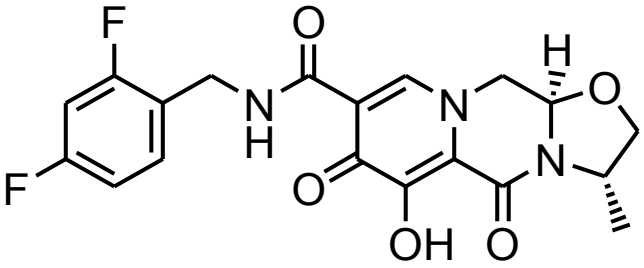
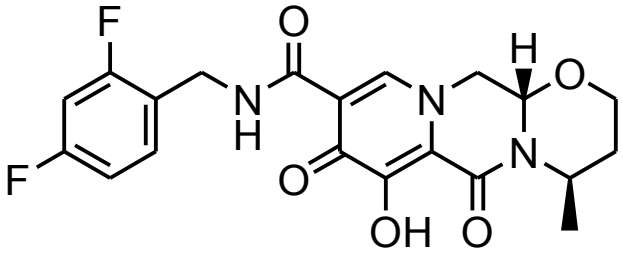
GSK744 is a potent inhibitor of integrase-mediated strand transfer and HIV-1 replication

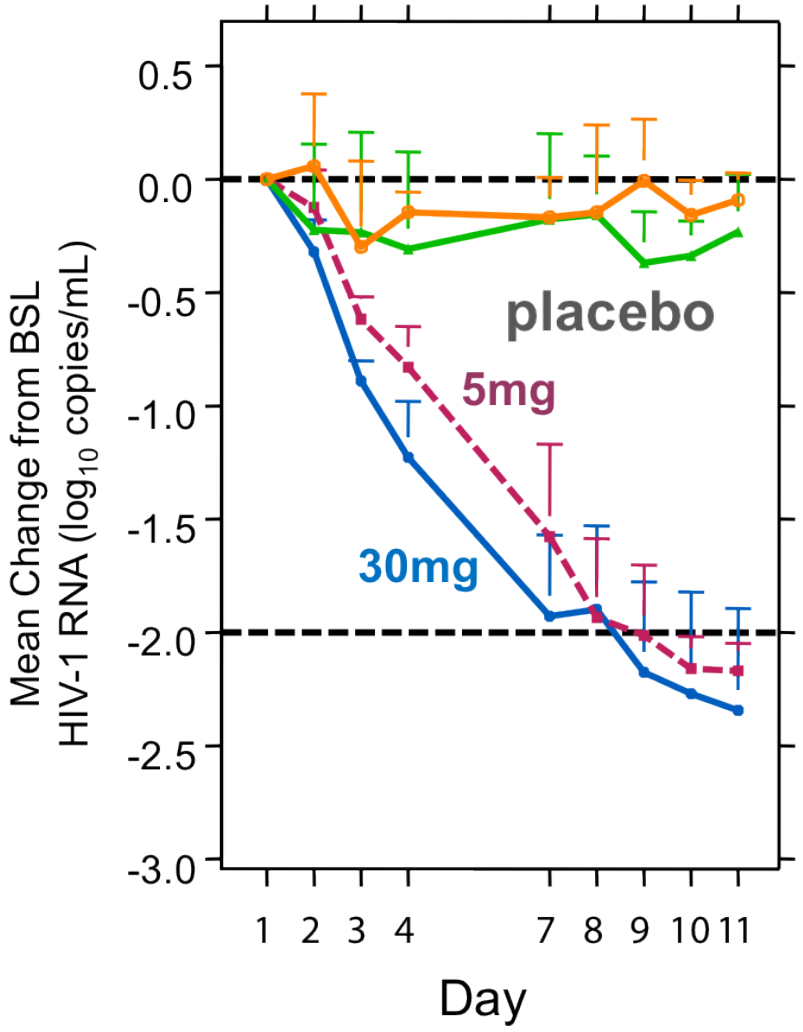
GSK1265744 (GSK744)



Dolutegravir

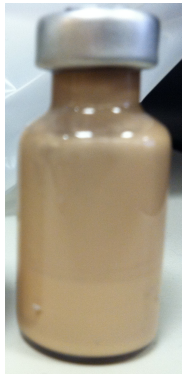


Protein adjusted IC_{90}= 166ng/mL

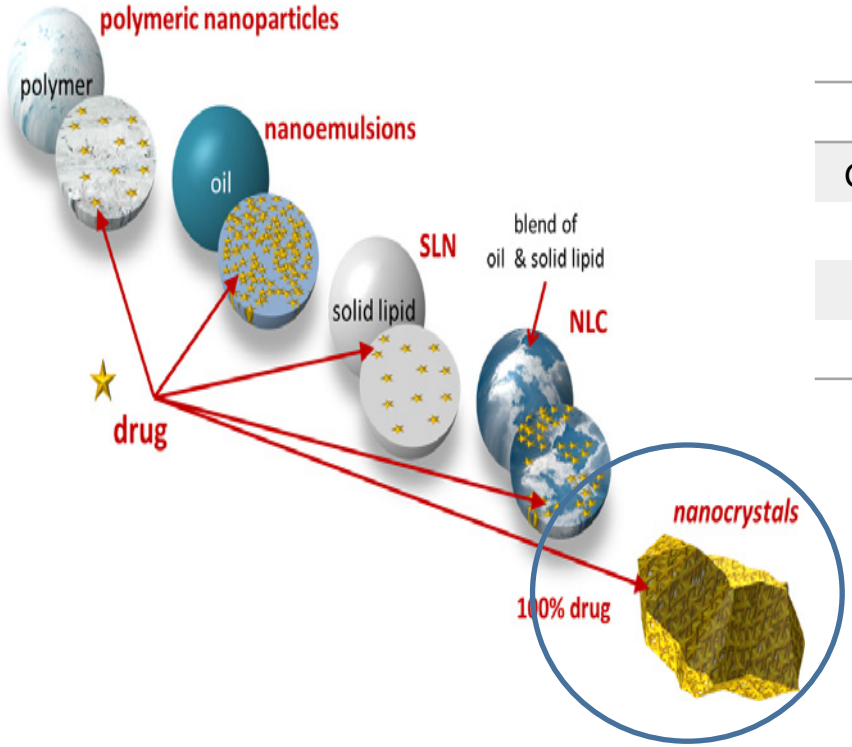


W. Spreen, et al, 19th IAC July 2012. Abstract TUPE040
S. Min, et al, 49th ICAAC, Sept 2009. Abstract H-1228
Y. Taoda, et al, 11th International Congress on Drug Therapy in HIV Infection, Nov 2012. Abstract P206

GSK744 LA nanosuspension



- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading vs. matrix approaches for lower inj. volumes



GSK744 LA 200 mg/mL

Component	Function
GSK1265744A (d50 ~200 nm)	Active
Mannitol	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

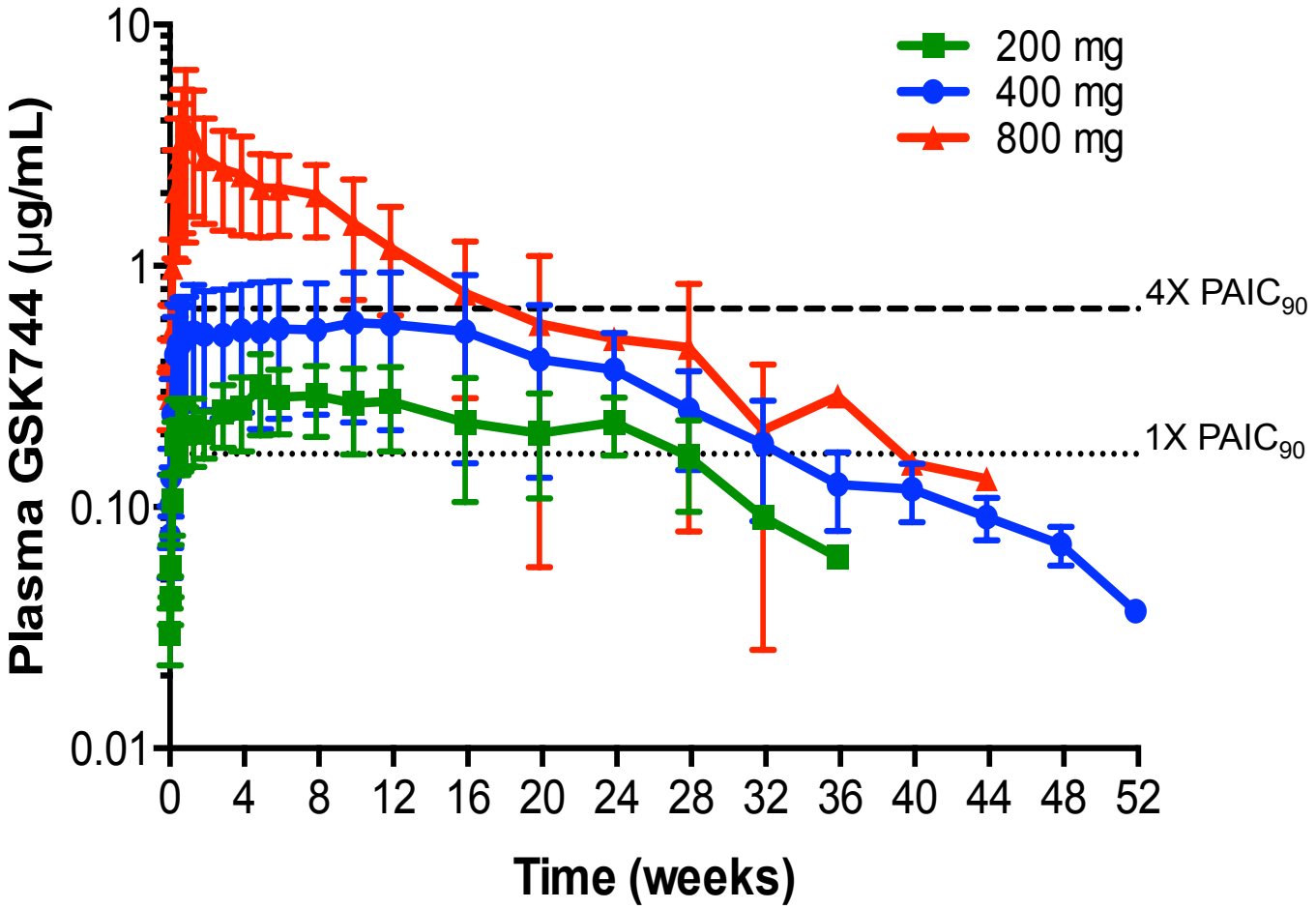
R H. Müller, et al. European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 1-9

GSK744 Clinical Trial Exposure Data (through June 30th, 2013)

Treatment Population/ Dose	Duration	Total
Healthy Volunteers		**287[a]**
5 to 150 mg	Single dose	91
10 to 30 mg once daily	10 to 14 days	138
100 – 800 mg IM/SC LA	Max 389 days	136
HIV infected patients		**196**
5 to 30 mg once daily (Ph IIa)	10 days	15
10 to 60 mg once daily (Ph IIb)	Max 306 days	181
Total		**483**

[a]78 subjects received oral and LA

Pharmacokinetic evaluation of a single intramuscular GSK744 LA injection in human volunteers



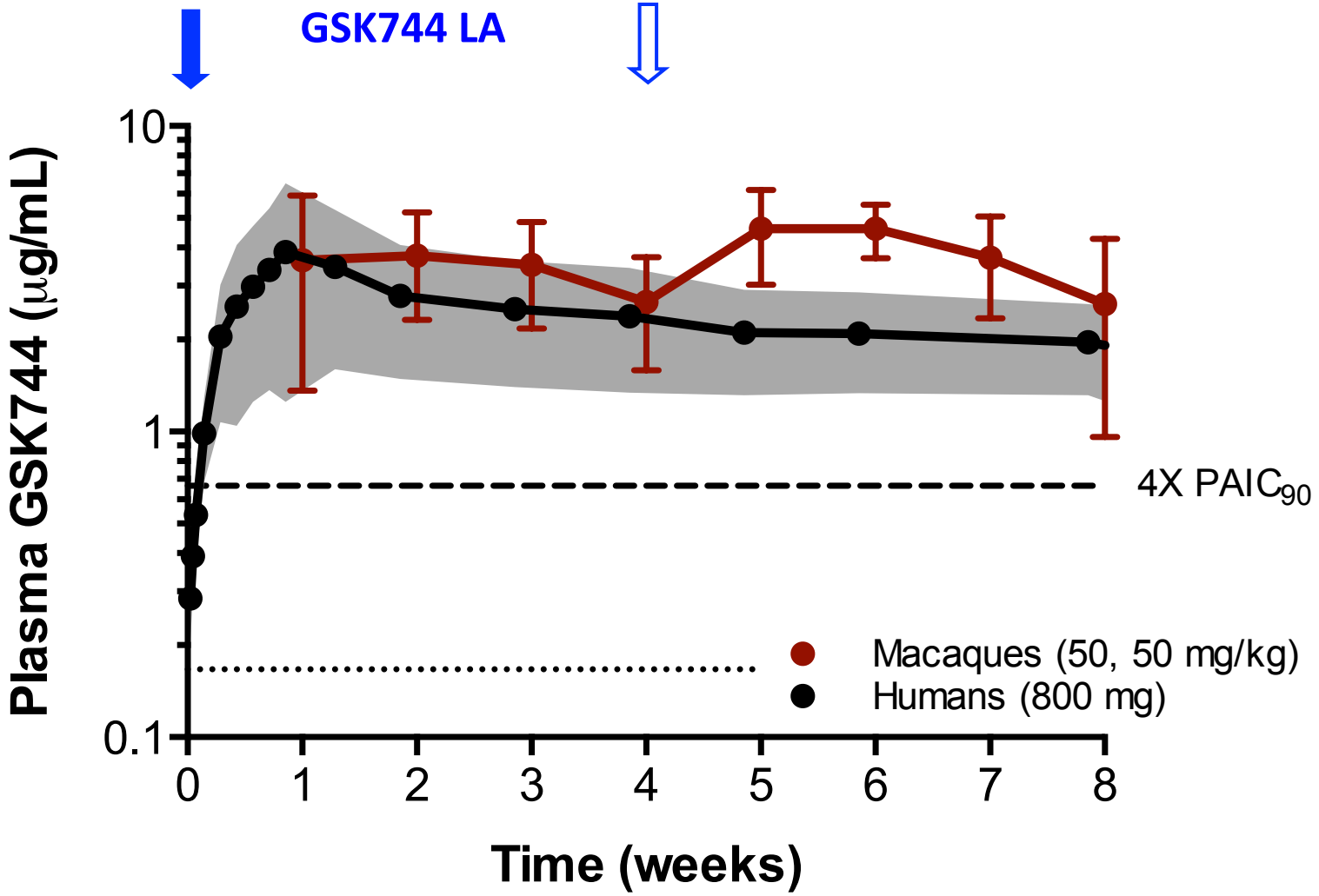
Injection Site Safety Results: Local Injection Site Reactions (ISRs) Are Common but Generally Well-tolerated and Self-limited

	GSK744 (IM)		
No. subjects w/ injections	N=40		
Max no. inj. per subject/ actual total per group	5 / 156		
No. subjects reporting any ISR on study	32 (80%)		
	ISR: n (%) or mean (range)		
ISR Events, n (% of total events)	mild	moderate	duration (days)
Any	116 (81)	28 (19)	--
Pain	76 (53)	28 (19)	5 (1-32)
Erythema	11 (8)	0	9 (1-31)
Nodule	6 (4)	0	31 (5-71)

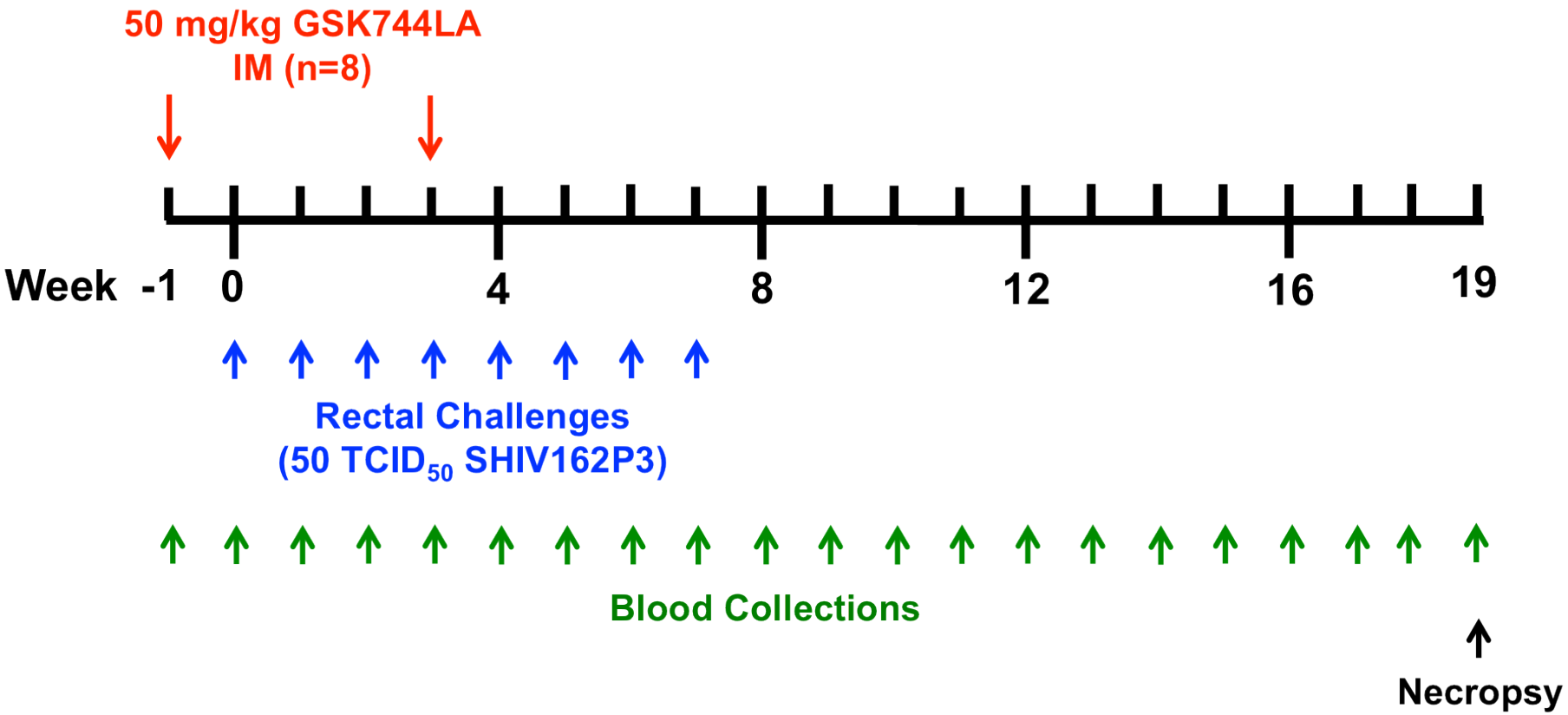
Development of GSK744 LA as PrEP

- Low dose intrarectal challenge studies in rhesus macaques
  - To provide rationale for efficacy studies in high risk MSM
- High dose intravaginal challenge in rhesus macaque and low dose intravaginal challenge in pigtail macaques
  - To provide rationale for efficacy studies in high risk women
- Phase 2 clinical trials: N=280 subjects
  - Safety
  - Acceptability
- Phase 3 clinical trials: N= 2400+ subjects
  - Minimum of 2 trials with at least 1200 subjects each in high-risk MSM and high-risk women
  - Primary endpoint: efficacy

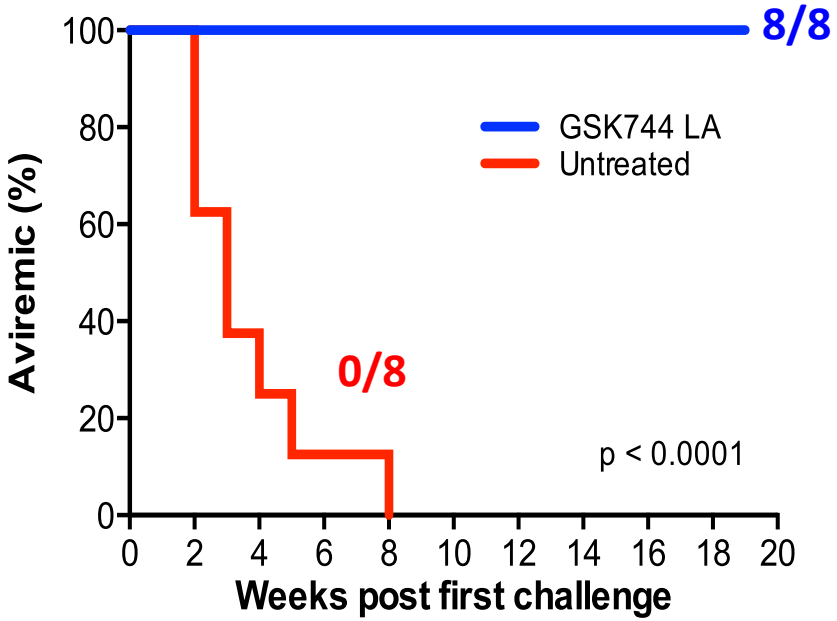
GSK744 plasma concentrations in protected macaques are comparable to those achieved in humans

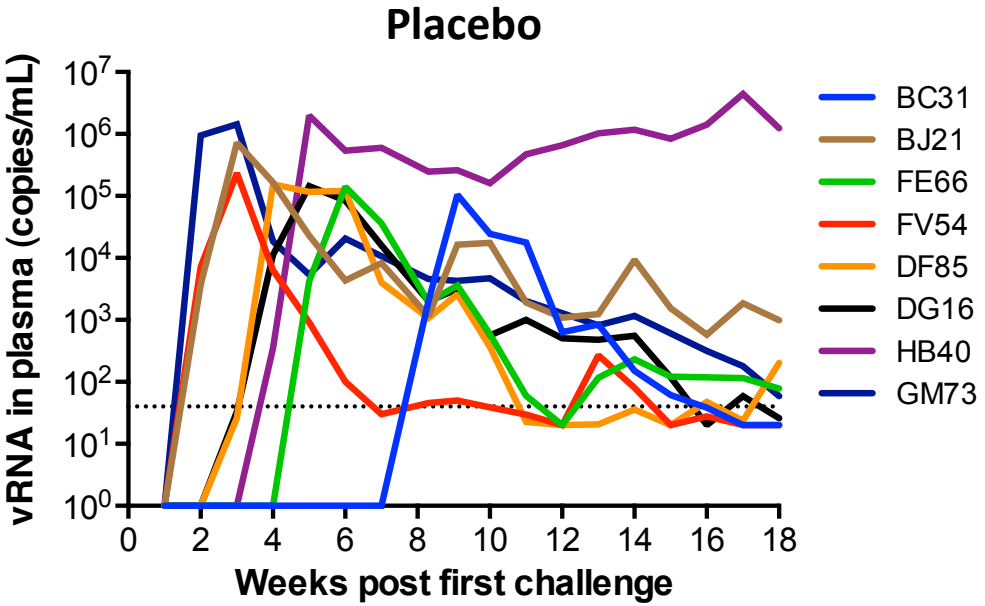


Repeated low-dose intrarectal challenges to evaluate GSK744 LA as PrEP in 16 Indian rhesus macaques

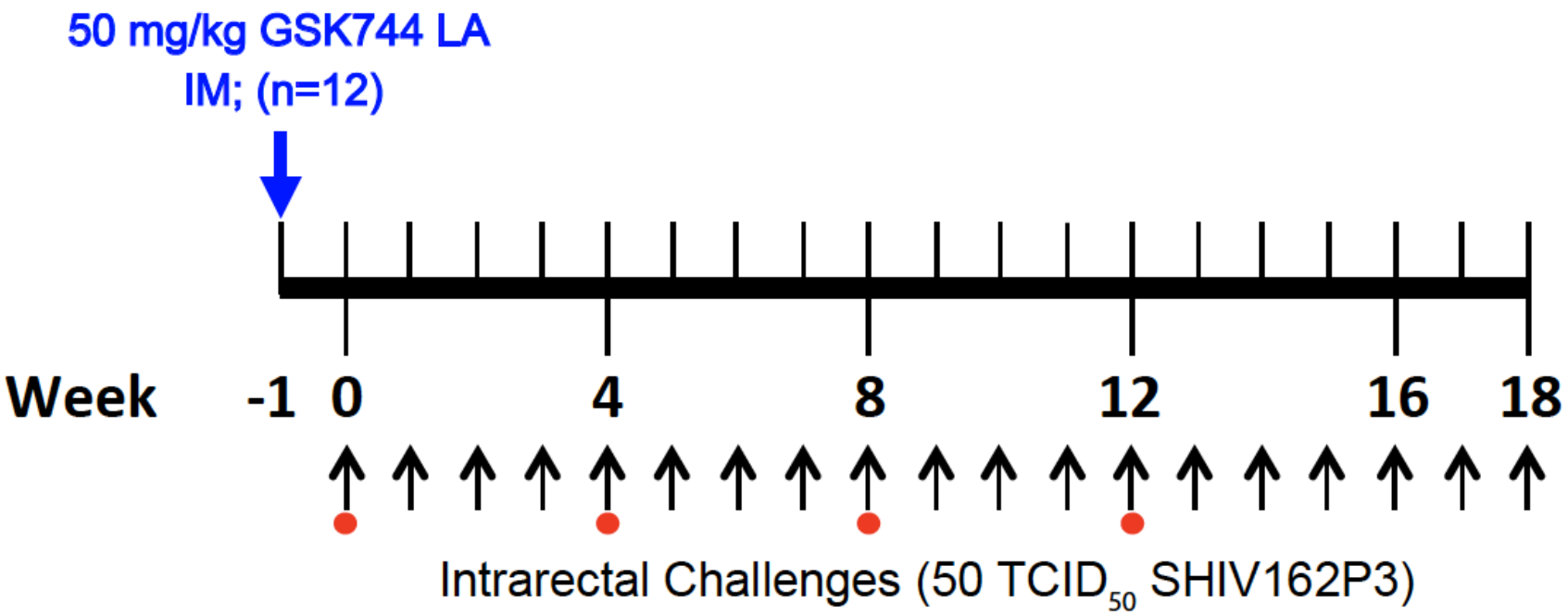


GSK744LA is an effective PrEP agent in rhesus macaques



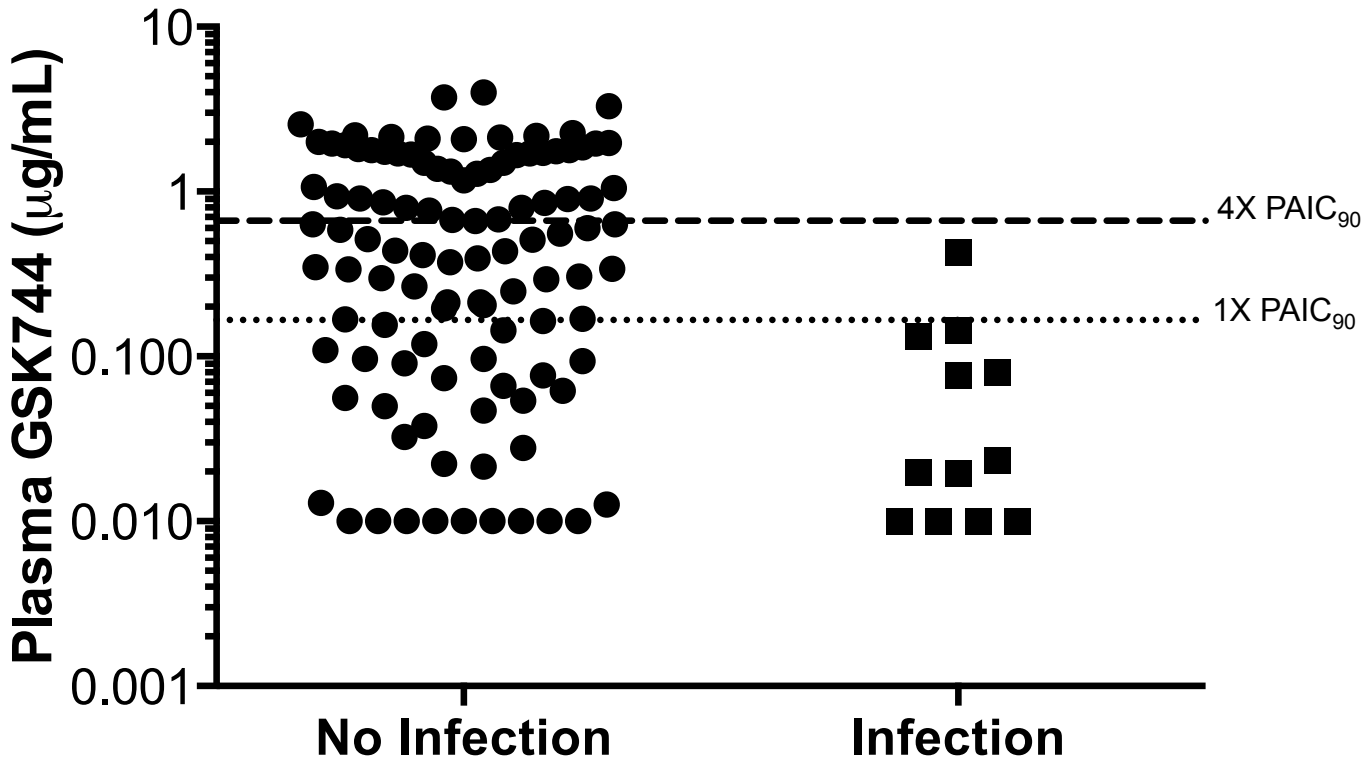


Repeated low-dose IR challenges to evaluate threshold GSK744 LA concentrations for protection in 16 macaques

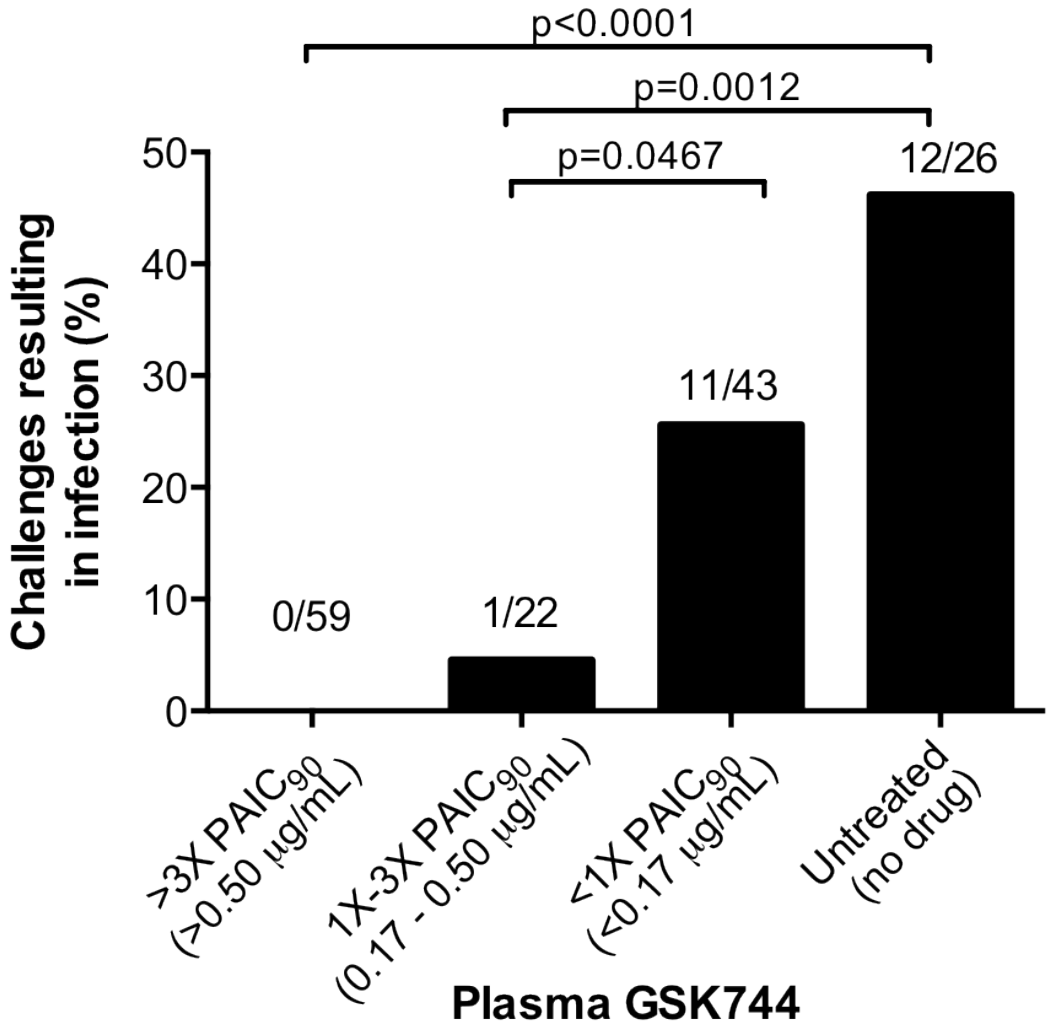


● = 1 control macaque begins challenge

GSK744 plasma concentrations resulting in infection during repeated low-dose IR challenges are <3X $PAIC_{90}$



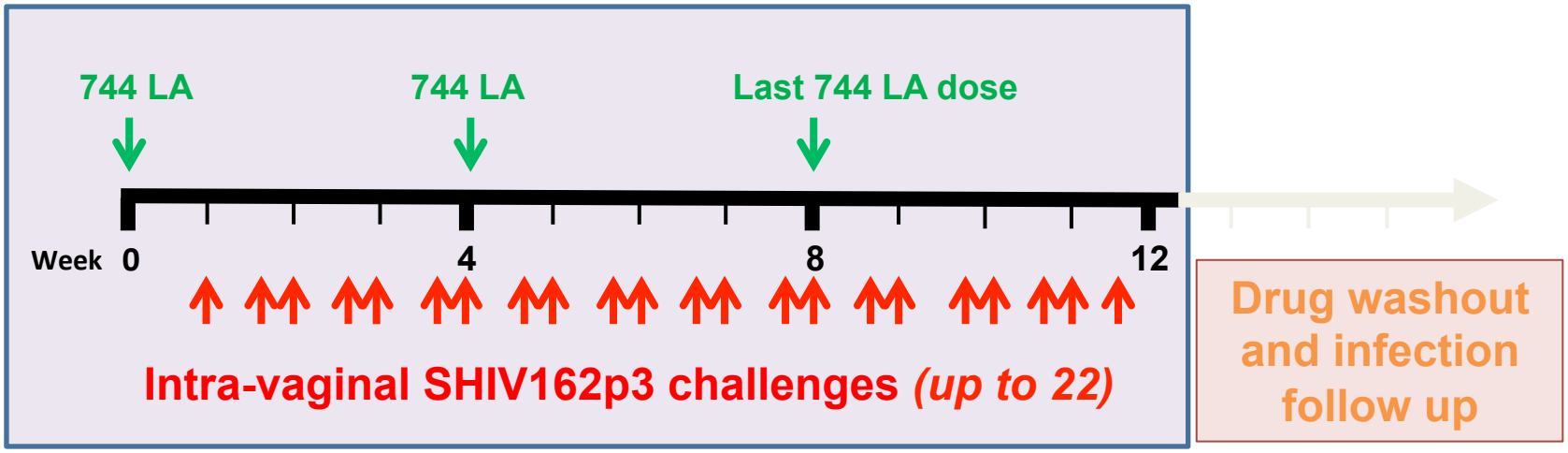
GSK744 plasma concentrations >3X $PAIC_{90}$ result in 100% protection, while ≥1X$PAIC_{90}$ are 97% effective



Summary of Preclinical Evaluation in Male Rhesus Macaques

- GSK744 LA has afforded high-level protection against repeated intrarectal SHIV challenges in rhesus macaques
- GSK744 plasma concentrations >3X $PAIC_{90}$ result in 100% protection, while levels ≥1X $PAIC_{90}$ provide ~97% protection
- GSK744 plasma levels corresponding to protection can be readily achieved in man with quarterly 800 mg intramuscular injections
- These data support moving GSK744 LA into clinical evaluation as PrEP in high-risk men who have sex with men

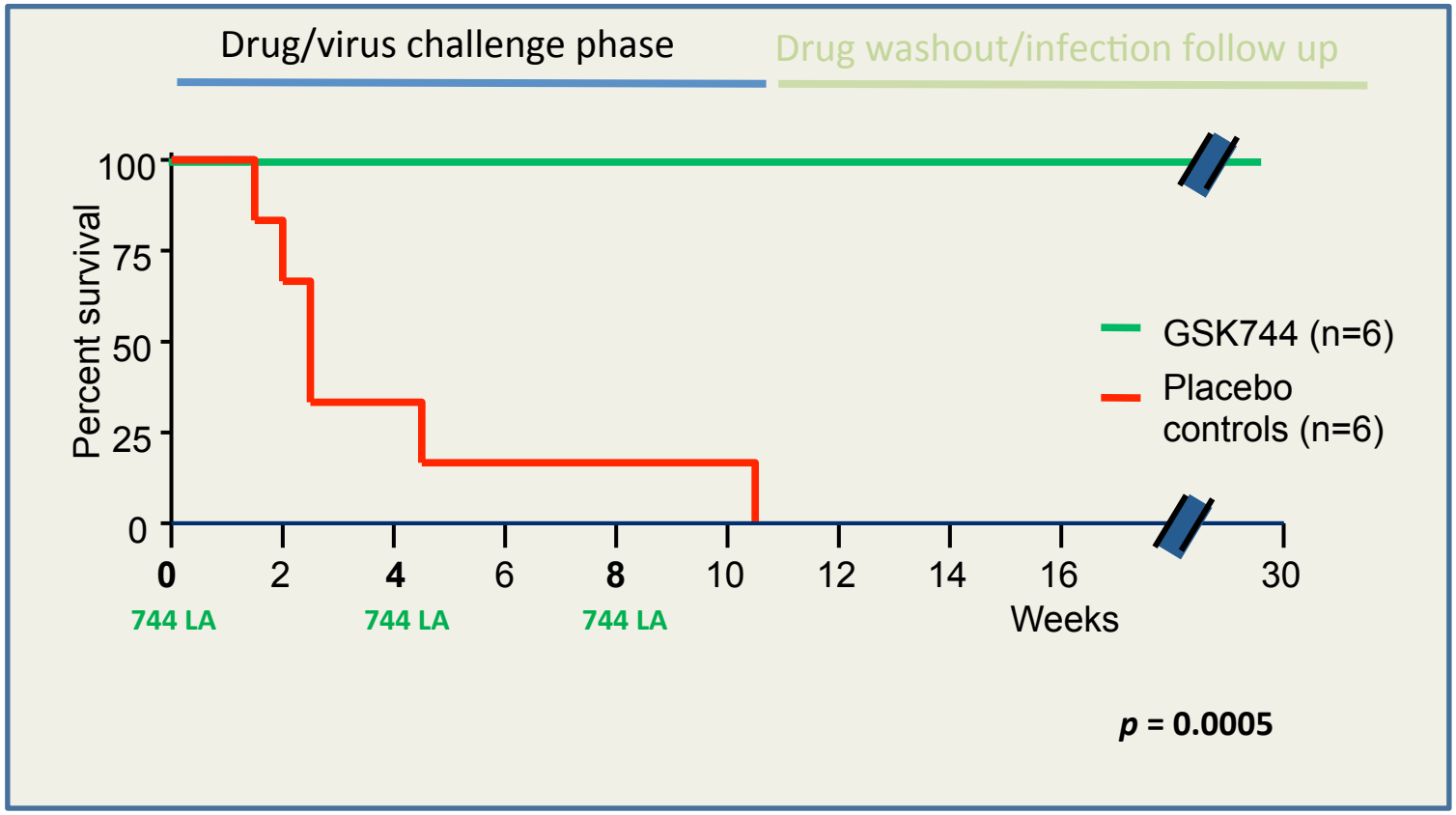
Efficacy of GSK744 LA against vaginal SHIV transmission



Plasma RNA
Proviral DNA
Serology
GSK744 concentrations in plasma

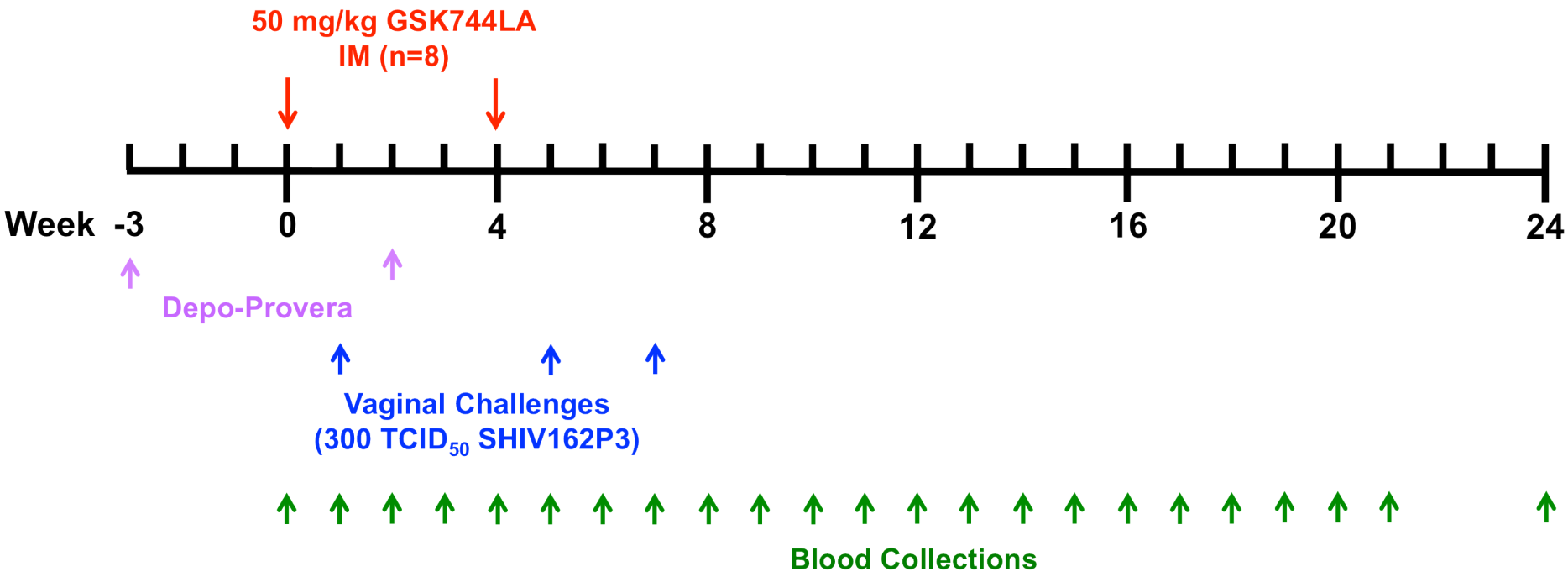
Radzio et al CROI2014 Abs. 40LB

Monthly GSK744 LA injections protect macaques against repeated vaginal SHIV exposures

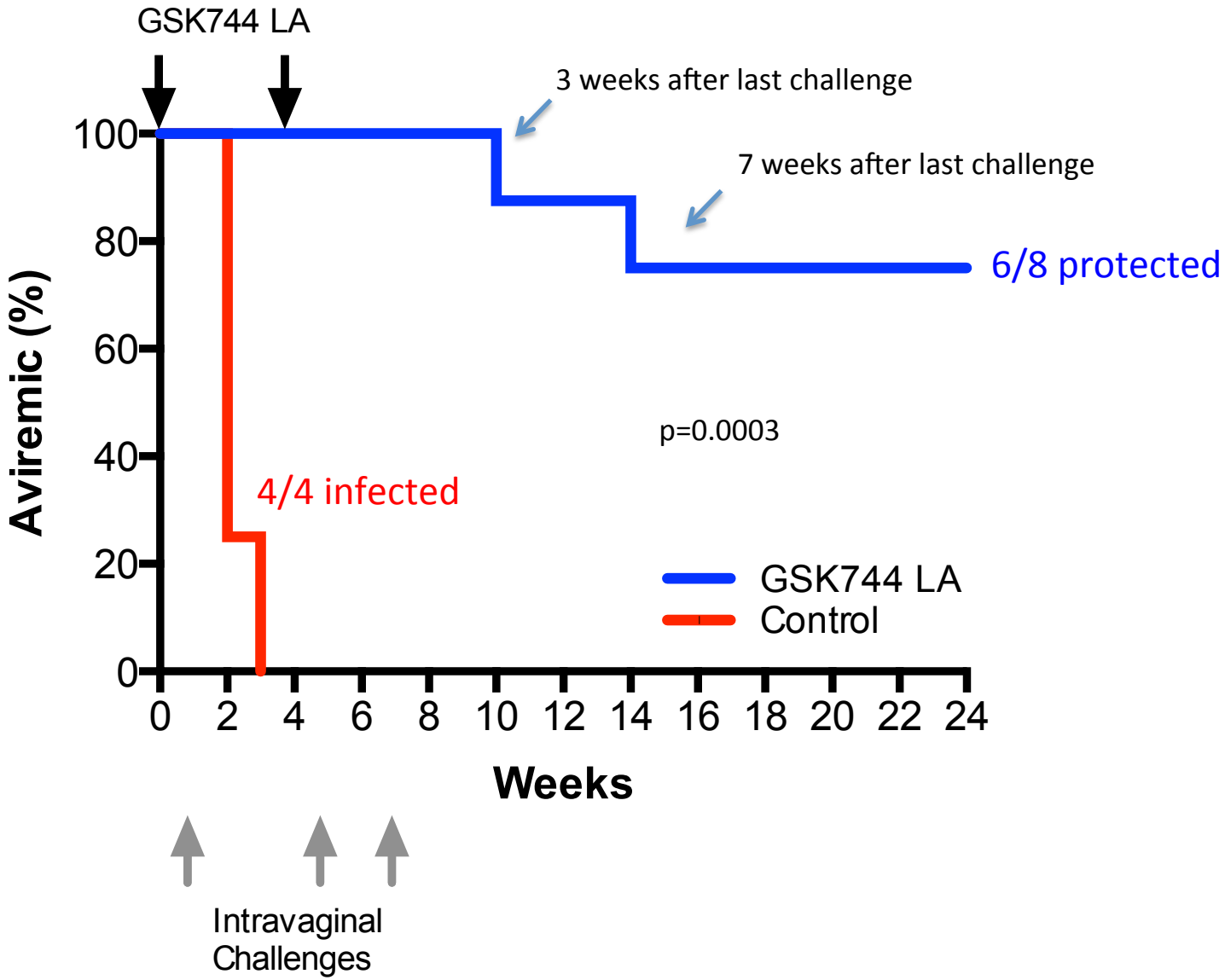


Radzio et al CROI2014 Abs. 40LB

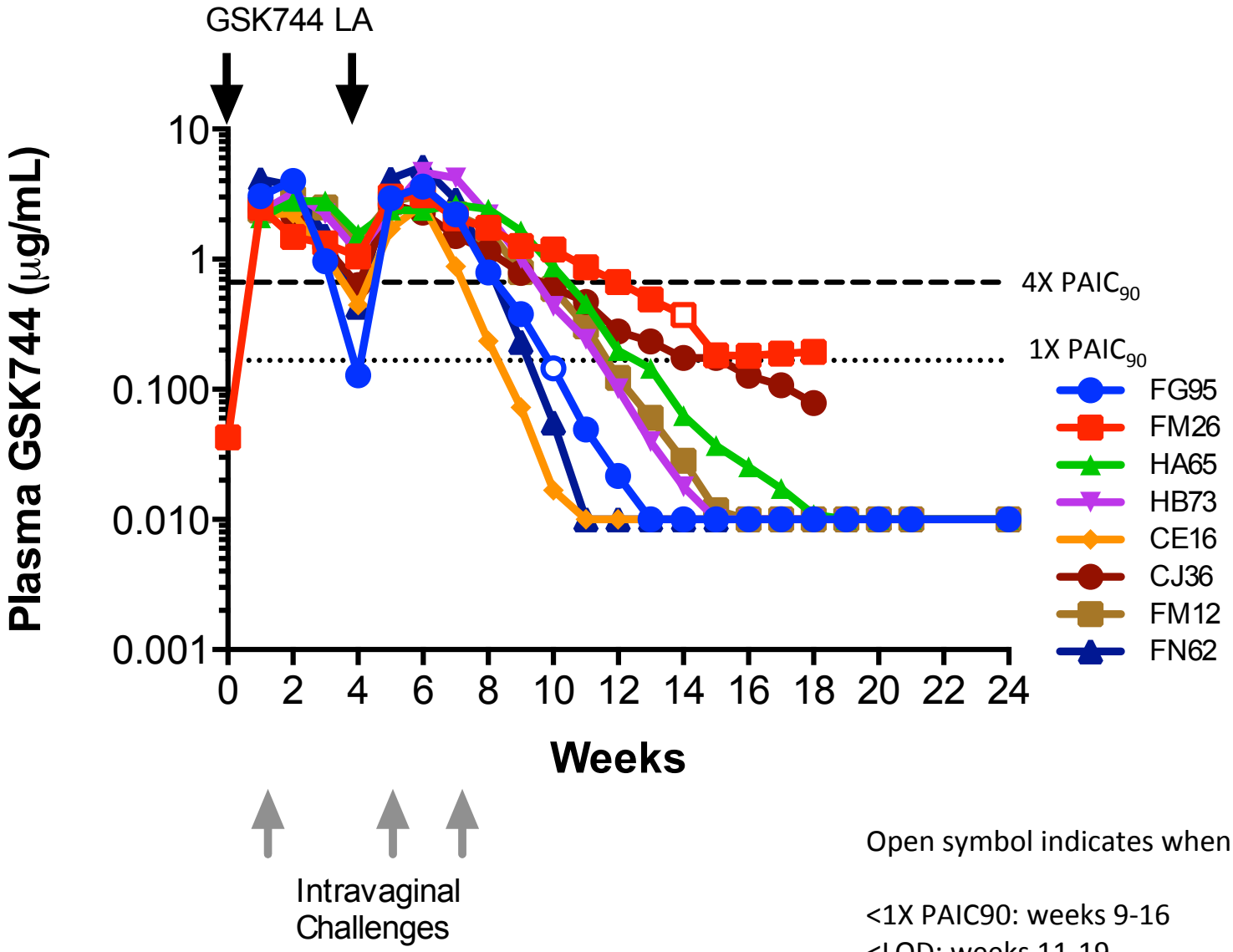
Repeated High-Dose Intravaginal Challenges to Evaluate GSK744 LA as PrEP in 12 Indian Rhesus Macaques



GSK744 LA is an Effective PrEP Agent in a High-Dose Intravaginal Challenge Model in Rhesus Macaques



GSK744 LA Plasma Concentrations During IVAG Challenges



Open symbol indicates when vRNA was detected

<1X PAIC90: weeks 9-16
<LOD: weeks 11-19

Summary of Preclinical Evaluation in Female Rhesus Macaques

- Monthly injections of GSK744 LA reproducing the human dose fully protect female macaques against repeated low dose vaginal SHIV exposures

- High levels of protection were displayed in female rhesus macaques exposed to repeated high virus dose SHIV challenges under depo provera

- Our results support the advancement of GSK744 LA for PrEP in high-risk women

Complementary Phase 2 Studies

201120 (Éclair)

- At risk men (60% MSM)
- n=120 (5:1)
- US
- First subject first visit – Mar 2014

HPTN 077

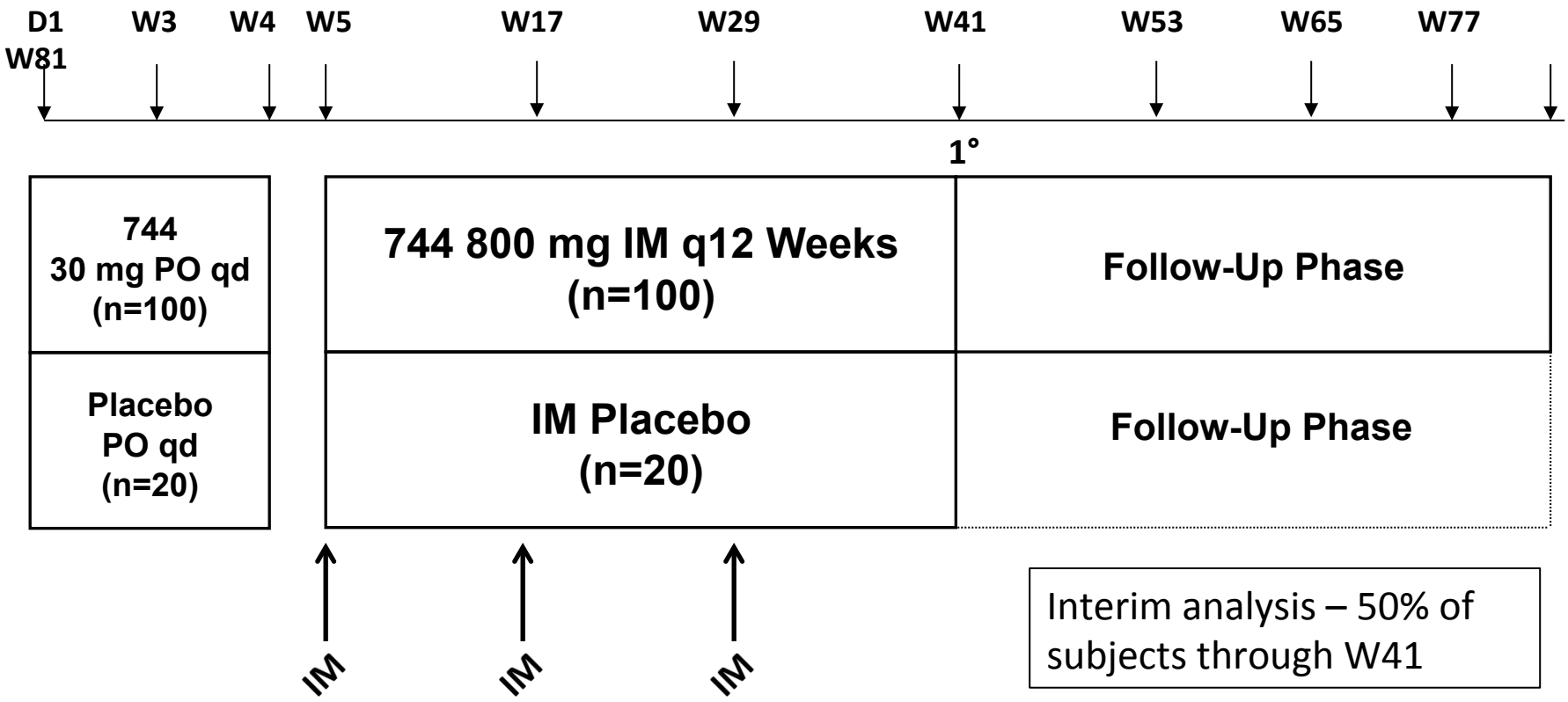
- At risk women (60%) and men
- n=160 (3:1)
- US, South America, SS Africa
- First subject first visit – June 2014

Study Objectives

- Primary Objective(s)
  - To evaluate the safety and tolerability of 744 LA (800 mg dose administered at three time points at 12 week intervals) through Week 41 in HIV-uninfected men.

- Secondary Objective(s)
  - Evaluate the pharmacokinetics of 744 LA following each IM injection through 41 weeks.
  - Describe the pharmacokinetics of 744 LA by age, race, weight, and ethnicity.
  - Evaluate the acceptability of 744 LA injections through 41 weeks.
  - Explore concentration-effect relationships for various safety parameters, if appropriate.

Éclair – Study Design



Interim analysis – 50% of subjects through W41

1st internal safety review – 50% of subjects through W17

ÉCLAIR Study – 201120
Milestone Timeline

- First subject screened — Mar 2014
- First subject enrolled — Apr 2014
- Last subject enrolled — July 2014
- First subject completes Wk 41 — January 2015
- Last subject completes Wk 41 — May 2015
- Last subject completes Wk 81 — March 2016

Acknowledgements

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Long-acting rilpivirine for HIV PrEP

Ponni Subbiah
Heather Kelly
Elena Pantjushenko

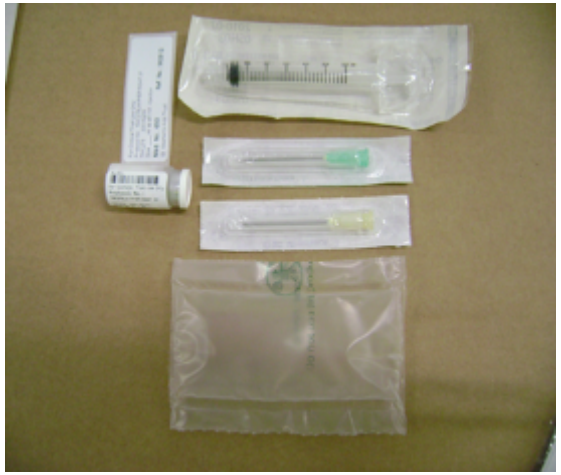
April 7, 2014

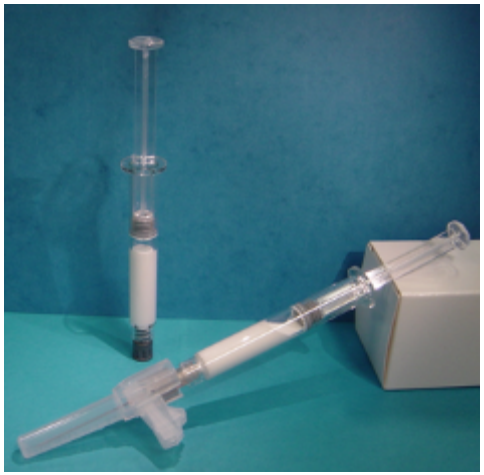
PATH
A catalyst for global health

Photo: PATH/Eric Becker

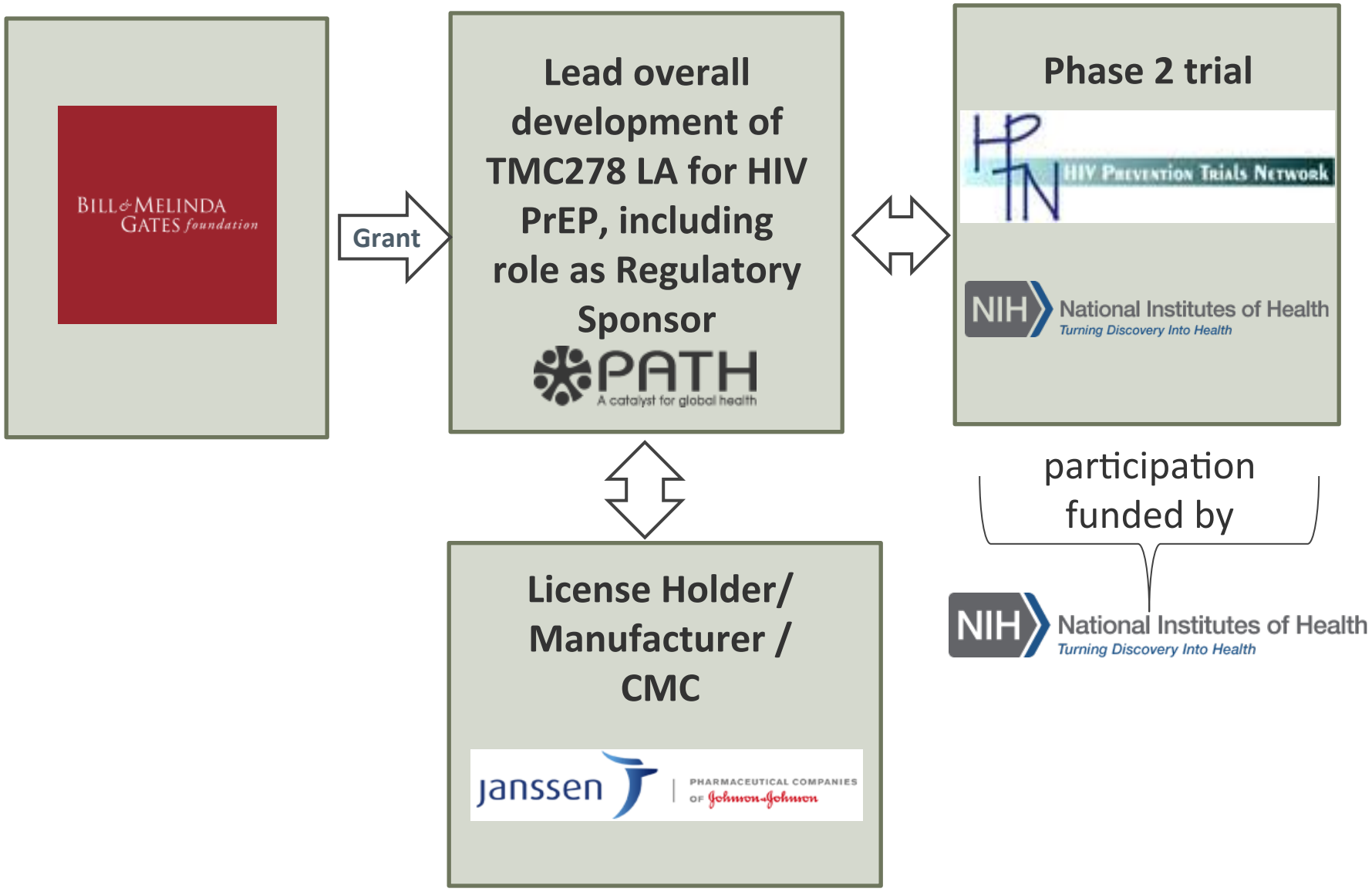
Long-acting rilpivirine (TMC278 LA)

- Rilpivirine is widely approved as part of combination therapy (EDURANT, COMPLERA) for oral use
- Injectable nanosuspension formulation (G001)
  - 300mg/mL, sparingly soluble drug substance
  - Aqueous aseptic product, neutral pH
- Intramuscular (buttock) dosing, every 8 weeks





Project partners for HPTN076



Overview of HPTN076 study

- **Purpose:** To evaluate the safety and acceptability of the injectable product, TMC278 LA, in healthy, HIV-uninfected women
- **Study design:** multi-site, blinded randomized trial comparing the safety of an intramuscular (IM) injection of TMC278 LA to a placebo
- **Four clinical sites:** United States (New York, New Jersey), South Africa (Cape Town), Zimbabwe (Harare)
- **Study population:** 132 HIV-uninfected women, ages 18-45
- **Treatment regimen:** 1200mg administered intramuscularly once every eight weeks over a 44 week period, with a six month follow-up period

License and early development agreement

- PATH and Janssen R&D Ireland – licensing agreement, September 2013
- Royalty-free rights to PATH to develop rilpivirine as a long-acting injectable formulation for PrEP

Advocacy

- Inform HIV prevention community about the ongoing injectable PrEP research and related activities
- Collaborate with AVAC to align our work
- Understand national-level history with the introduction of new health technologies and potential policy barriers (i.e., policies, ongoing advocacy work, stakeholders, partners)

THANK YOU

Photo: PATH/Gabe Bienczycki

DISCUSSION

To ask a question:

- Unmute your line by pressing *7 and ask it on the line (remute your line by pressing *6)
- Enter it into the chat box in ReadyTalk
- Email your question to avac@avac.org

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