associazione NADIR onlus

PROGRAMMA SEMINARIO 2016

presso il Centro Congressi Conte di Cavour Via Cavour 50/A, 00184 Roma – Zona Stazione Termini

SOMMINISTRAZIONE A LENTO RILASCIO DELLA TERAPIA ANTI-HIV: QUALI SARANNO LE SFIDE, LE OPPORTUNITÀ E LE CRITICITÀ? (2)

Venerdì, 16 settembre 2016

Razionali delle formulazioni a lento rilascio: trattamento e prevenzione

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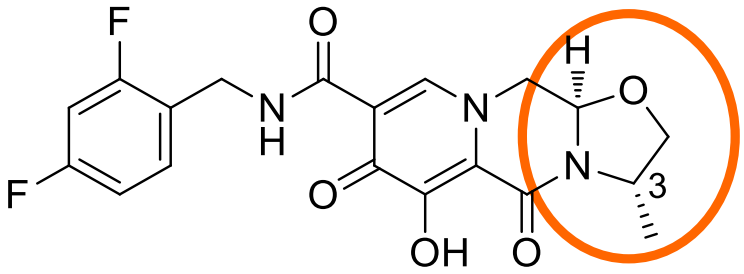
Strengths and limitations of current ART

Current ART strengths	Current ART limitations
Highly potent	Dependence on daily adherence
Few side-effects, well tolerated	Long-term toxicity of ART
Low pill burden	Drug–drug interactions
	Long-term effects of HIV even in setting of viral suppression
	Cost
	Limited treatment options in patients with multiclass resistance
	Treatment is noncurative

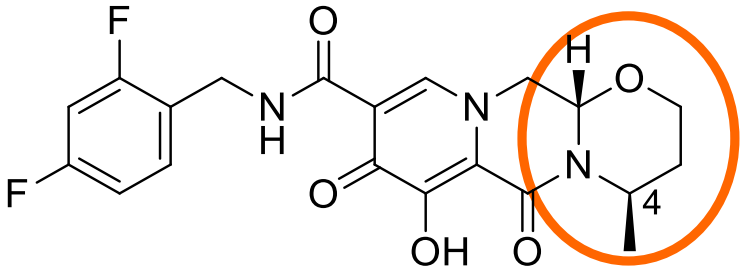
ART, antiretroviral therapy

Salomon D & Sax P. Curr Opin HIV AIDS, 2015

CABOTEGRAVIR



DOLUTEGRAVIR

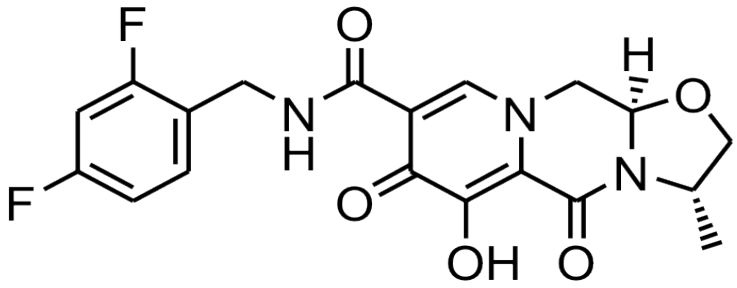


The investigational InSTI cabotegravir has a similar chemical structure and resistance profile to dolutegravir but may allow for less frequent parenteral dosing.

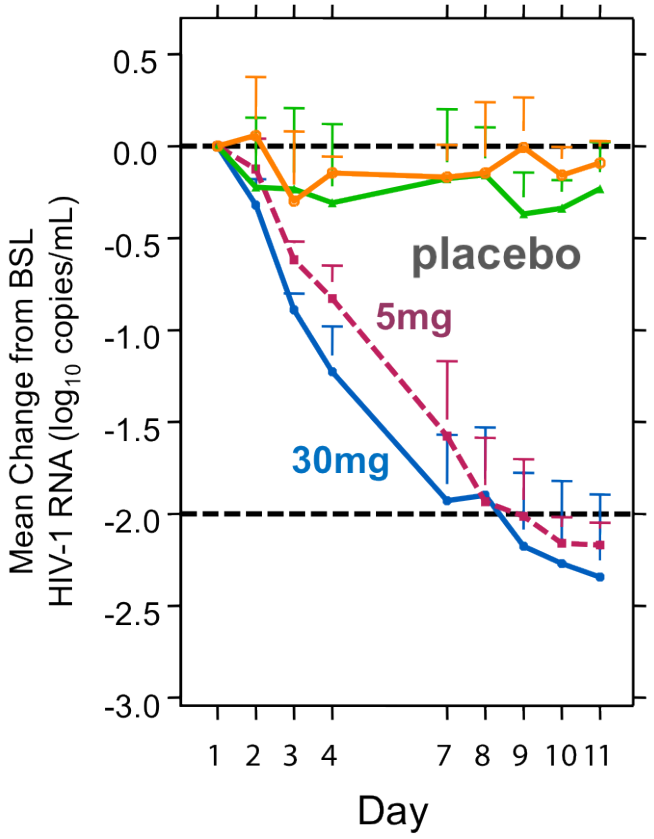
A new investigational nanotechnologic formulation of cabotegravir may be subcutaneously or intramuscularly injected and has a half-life of 21 days to 50 days, supporting monthly or even quarterly dosing.

Dudas K *et al.* IWDR 2015. Poster 13

GSK1265744 (744)



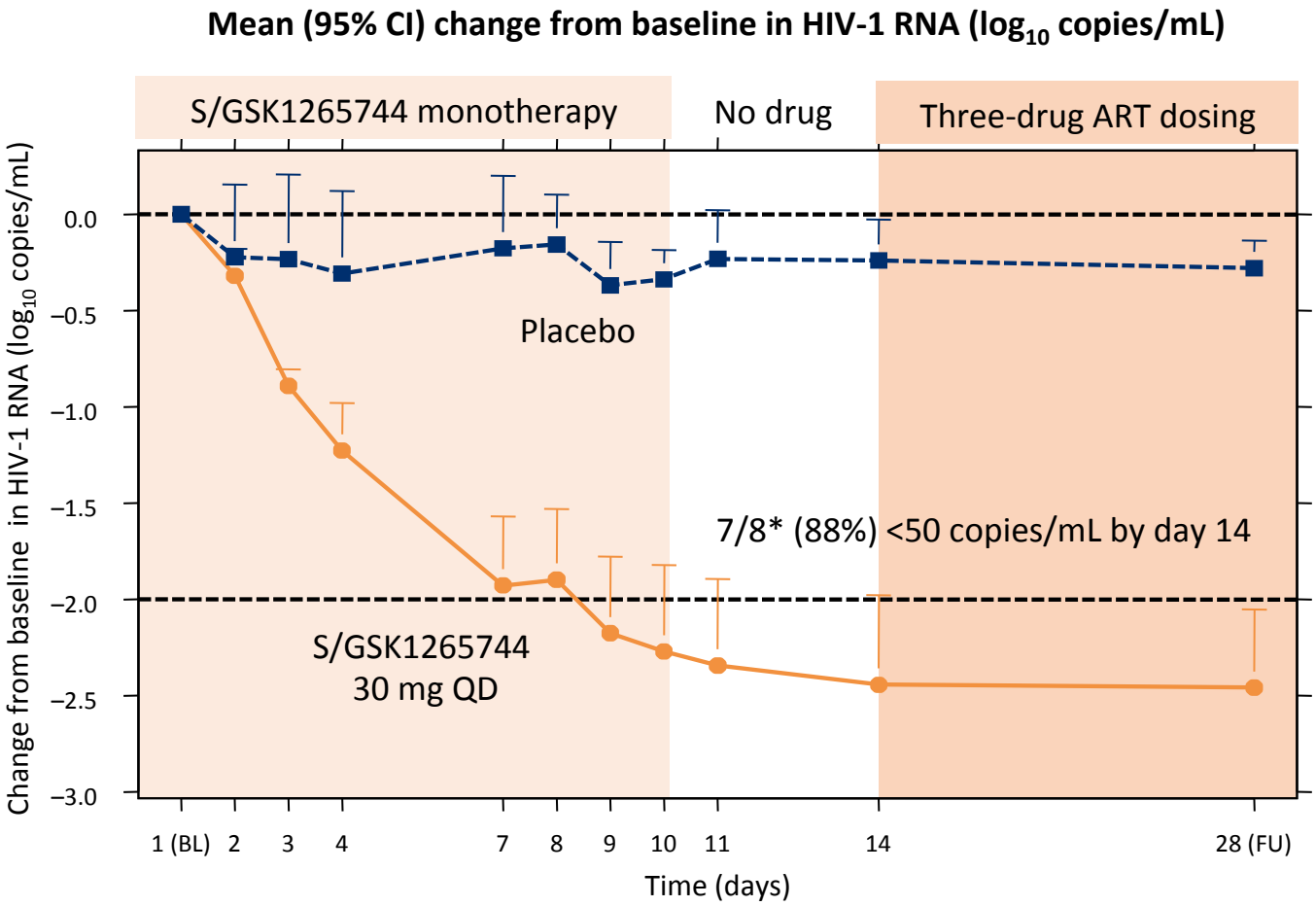
- HIV-1 integrase inhibitor, dolutegravir analogue
- Oral drug ($t_{½}$ = 40 hours)
- Long-acting SC or IM injection (apparent $t_{½}$ ≈ 40 days)
- Good virologic response (mean decrease -2.3 log_{10} copies/mL) at 5 and 30 mg/day as oral 10-day monotherapy



Spreen W, et al. *HIV Clin Trials*. 2013;14:192-203.

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

GSK1265744 (cabotegravir) Antiviral activity



Median* HIV-1 RNA decline
Baseline to day 11

744: –2.6 log_{10} copies/mL
Range: –3.0, –1.0

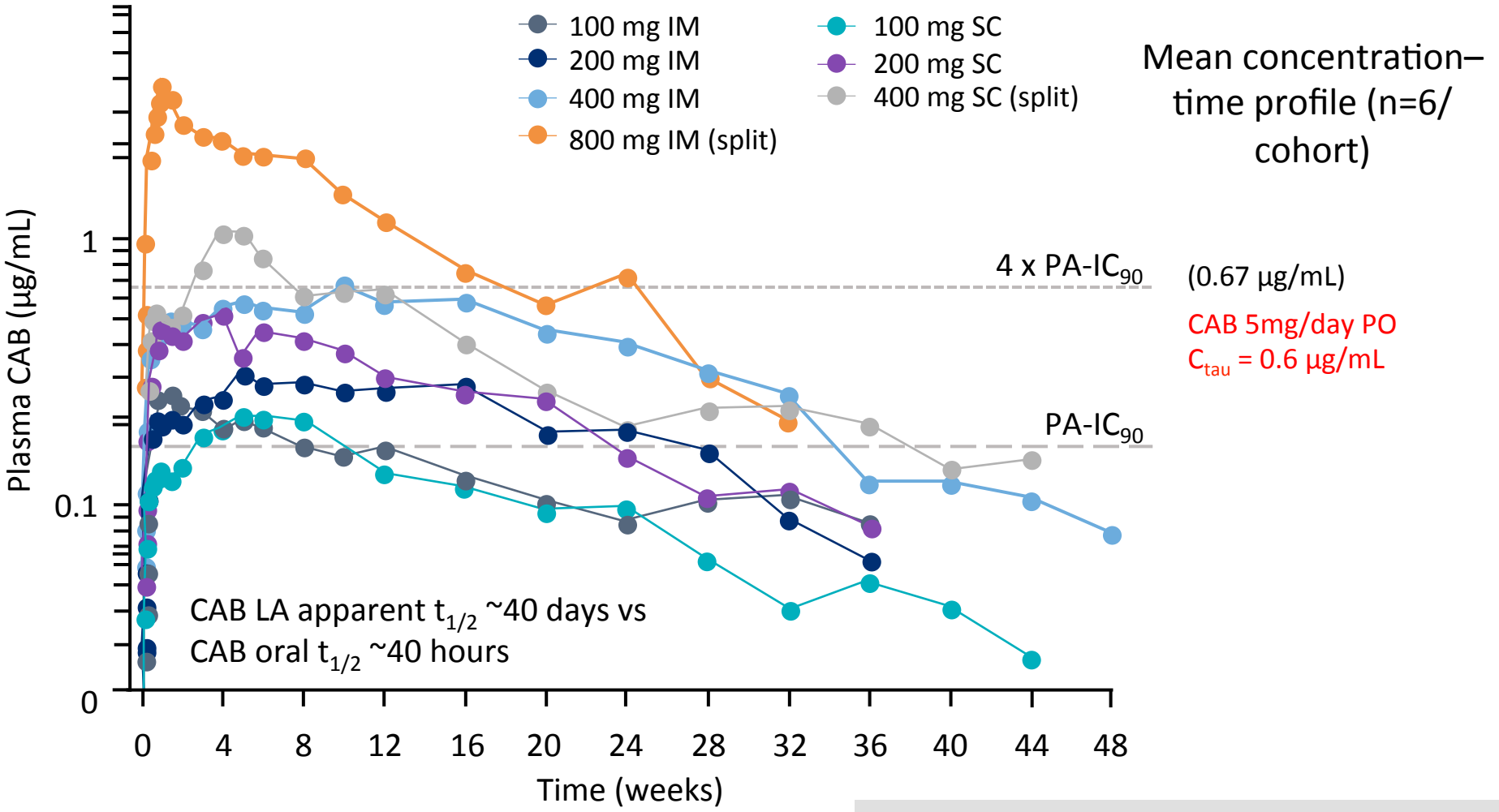
Placebo: –0.27 log_{10} copies/mL
Range: –0.4, 0.0

CD4 (cells/mm^3; day 11)
744: +15 (–100, +100)
Placebo: –90 (–190, –20)

*1 subject with screening viral load of 8410 copies/mL had HIV-1 RNA of 474 copies/mL at day 1

Min S *et al*. ICAAC 2009. Abstract H-1228

GSK1265744 (cabotegravir) LA single injection provides detectable drug in plasma for 48 weeks



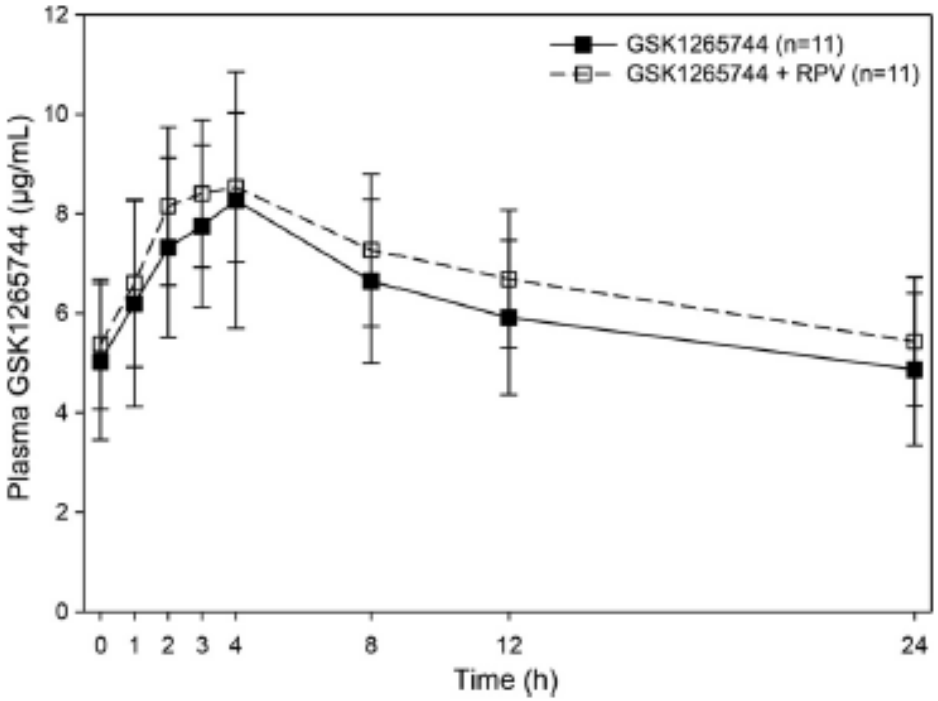
Spreen W, et al. J Acquir Immune Defic Syndr, 2014

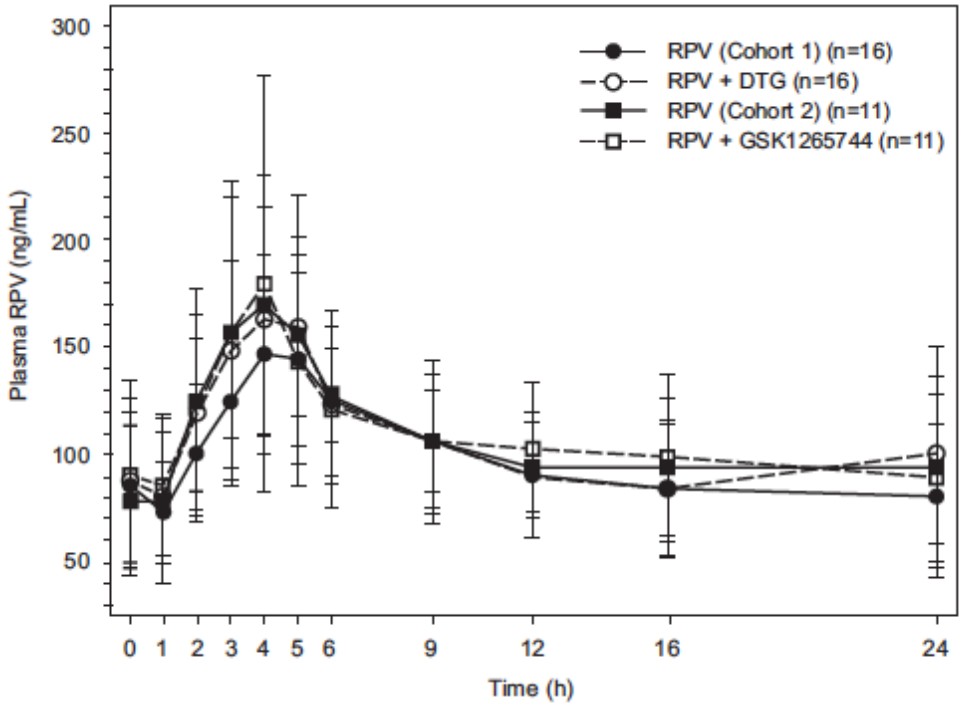
CAB, cabotegravir; C_{tau}, trough concentration; IM, intramuscular; LA, long acting; PA-IC_{90}, protein-adjusted 90% inhibitory concentration; PO, oral; SC, subcutaneous; $t_{1/2}$, half-life

Lack of pharmacokinetic interaction between rilpivirine and integrase inhibitors GSK1265744

TABLE 3 PK parameter treatment comparisons

Plasma PK parameter	Geometric least-squares mean ratio [90% CI]			
	DTG + RPV versus DTG	GSK1265744 + RPV versus GSK1265744	DTG + RPV versus RPV	GSK1265744 + RPV versus RPV
$AUC_{0-\tau}$	1.12 [1.05, 1.19]	1.12 [1.05, 1.19]	1.06 [0.976, 1.16]	0.987 [0.890, 1.09]
C_{max}	1.13 [1.06, 1.21]	1.05 [0.963, 1.15]	1.10 [0.992, 1.22]	0.963 [0.849, 1.09]
C_{τ}	1.22 [1.15, 1.30]	1.14 [1.04, 1.24]	1.21 [1.07, 1.38]	0.919 [0.789, 1.07]

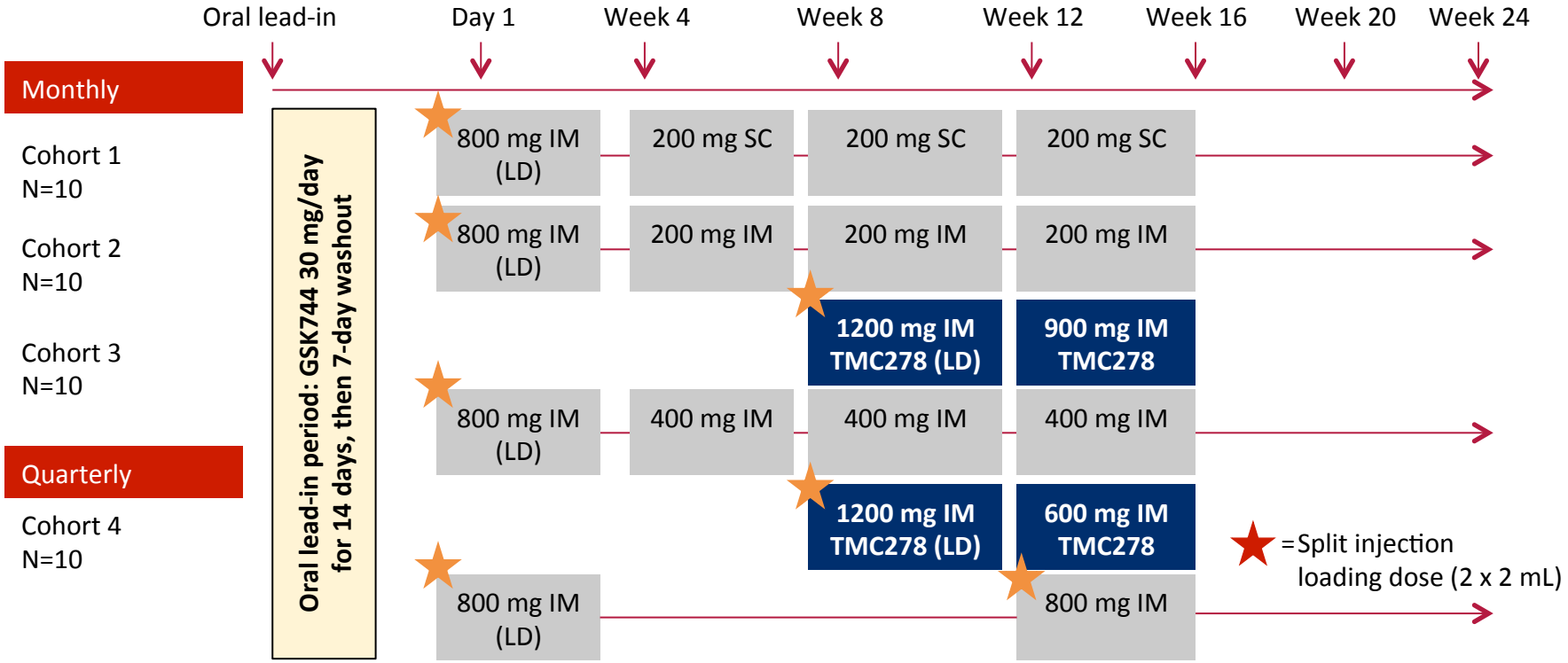




Ford SL, et al. Antimicrob Agents Chemother, 2013

LAI115428 Study
Repeat dose co-administration of GSK1265744 and TMC278 long-acting parenteral nanosuspensions

- Two-center, Phase I, randomized, open-label, repeat-dose study in healthy adults
- GSK744 200 mg/mL given as IM (gluteal) or SC (abdominal) injection; TMC278 given as IM (gluteal) injection
- Subjects followed 52 weeks after last injection (ongoing)



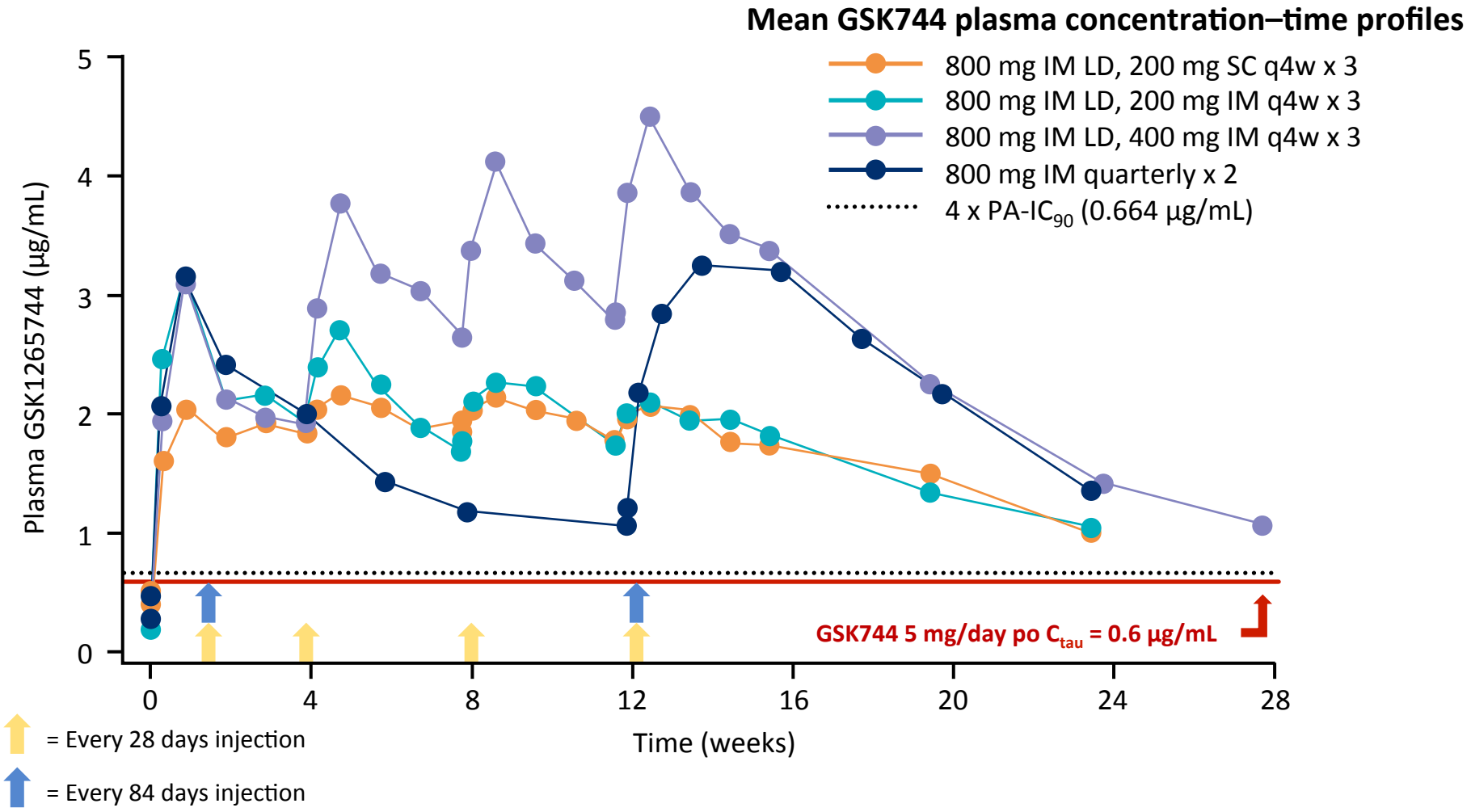
Spreen W, et al. J Acquir Immune Defic Syndr, 2014

LAI115428 Study
Baseline characteristics and subject disposition

Baseline characteristics	Overall (N=47)			
Mean age, years (SD)	39.5 (13.9)			
Female/male, n	17/30			
Race, black/white/other, n	10/35/2			
BMI, kg/m^2 (SD)	26.1 (2.9)			
Subject disposition				
No. dosed 744 oral lead-in No. dosed LAP injection	47 40			
Withdrawn oral lead-in Withdrawn from LAP injection	7 subjects (AE = 1, not drug related = 6) 3 subjects (AE = 1, not drug related = 2)			
	Cohort 1 744 SC every 28 days	**Cohort 2 744 + 278 IM every 28 days**	**Cohort 3 744 + 278 IM every 28 days**	**Cohort 4 744 IM every 84 days**
No. dosed LAP injection	10	10	10	10
No. withdrew consent or AE during injection dosing phase	1	1	0	1

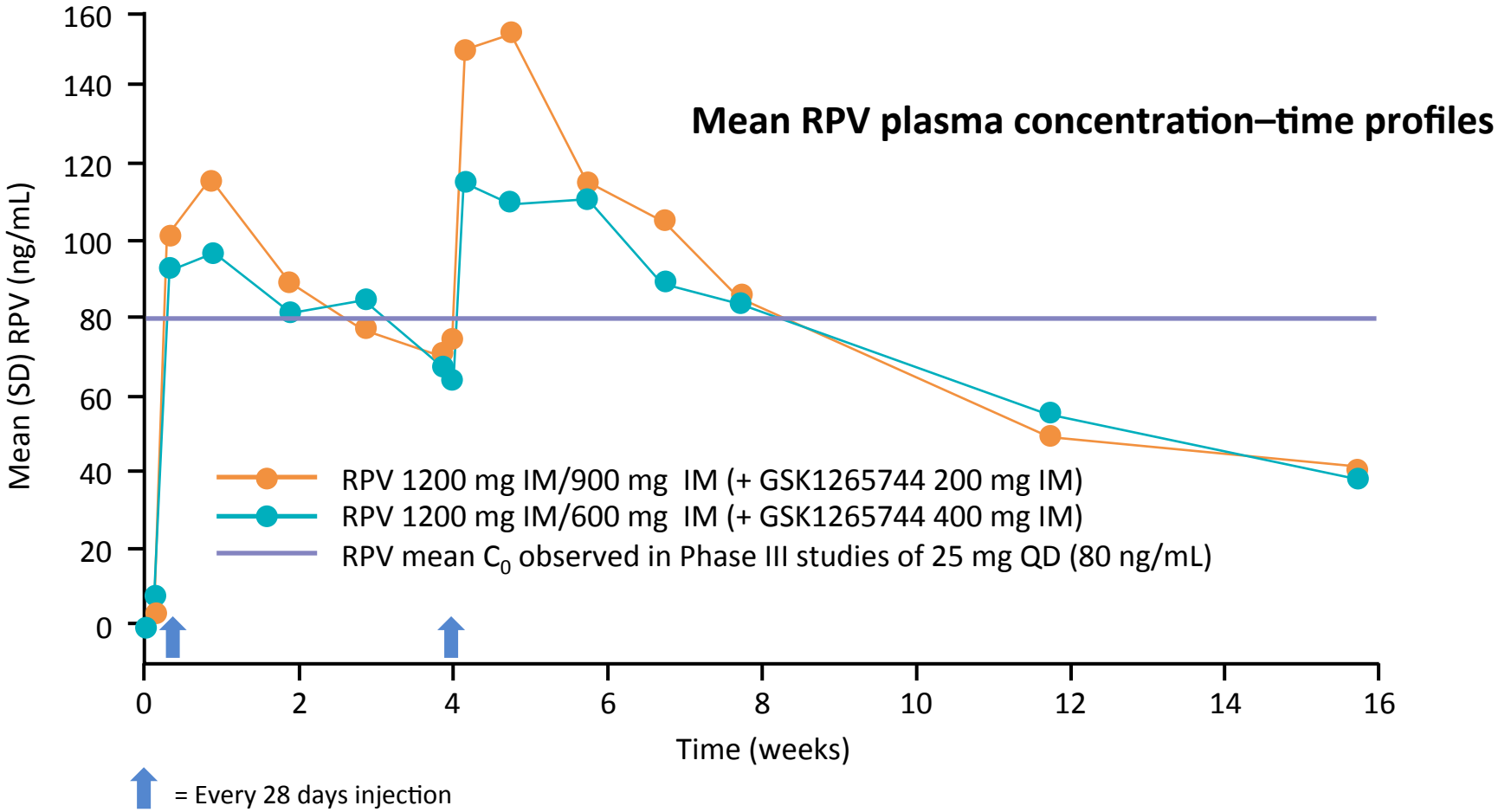
Spreen W, et al. J Acquir Immune Defic Syndr, 2014

GSK744 LAP every 4 or 12 weeks achieved plasma concentrations >4 x PA-IC_{90} in healthy adults



Spreen W, et al. J Acquir Immune Defic Syndr, 2014

Rilpivirine plasma concentrations following TMC278 LA injections are comparable to oral 25 mg/day in HIV-infected subjects



Spreen W, et al. J Acquir Immune Defic Syndr, 2014

Injection-site safety results: Local injection-site reactions (ISRs) are common but generally well tolerated and self-limited

	GSK744 (IM)			GSK744 (SC)			TMC278 (IM)		
Subjects with injections, n	40			10			19		
Maximum injections per subject/actual total per group, n	5/156			3/30			3/57		
Subjects reporting any ISR during study, n (%)	32 (80)			10 (100)			18 (95)		
ISR: n (%) or mean (range)									
ISR events	Mild	Moderate	Duration (days)	Mild	Moderate	Duration (days)	Mild	Moderate	Duration (days)
Any	116 (81)	28 (19)	–	130 (98)	2 (2)	–	39 (87)	6 (13)	–
Pain	76 (53)	28 (19)	5 (1–32)	25 (19)	1 (1)	7 (3–14)	31 (69)	6 (13)	5 (1–10)
Erythema	11 (8)	0	9 (1–31)	28 (21)	0	11 (1–33)	2 (4)	0	5 (5–5)
Nodule	6 (4)	0	31 (5–71)	23 (17)	0	59 (5–140)	3 (7)	0	48 (24–65)

Spreen W, et al. J Acquir Immune Defic Syndr, 2014

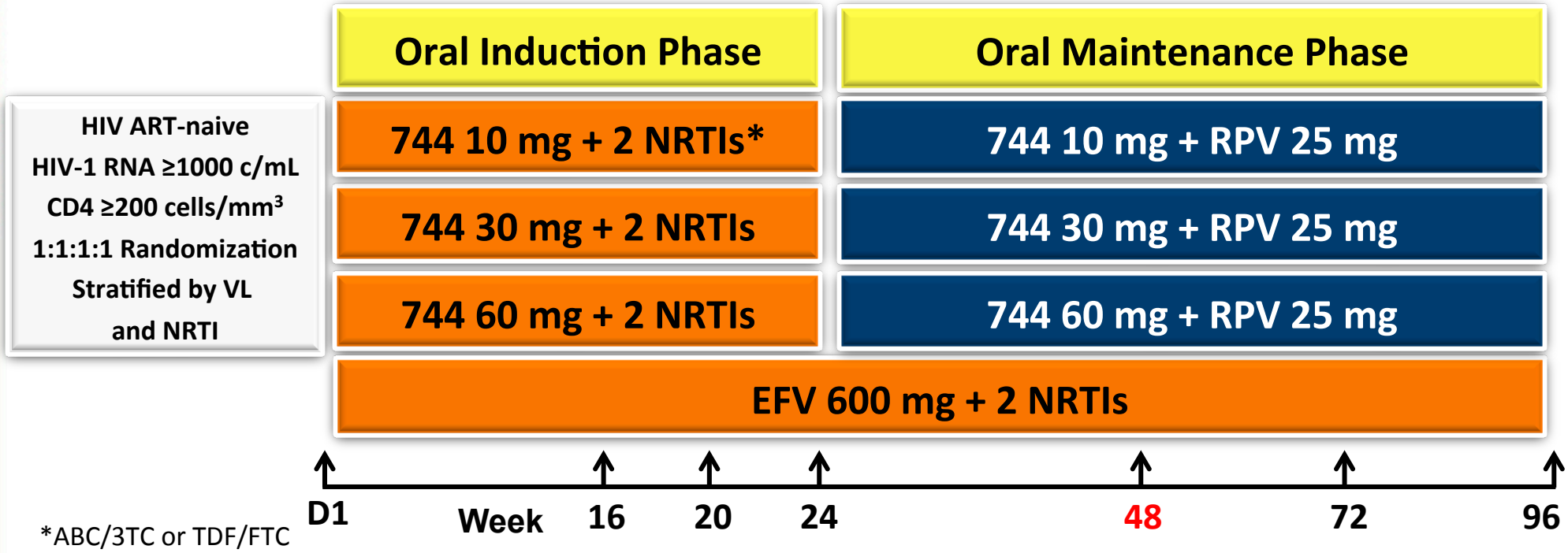
LATTE Objectives

- Investigate the safety, tolerability and efficacy of oral 744 across 3 doses for HIV treatment
- Select an oral dose of 744 for further evaluation
- Demonstrate safety and efficacy with a novel 2-drug regimen for maintenance therapy, 744 + rilpivirine
- Facilitate the conduct of a second phase IIb study, evaluating the long-acting injectable regimen, 744 LA + TMC278 (rilpivirine) LA

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

LATTE Study Design

- Phase IIb, randomized, multicenter, partially blind, dose-ranging study
- 744 + NRTI subjects with a W20 HIV-1 RNA <50 c/mL simplified to 744 + RPV at W24



*ABC/3TC or TDF/FTC

- Primary endpoint: % HIV-1 RNA <50 c/mL at 48 weeks (FDA "Snapshot")
  - Intent-to-treat exposed (ITT-E) – received at least one dose of Investigational Product (IP)
  - Intent-to-treat maintenance exposed (ITT-ME) – received at least one maintenance dose

Baseline Characteristics – ITT-E

		744 10 mg n=60	744 30 mg n=60	744 60 mg n=61	EFV 600 mg n=62
Age	Median (y)	32.0	32.5	36.0	32.5
Gender	Male	95%	97%	93%	98%
Race	White	62%	65%	59%	63%
	African American/African	35%	28%	30%	32%
Ethnicity	Hispanic/Latino	15%	27%	23%	19%
Baseline HIV-1 RNA	Median (log_{10} c/mL)	4.281	4.178	4.349	4.343
	Median (c/mL)	19,099	15,066	22,336	22,029
	≥100,000 c/mL	13%	12%	20%	13%
Baseline CD4+	Median (cells/mm^3)	415.0	404.0	420.0	416.5
	<200 cells/mm^3	3%	7%	3%	2%
Hepatitis coinfection	HCV Ab +	0%	8%	7%	2%
Investigator-selected dual NRTIs at Day 1	TDF/FTC	62%	62%	61%	61%
	ABC/3TC	38%	38%	39%	39%

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

Subject Disposition - ITT-E

Subjects withdrawn through W48	744 10 mg n=60	744 30 mg n=60	744 60 mg n=61	744 total n=181	EFV 600 mg n=62
Total	**10 (17%)**	**10 (17%)**	**7 (11%)**	**27 (15%)**	**18 (29%)**
Adverse event	**1 (2%)**	**1 (2%)**	**4 (7%)**	**6 (3%)**	**8 (13%)**
Lack of efficacy	**5 (8%)**	**2 (3%)**	**2 (3%)**	**9 (5%)**	**5 (8%)**
Insufficient viral load	**3 (5%)***	**0**	**1 (2%)†**	**4 (2%)**	**1 (2%)‡**
PDVF	**2 (3%)**	**2 (3%)**	**1(2%)**	**5 (3%)**	**4 (6%)**
Protocol deviation	**1 (2%)**	**1 (2%)**	**1 (2%)**	**3 (2%)**	**0**
Lost to follow-up	**1 (2%)**	**2 (3%)**	**0**	**3 (2%)**	**3 (5%)**
Withdrew consent	**2 (3%)**	**3 (5%)**	**0**	**5 (3%)**	**1 (2%)**

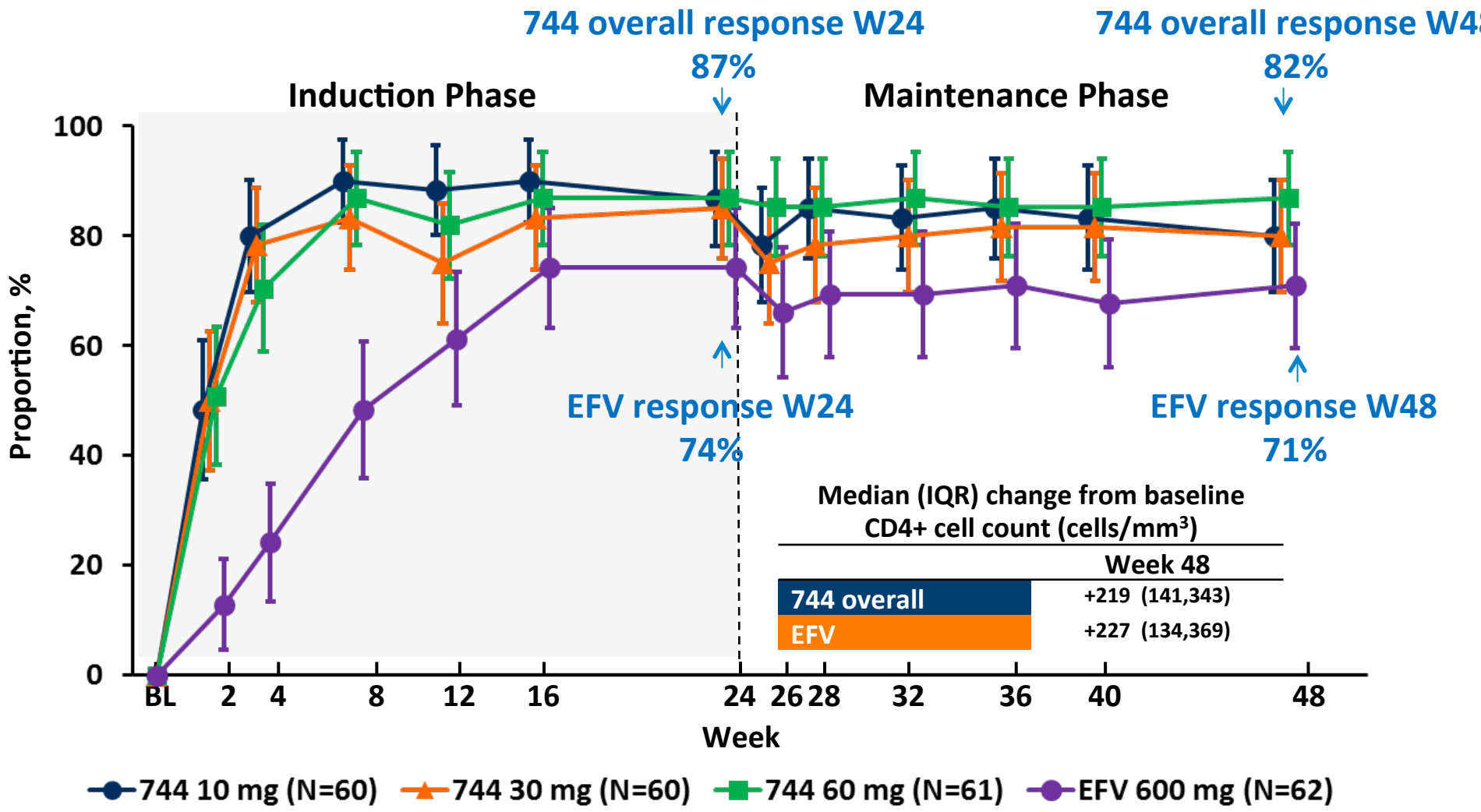
Week 20 HIV-1 RNA = *744 10 mg - 51; 107; 189 c/mL; †744 60 mg - 108 c/mL; ‡EFV 600 mg - 146 c/mL

Subjects withdrawn W24-W48	744 10 mg n=60	744 30 mg n=60	744 60 mg n=61	744 total n=181	EFV 600 mg n=62
Subtotal	**2 (3%)**	**3 (5%)**	**1 (2%)**	**5 (3%)**	**3 (5%)**

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

Primary Endpoint

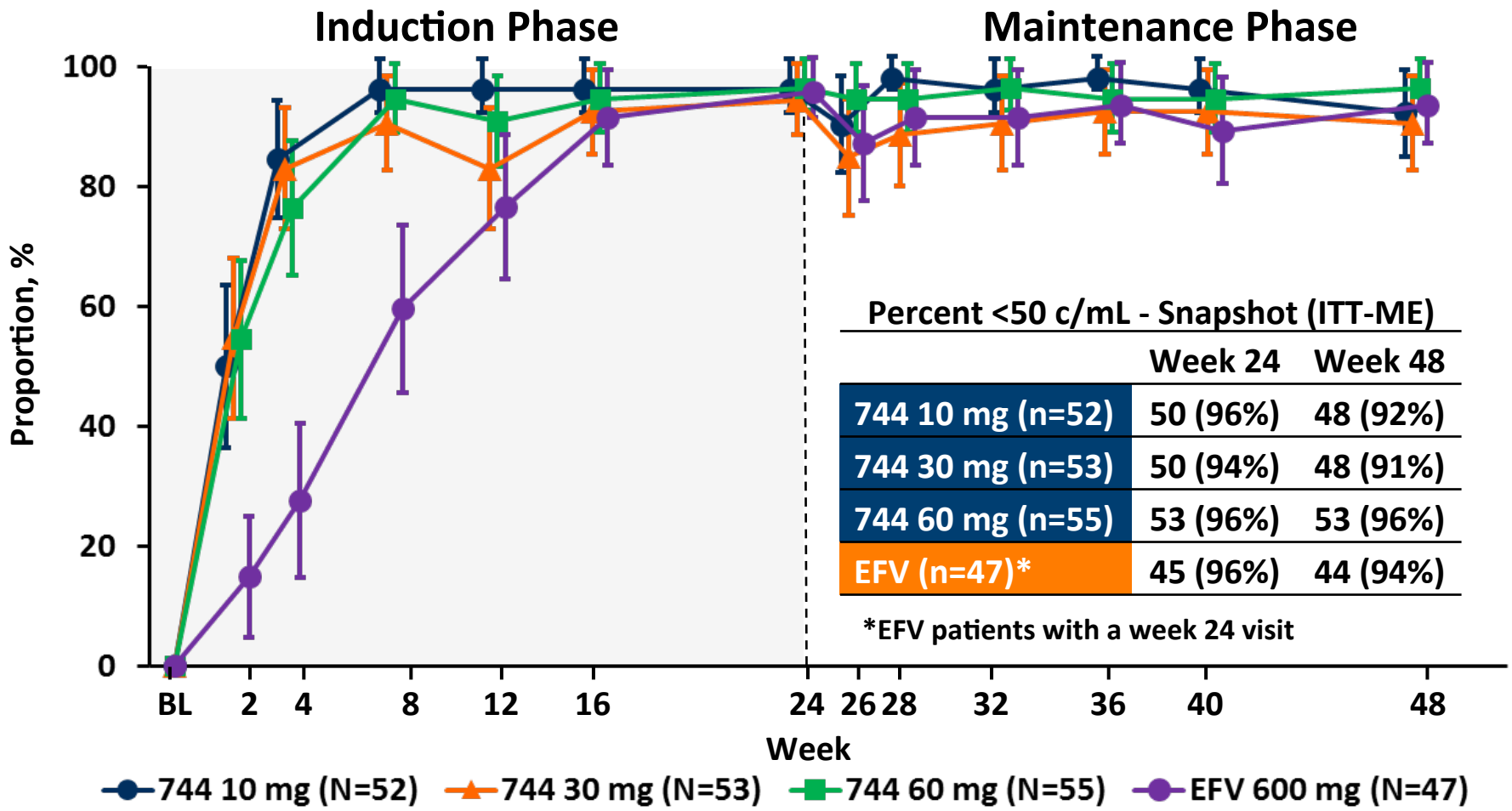
Virologic Success: HIV-1 RNA <50 c/mL by FDA Snapshot (ITT-E)



Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

Secondary Endpoint – Maintenance Population

Virologic Success: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



Percent <50 c/mL - Snapshot (ITT-ME)

	Week 24	Week 48
744 10 mg (n=52)	50 (96%)	48 (92%)
744 30 mg (n=53)	50 (94%)	48 (91%)
744 60 mg (n=55)	53 (96%)	53 (96%)
EFV (n=47)*	45 (96%)	44 (94%)

*EFV patients with a week 24 visit

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

Treatment Outcomes - Maintenance Population

HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

- Similar response rate for 744 + RPV, relative to continuing EFV + NRTIs
- Similar response across 744 doses

Outcome at Week 48	744 10 mg n=52	744 30 mg n=53	744 60 mg n=55	744 total n=160	EFV 600 mg n=47*
Virologic success	**48 (92%)**	**48 (91%)**	**53 (96%)**	**149 (93%)**	**44 (94%)**
Virologic failure	**3 (6%)**	**5 (9%)**	**1 (2%)**	**9 (6%)**	**2 (4%)**
Data in window not <50 c/mL	3 (6%)	3 (6%)	1 (2%)	7 (4%)	1 (2%)
Discontinued for lack of efficacy	0	0	0	0	1 (2%)
Change in ART	0	2 (4%)†	0	2 (1%)	0
No virologic data at Week 48	**1 (2%)**	**0**	**1 (2%)**	**2 (1%)**	**1 (2%)**
Discontinued due to AE‡	1 (2%)	0	1 (2%)	2 (1%)	1 (2%)

*EFV patients with a W24 visit
†Carried forward from Induction Phase
‡Abnormal ECG (10 mg); anxiety (60 mg); colitis (EFV)

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

Protocol-Defined Virologic Failure

	744 total n=181	EFV n=62
Subjects with PDVF during Induction	**3* (2%)**	**3 (5%)**

*1 subject per 744 dose
No NRTI, NNRTI or INI treatment-emergent mutations

	744 total n=160	EFV n=47
Subjects with PDVF during Maintenance	**2** (1%)**	**1 (2%)**
IN genotypic results at BL and time of PDVF	1	1
INI-r mutations	**1**	**0**
PR/RT genotypic results at BL and time of PDVF	2	1
NRTI-r mutations	**0**	**0**
NNRTI-r mutations	**1**	**0**

**744 10 mg – treatment emergent INI (Q148R) and NNRTI (E138Q) at W48; 744 FC = 3; RPV FC = 2
- ➢744 and RPV concentrations <50% of expected; extreme calorie restricted diet W40-W48

**744 30 mg – PDVF at W36; no treatment-emergent mutations

PDVF: <1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4
OR confirmed HIV-1 RNA ≥200 c/mL at or after Week 16 or after prior suppression to <200 c/mL

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

Adverse Events

- Neuropsychiatric AEs more commonly seen with EFV
- Headache was more commonly seen with 744 (22%) than EFV (11%)
  - Predominantly Grade 1 and 2; no withdrawals due to headache

	744 10 mg n=60	744 30 mg n=60	744 60 mg n=61	EFV 600 mg n=62
Grade 2-4 drug-related events (total)	**5 (8)**	**8 (13)**	**13 (21)**	**12 (19)**
(>3% any arm)				
Insomnia	**1 (2)**	**2 (3)**	**0**	**4 (6)**
Nausea	**0**	**2 (3)**	**3 (5)**	**1 (2)**
Fatigue	**0**	**2 (3)**	**1 (2)**	**1 (2)**
Headache	**1 (2)**	**1 (2)**	**3 (5)**	**0**
Rash	**0**	**0**	**1 (2)***	**5 (8)**
Grade 2-4 drug-related events (W24+)†	**1 (2)**	**2 (4)**	**3 (5)**	**2 (4)**
Serious adverse events (all)	**6 (10)**	**2 (3)**	**3 (5)**	**3 (5)‡**
AEs leading to withdrawal	**1(2)**	**1 (2)**	**4 (7)**	**8 (13)**
Events with >1 subject				
Dizziness	**0**	**0**	**0**	**2 (3)**
ALT increased	**0**	**0**	**2 (3)****	**0**

*Grade 2; concomitant acute syphilis

†All Grade 2

‡One drug-related SAE: suicide attempt (EFV)

**Two subjects with steatohepatitis developed asymptomatic Grade 4 ALT elevations, with normal bilirubin levels, at Week 4 and Week 8, which resolved off IP.

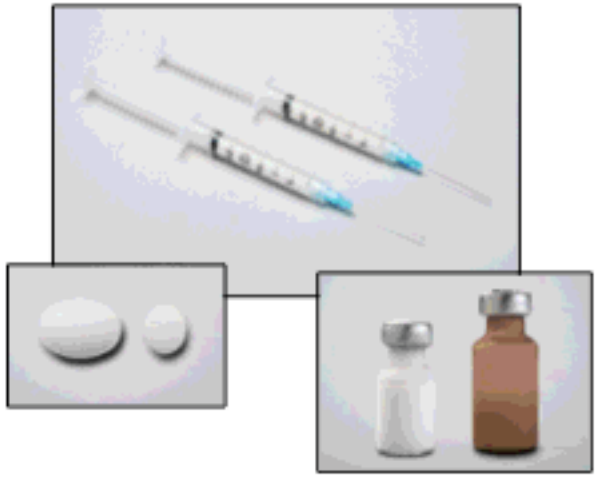
LATTE Study – Week 48 Analysis Conclusions

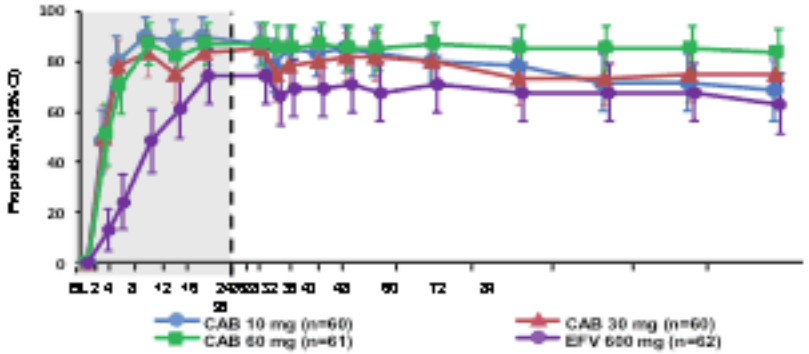
- **Following induction therapy, oral 744+RPV maintained virologic suppression at a rate similar to EFV+NRTIs**
  - Primary Endpoint: 82% of 744+RPV and 71% of EFV+NRTIs subjects had HIV-1 RNA <50 copies/mL
  - Secondary Endpoint (ITT-ME): 93% of 744+RPV and 94% of EFV+NRTIs subjects had HIV-1 RNA <50 copies/mL
  - Similar response rate across 744 10mg, 30mg, and 60mg arms
    - One subject, with persistently low 744 and RPV drug concentrations, developed treatment emergent INI and NNRTI mutations
- **744+RPV was well tolerated, with few drug related AEs leading to withdrawal**
- **Long-term data needed, however, these regimen POC results support evaluation of long-acting injectable regimen of 744 LA + TMC278 LA as maintenance therapy**

Margolis et al. CROI 2014; Boston, MA. Abstract 91LB.

Background

- CAB is an HIV-1 integrase inhibitor
  - Oral 30 mg tablet ($t_{½}$, ~40 hours)
  - LA nanosuspension 200 mg/mL ($t_{½}$, ~20-40 days)
- RPV is an HIV-1 NNRTI
  - Oral 25 mg tablet ($t_{½}$, ~50 hours)
  - LA nanosuspension 300 mg/mL ($t_{½}$, ~30-90 days)
- Oral 2-drug CAB + RPV proof of efficacy through Week 96 in LATTE-1





BL, baseline; CAB, cabotegravir; CI, confidence interval; EFV, efavirenz; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPV, rilpivirine; $t_{½}$, half-life.

Margolis et al. *Lancet Infect Dis*. 2015;15:1145-1155.

LATTE-2 Objectives

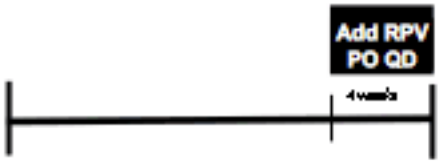
- Establish proof of principle for the first ever long-acting (LA) injectable HIV treatment regimen
- **Primary Objectives**
  - Evaluate the safety and efficacy of CAB LA + RPV LA as maintenance therapy
  - Select a dosing schedule of CAB LA + RPV LA for progression into phase III studies
- **Key Secondary Objectives**
  - Characterize pharmacokinetics after depot injections
  - Evaluate the tolerability and acceptability of intramuscular dosing

LATTE-2 Study Design

Induction period

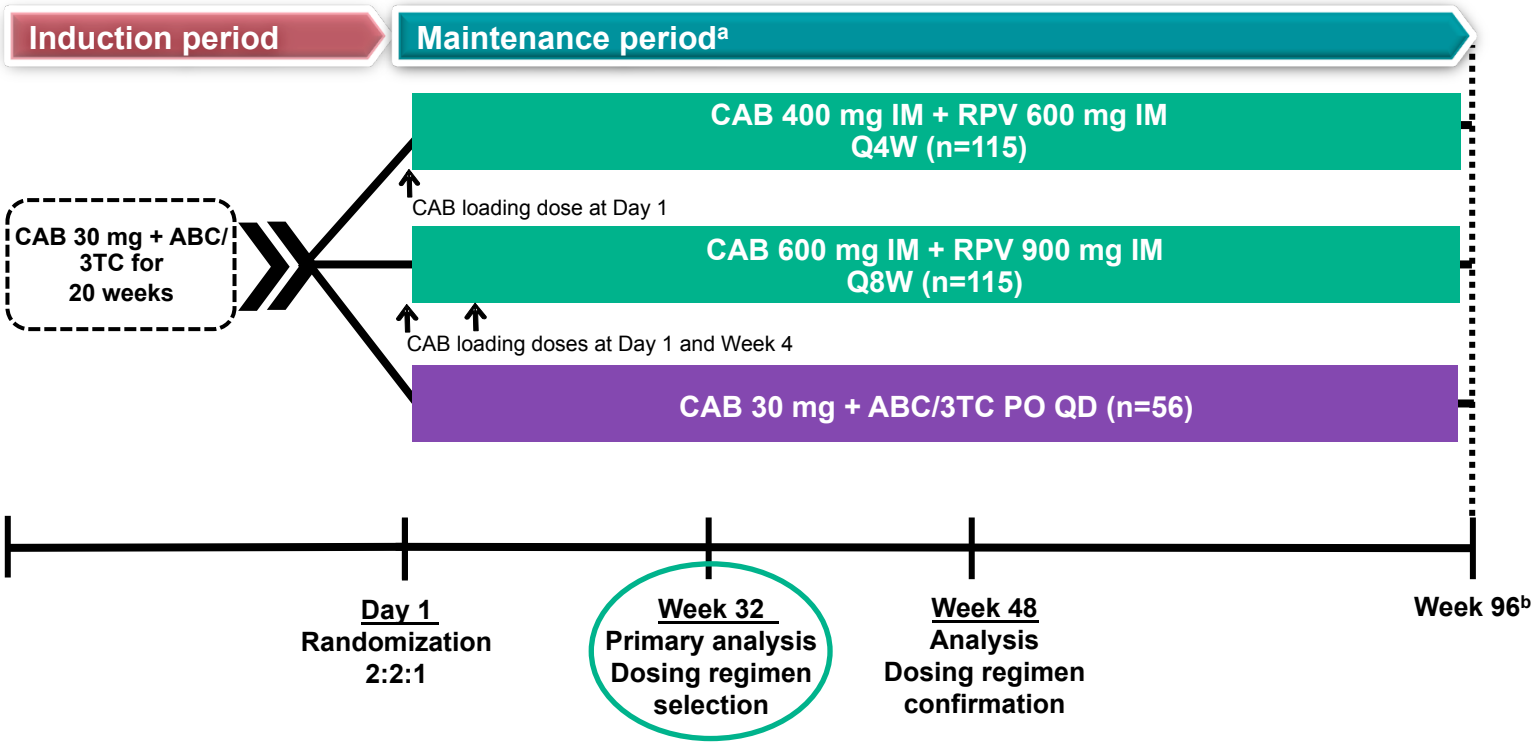
CAB 30 mg + ABC/3TC PO QD for 20 weeks (N=309)

Inclusion criteria	• >18 years old • Naive to antiretroviral therapy • CD4+ >200 cells/mm^3
Exclusion criteria	• Positive for hepatitis B • ALT ≥5 × ULN • Creatinine clearance <50 mL/min
Qualification for maintenance	• HIV-1 RNA <50 c/mL between Week -4 and Day 1



ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; ULN, upper limit of normal. [a]Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. [b]Subjects can elect to enter Q4W and Q8W LA Extension Phase beyond Week 96.

LATTE-2 Study Design



ABC/3TC, abacavir/lamivudine; IM, intramuscular; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; QD, once daily. [a]Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. [b]Subjects can elect to enter LA Extension Phase beyond Week 96.

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.

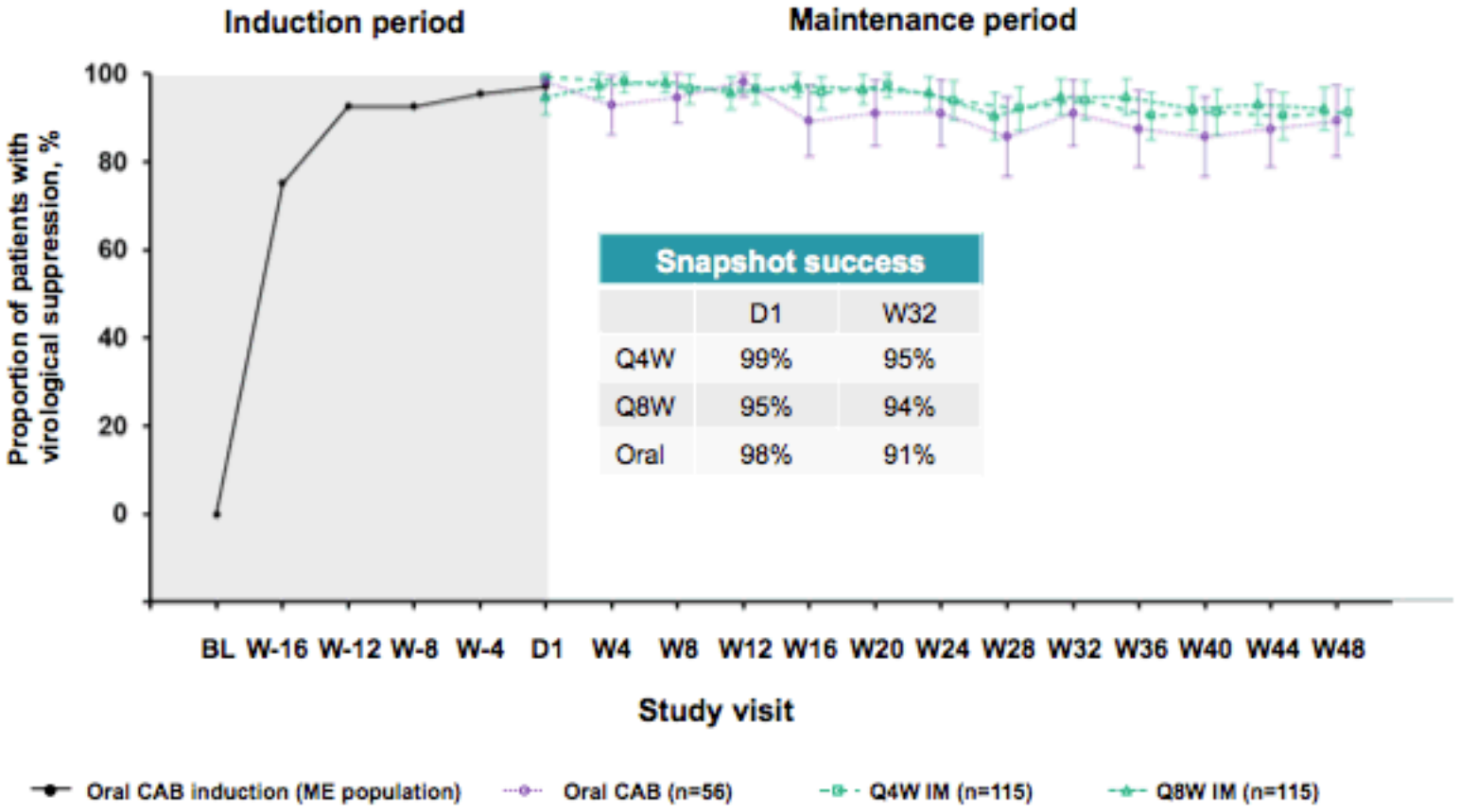
Baseline Characteristics: ITT-ME Population

	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)	Total (N=286)
Median age, years	35.0	36.0	35.0	35.0
Female, n (%)	8 (7)	6 (5)	10 (18)	24 (8)
African American/African heritage, n (%)	17 (15)	12 (10)	15 (27)	44 (15)
CDC class C, n (%)	1 (<1)	2 (2)	0	3 (1)
Median HIV-1 RNA, $\log_{10}$ c/mL	4.419	4.455	4.289	4.393
≥100,000, n (%)	16 (14)	28 (24)	7 (12)	51 (18)
Median CD4+, cells/mm^3	449.0	499.0	517.5	489.0

CDC, Centers for Disease Control and Prevention; ITT-ME, intent-to-treat maintenance exposed.

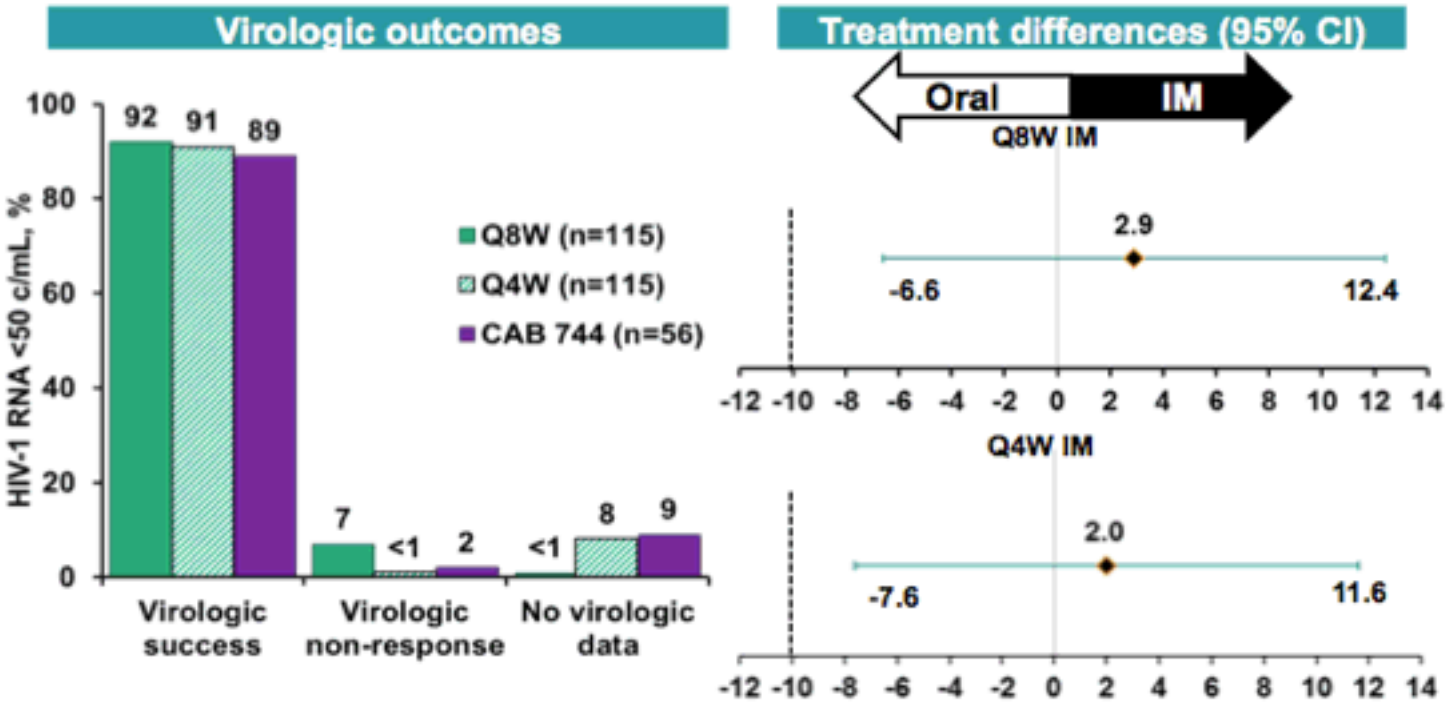
Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.

LATTE-2 Week 48 Results: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



Snapshot success		
	D1	W32
Q4W	99%	95%
Q8W	95%	94%
Oral	98%	91%

HIV-1 RNA <50 c/mL at Week 48
ITT-ME (Snapshot)



Both Q8W and Q4W comparable to Oral CAB at Week 48[a]

[a]Met prespecified threshold for concluding IM regimen is comparable to oral regimen (Bayesian Posterior Probability >90% that true IM response rate is no worse than -10% compared to the oral regimen). Observed Bayesian Probabilities: Q8W vs Oral = 99.7%; Q4W vs Oral = 99.4%.

Snapshot Outcomes: HIV-1 RNA <50 c/mL at Week 48 (ITT-ME)

Week 48 outcome	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)
Virologic success	**106 (92%)**	**105 (91%)**	**50 (89%)**
Virologic non-response	**8 (7%)**	**1 (<1%)**	**1 (2%)**
Data in window not <50 c/mL[a]	6 (5%)	1 (<1%)	0
Discontinued for lack of efficacy	1 (<1%)	0	1 (2%)
Discontinued for other reason while not <50 c/mL	1 (<1%)[b]	0	0
No virologic data in window	**1 (<1%)**	**9 (8%)**	**5 (9%)**
Discontinued due to adverse event or death[c]	0	6 (5%)	2 (4%)
Discontinued for other reasons[d]	1 (<1%)	3 (3%)	3 (5%)

[a]Week 48 HIV-1 RNA Q8W: 50 c/mL, 57 c/mL, 97 c/mL, 110 c/mL, 135 c/mL, 463/205 c/mL; Q4W: 59 c/mL; Q8W: 5 of 6 remain in the study, 4 of 6 have HIV-1 RNA <50 c/mL at all subsequent visits through W80. [b]Withdrew consent: intolerability of injections. [c]Q4W: hepatitis C, rash, depression, psychosis, epilepsy, and Churg-Strauss vasculitis; oral CAB: hepatitis C, DILI. [d]Q8W: ISR; Q4W: pregnancy, prohibited medication, relocation; oral CAB: lost to follow-up, relocation, withdrew consent (wanted injections rather than oral tablets).

Protocol-Defined Virologic Failure (PDVF): Genotype

Maintenance period[a]	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)
Subjects with PDVF	2 (1%)[b]	0	1 (2%)
INI-r mutations	1[c]	0	0
NRTI-r mutations	0	0	0
NNRTI-r mutations	1[c]	0	0

- NNRTI—**K103N, E138G, and K238T** (FC RPV=3.3; Etravirine=1.9); INI—**Q148R** (FC CAB=5.1; Dolutegravir=1.38)[c]
- No additional PDVFs beyond W48 on any arm (all subjects through W72)[d]

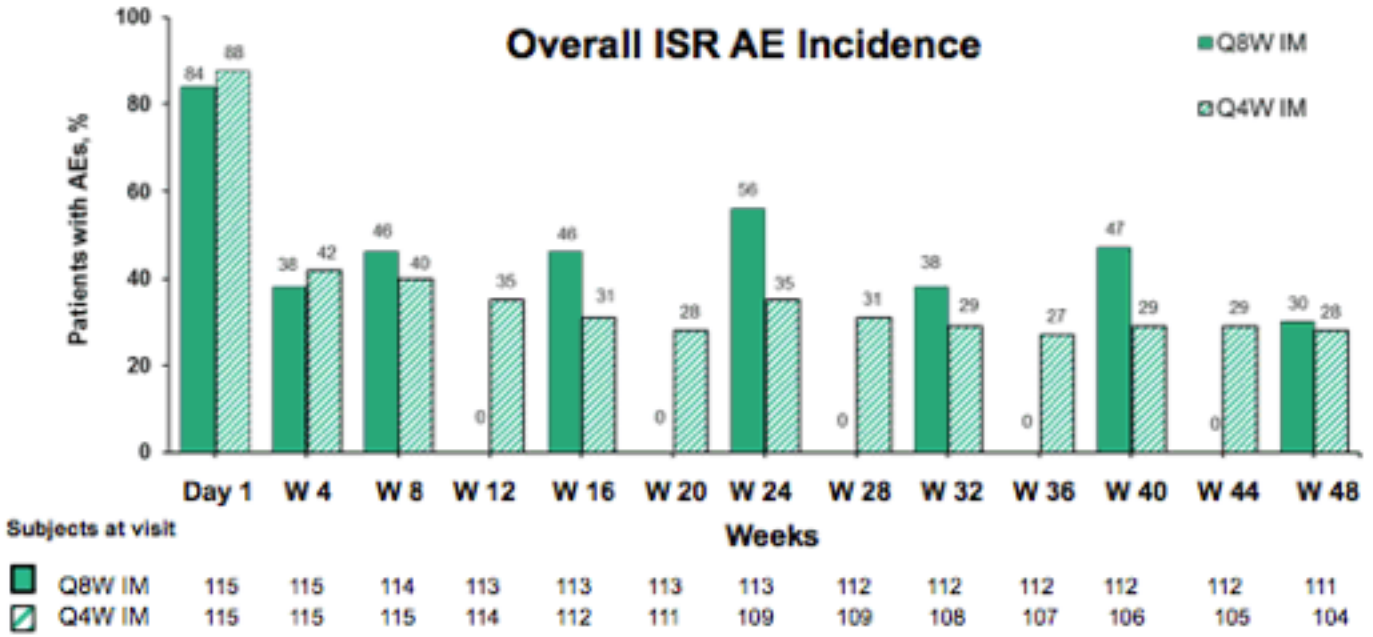
PDVF: <1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA ≥200 c/mL after prior suppression to <200 c/mL, OR >0.5 $\log_{10}$ c/mL increase from nadir HIV-1 RNA value ≥200 c/mL. [a]One additional PDVF without treatment-emergent resistance occurred during oral Induction Period due to oral medication non-adherence. [b]One PDVF at Week 4: no detectable RPV at Week 4 and Week 8, suggesting maladministration. [c]One PDVF at Week 48 at HIV-1 RNA 463 c/mL (confirmed at 205 c/mL). [d]Contains data beyond W48.

Adverse Events and Labs—Maintenance Period

ITT-ME population, n (%)	Q8W IM (n=115)	Q4W IM (n=115)	Oral CAB (n=56)	IM subtotal (N=230)
Drug-related AEs, excluding ISRs (≥3%)				
Pyrexia	3 (3)	5 (4)	0	8 (3)
Fatigue	2 (2)	4 (3)	1 (2)	6 (3)
Influenza-like illness	3 (3)	2 (2)	0	5 (2)
Headache	2 (2)	2 (2)	2 (4)	4 (2)
Rash	0	3 (3)	0	3 (1)
Grade 3 and 4 AEs, excluding ISRs	10 (9%)	13 (11%)	2 (4%)	23 (10%)
Drug-related Grade 3/4 AEs, excluding ISRs[a]	2 (2)	4 (3)	0	6 (3)
Serious AEs (none drug related)	8 (7%)	8 (7%)[b]	3 (5%)	16 (7%)
AEs leading to withdrawal[c]	2 (2%)	7 (6%)	1 (2%)	9 (4%)
Grade 3 and 4 labs[d]	18 (16)	23 (20)	9 (16)	41 (18)

AE, adverse event; ISR, injection-site reaction. [a]Q8W: influenza-like illness, chills and pain; Q4W: influenza-like illness, rash, depression, and psychosis. [b]one death (epilepsy). [c]Q8W: ISR, ISR/chills/body pain; Q4W: Churg-Strauss vasculitis, hepatitis C, depression, epilepsy, psychosis, rash, and mesenteric vein thrombosis; oral CAB: hepatitis C. [d]Maintenance emergent.

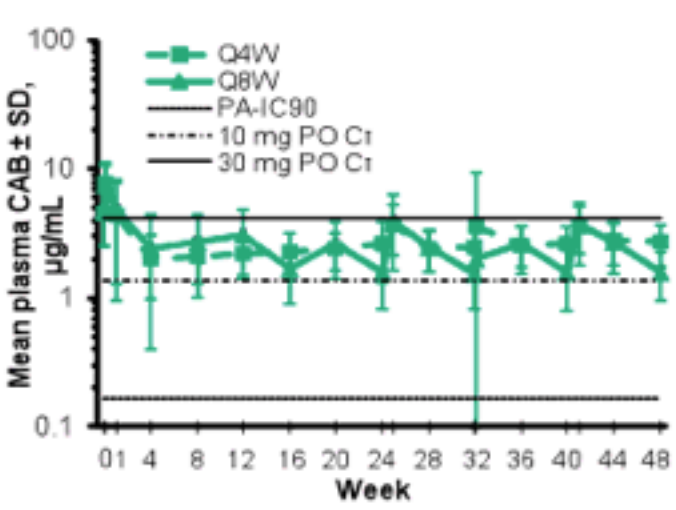
ISRs for CAB LA or RPV LA Over Time

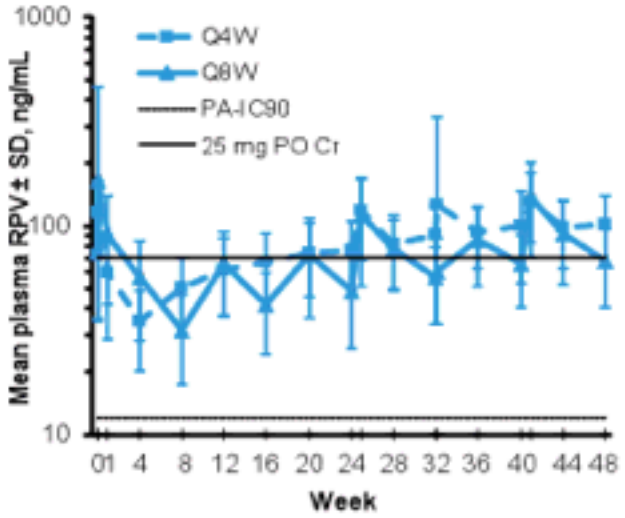


- **99% of ISRs were mild (82%) or moderate (17%), and 90% resolved within 7 days**
- **Most common ISR events overall were pain (67%), nodules (7%), and swelling (6%)**
- **2/230 subjects (<1%) withdrew as a result of injection reactions (Q8W)**

Bars represent incidence of onset ISR events relative to the most recent IM injection visit.

Pharmacokinetics





- Both Q4W and Q8W steady state exposures approximate once-daily oral dosing

C_T, trough concentration; PA-IC90, protein binding–adjusted 90% inhibitory concentration; SD, standard deviation.

Conclusions

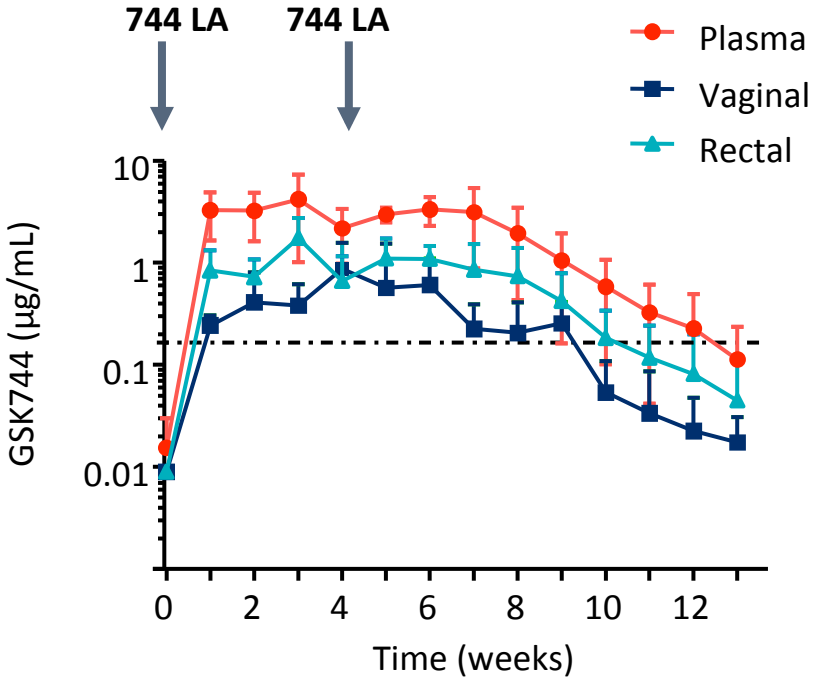
- LATTE-2 results successfully demonstrate ability to maintain HIV-1 viral load <50 c/mL with LA IM CAB + RPV, dosed every 4 or 8 weeks
- Three subjects met PDVF criteria during maintenance
  - Q8W (n=2), oral CAB (n=1); one Q8W subject with emergent RPV and CAB resistance
- Injection tolerability
  - Majority of ISRs were Grade 1 to 2 pain, with a median duration of 3 days
  - Few subjects had an ISR that led to discontinuation
  - High overall reported satisfaction
- Dose selection
  - Q4W dosing resulted in lower rates of virologic non-response with similar safety to Q8W
  - Q4W dosing was selected for pivotal phase III studies
  - Q8W dosing remains under evaluation within LATTE-2

Other Potential Long-Acting ARVs

Agent	MoA	Study results
MK-8591 (EFdA)	NRTI[1]	▪ Phase I study: treatment-naive pts, single 10-mg dose (N = 6) ▪ Mean $t_{1/2}$: 108 hrs ▪ Mean VL reduction at 10 days postdose: 1.78 log_{10}
3BNC117, VRC01	Broadly neutralizing antibodies (bNAbs)	▪ 3BNC117: single infusion reduced VL up to 2.5 log_{10} (n = 17); mean $t_{1/2}$: 9 days[2] ▪ VRC01: single infusion reduced VL up to 1.8 log_{10} in treatment-naive pts (n = 8); 2 minimal responders exhibited resistant virus at BL[3]

1. Friedman EJ, et al. CROI 2016. Abstract 437LB.
2. Caskey M, et al. Nature. 2015;522:487-491.
3. Lynch RM, et al. Sci Transl Med. 2015;7:319ra206.

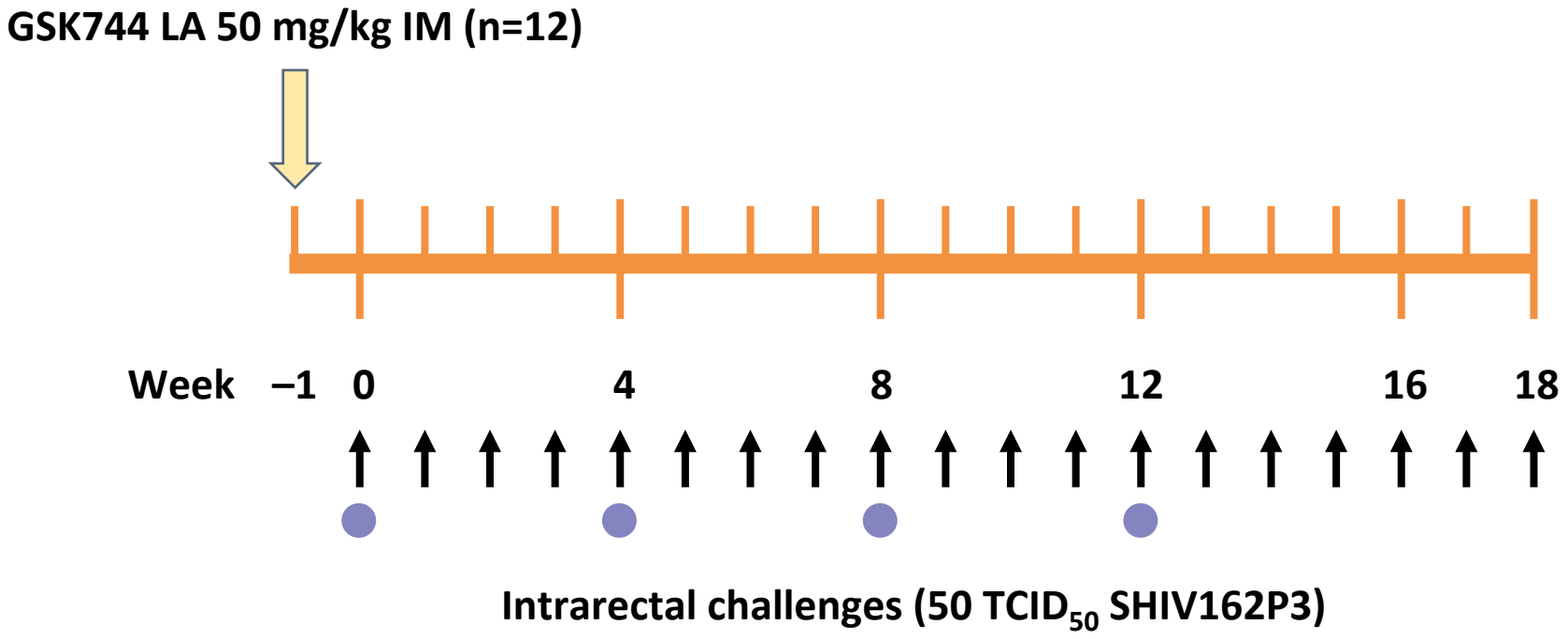
GSK744 concentrations in vaginal and rectal secretions after 50 mg/kg GSK744 LA



	C_{max} (µg/mL)	$AUC_{0–28d}$ (µg·days/mL)
Plasma	3.4 (2.5–9.9)	70.3 (40–169)
Vaginal secretions	0.9 (0.4–1.9)	11.5 (4–14)
Vaginal: plasma ratio	0.26	0.16
Rectal secretions	2.2 (0.6–2.4)	26.7 (10.1–40)
Rectal: plasma ratio	0.65	0.38

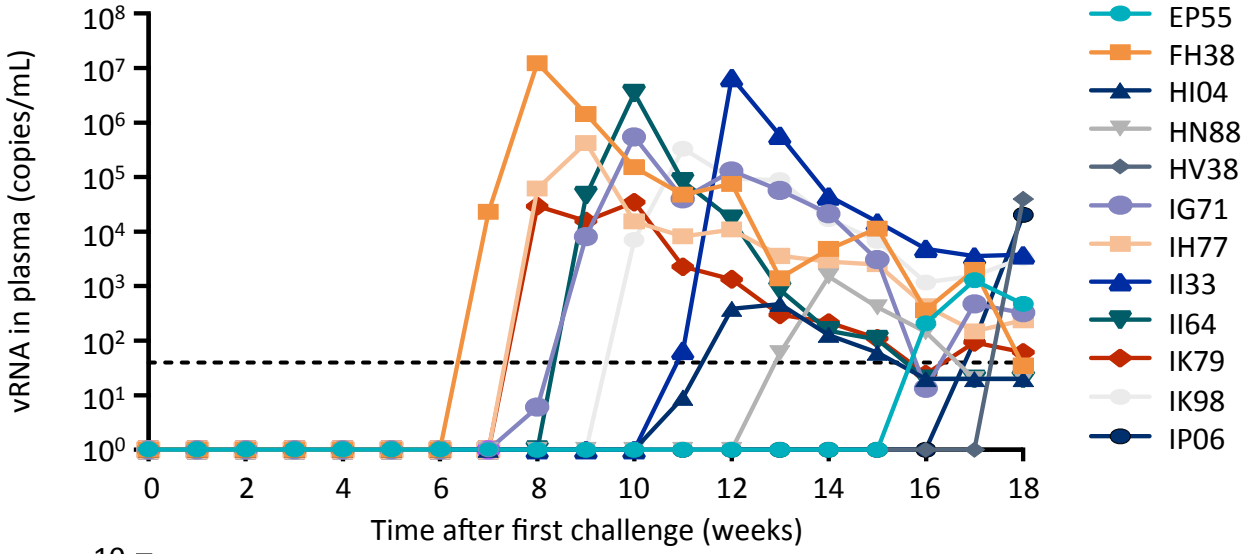
García-Lerma *et al*. CROI 2014; Boston, MA. Abstract #40LB

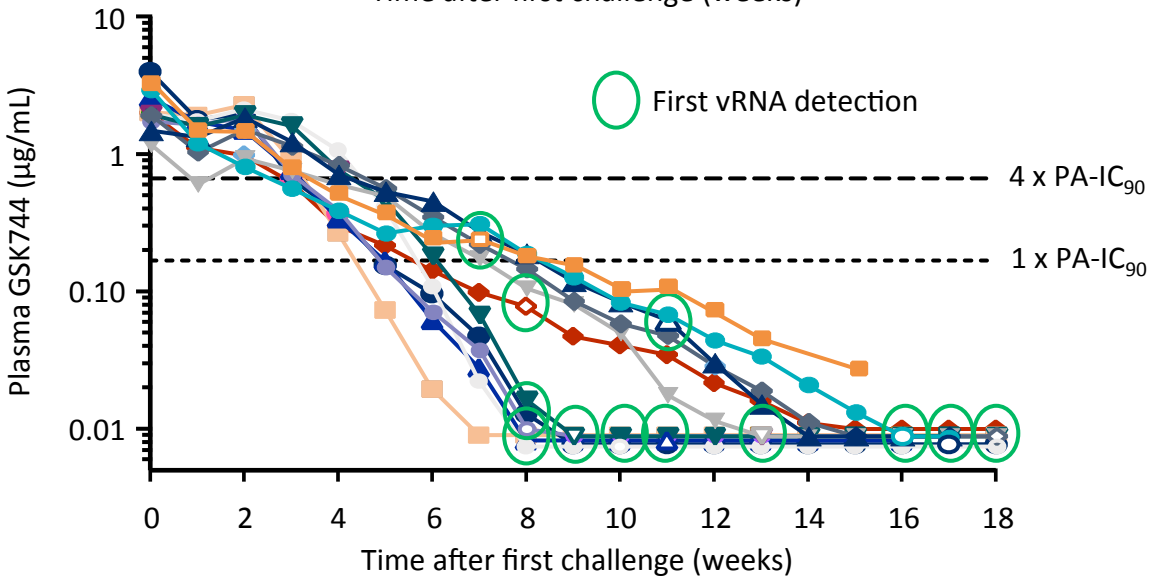
Repeated low-dose intrarectal challenges to evaluate threshold GSK744 LA concentrations for protection in 16 macaques



Andrews *et al.* CROI 2014; Boston, MA. Abstract #39

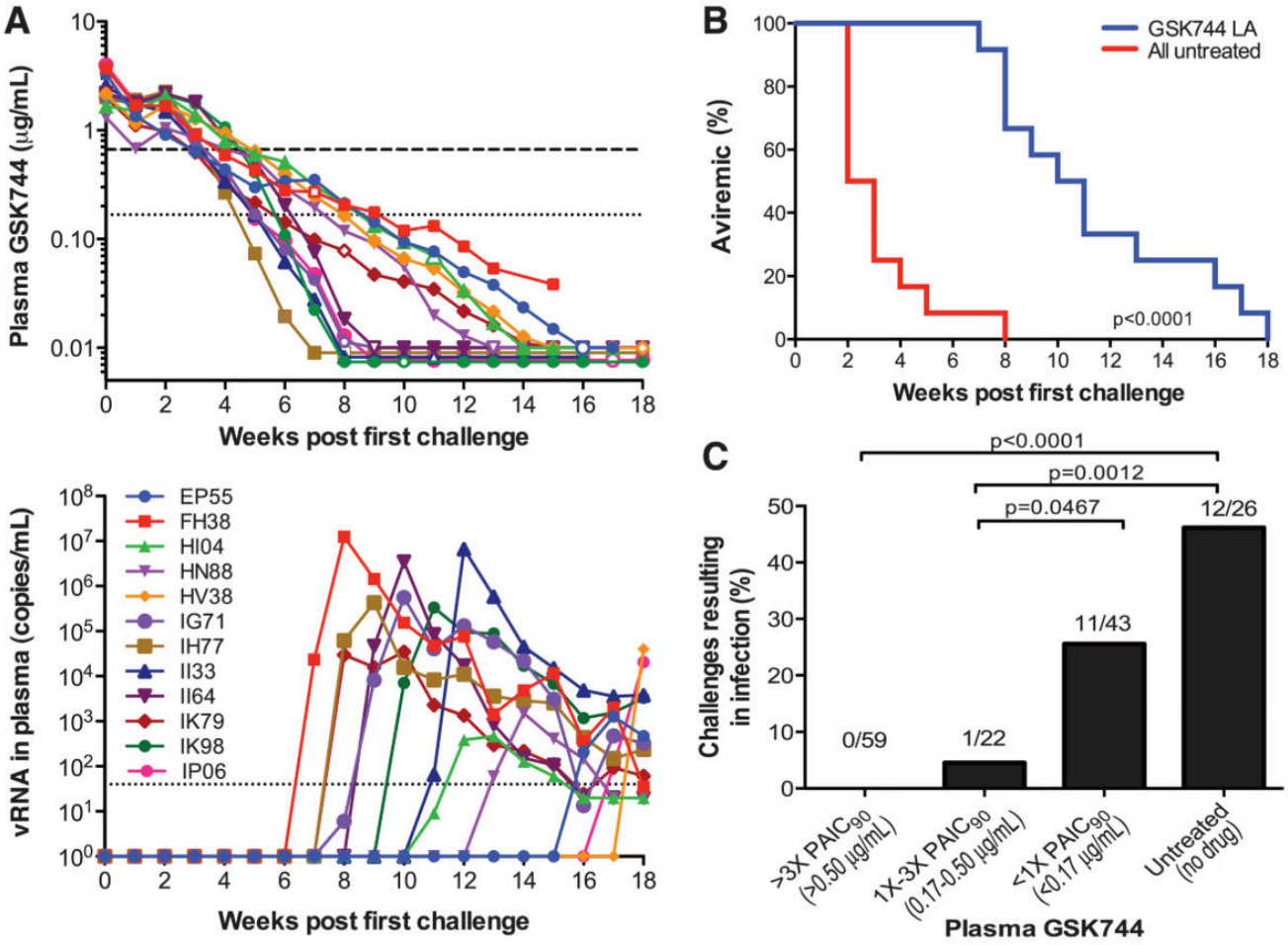
One 50 mg/kg dose of GSK744 LA protects macaques for at least five challenges





Andrews *et al.* CROI 2014; Boston, MA. Abstract #39

Long-Acting integrase inhibitor GSK1265744 protects macaques from intrarectal Simian/ Human Immunodeficiency Virus



Twelve male macaques were injected IM with GSK744 LA at 50 mg/kg (four of 12.5 mg/kg) 1 week before the first virus exposure.

Four macaques remained untreated as controls.

All animals were challenged IR each week with 50 $TCID_{50}$ of SHIV162P3 until infection was confirmed.

Andrews CD, et al. Science, 2014

Pharmacokinetic evaluation of long-acting rilpivirine in HIV-negative volunteers for pre-exposure prophylaxis

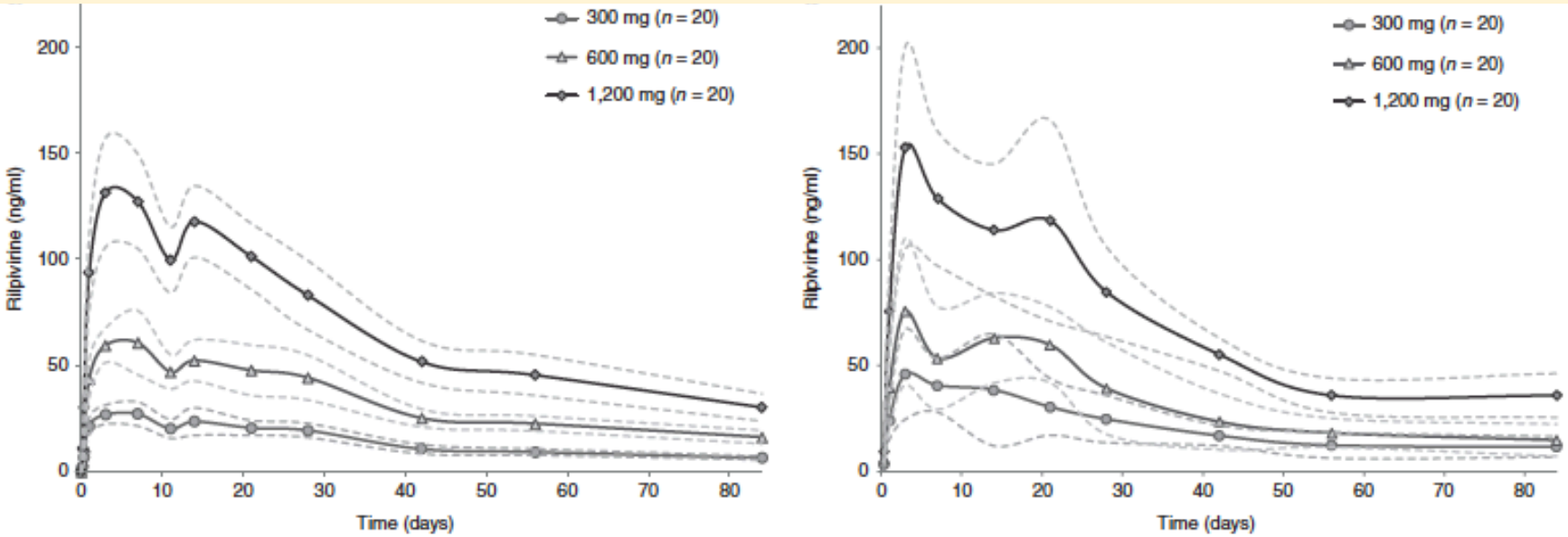
Rilpivirine long-acting (RPV-LA) is a parenteral formulation enabling prolonged plasma exposure. We explored its multiple-compartment PK after a single dose, for PrEP.

Sixty-six HIV-negative volunteers were enrolled: women received an intramuscular dose of 300, 600, or 1,200 mg, with plasma and genital levels measured to 84 days postdose; men receiving 600 mg had similar PK determined in plasma and rectum. Ex vivo antiviral activity of cervicovaginal lavage (CVL) was also assessed.

After a single dose, RPV concentrations peaked at days 6–8 and were present in plasma and genital-tract fluid to day 84. Vaginal and male rectal tissue levels matched those in plasma.

At the 1,200 mg dose, CVL showed greater antiviral activity, above baseline, at days 28 and 56. All doses were well tolerated.

All doses gave prolonged plasma and genital-tract rilpivirine exposure.



Jackson AG, et al. Clin Pharmacol Ther, 2014

ECLAIR: Phase 2A Safety and PK Study of Cabotegravir LA in HIV-Uninfected Men

Martin Markowitz,[1] Ian Frank,[2] Robert M. Grant,[3] Kenneth H. Mayer,[4] David A. Margolis,[5] Krischan J. Hudson,[5] Britt S. Stancil,[6] Susan L. Ford,[6] Alex R. Rinehart,[5] William R. Spreen[5]

[1]The Aaron Diamond AIDS Research Center, an affiliate of the Rockefeller University, New York, NY; [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [3]Institute of Virology & Immunology, Gladstone Institutes, San Francisco, CA; Department of Medicine, University of California, San Francisco, CA; [4]The Fenway Institute, Fenway Health, Boston, MA; Beth Israel Deaconess Medical Center, Boston, MA; Harvard Medical School, Boston, MA; [5]ViiV Healthcare, Research Triangle Park, NC; [6]PAREXEL International (formerly employed by GlaxoSmithKline), Research Triangle Park, NC

23rd Conference on Retroviruses and Opportunistic Infections; February 22-25, 2016; Boston, MA

Objectives

Primary

- To evaluate the safety and tolerability of IM CAB LA injections through Week 41

Secondary

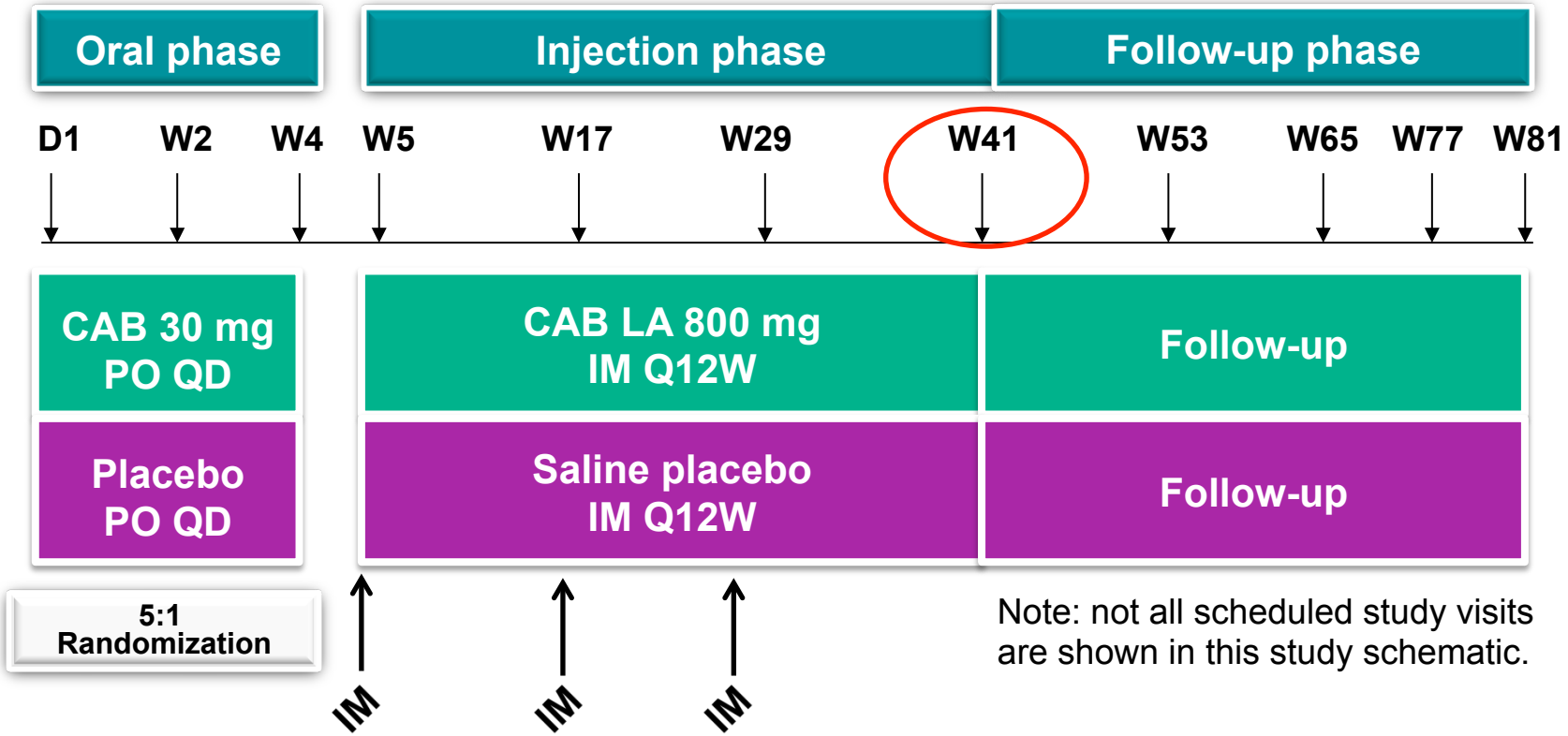
- To evaluate the pharmacokinetics of CAB LA injection through Week 41
- To evaluate the safety and tolerability of oral CAB
- To assess the acceptability of CAB LA injections

IM, intramuscular.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

ECLAIR Study Design

Phase IIa, randomized, multi-site, 2-arm, double-blinded study in men at low risk of acquiring HIV



Note: not all scheduled study visits are shown in this study schematic.

PO, orally; Q12W, every 12 weeks; QD, once daily.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

Baseline Characteristics of the Randomized Population

	PBO (N=21)	CAB (N=106)
Median age, years (min-max)	30 (21-57)	31 (20-61)
Race		
White	57%	56%
African American/African	33%	31%
Hispanic/Latino ethnicity	14%	15%
Median height, cm (min-max)	175 (158-193)	176 (160-198)
Median weight, kg (min-max)	79 (48-132)	81 (52-167)
Median BMI, kg/m^2 (min-max)	25 (18-40)	26 (18-48)
Risk factors for HIV acquisition		
Homosexual contact	76%	85%
Heterosexual contact	29%	21%
Occupational exposure	5%	2%

BMI, body mass index; PBO, placebo.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

Adverse Events—Oral Phase

	PBO (N=21) n (%)	CAB (N=105) n (%)
Grade 2-4 adverse events	4 (19)	24 (23)
Drug-related adverse events (by maximum toxicity)		
Grade 2	3 (14)	9 (9)
Grade 3	0	1 (1)
Grade 4	0	2 (2)
Serious adverse events	0	0
Adverse events leading to withdrawal	0	7 (7)
Blood creatine phosphokinase increased	0	3 (3)[a]
Neutropenia	0	3 (3)[b]
Fatigue	0	1 (<1)[c]

[a]Grade 2 (n=1), Grade 4 (n=2). [b]Grade 2 (n=2), Grade 3 (n=1). [c]Grade 2.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

Adverse Events—Injection Phase (Primary Safety Evaluation)

	PBO (N=21) n (%)	CAB (N=94) n (%)
Grade 1-4 adverse events	19 (90)	92 (98)
Grade 2-4 adverse events (>5% in CAB arm)	10 (48)	75 (80)
Injection site pain	1 (5)	55 (59)
Pyrexia	0	7 (7)
Injection site pruritus	0	6 (6)
Injection site swelling	0	6 (6)
Serious adverse events[a]	1 (5)	1 (<1)

- No laboratory adverse events, including liver laboratory abnormalities, led to discontinuation throughout the injection phase

[a]PBO: deep vein thrombosis (drug-related); CAB: appendicitis.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

ISR Symptoms—Injection Phase

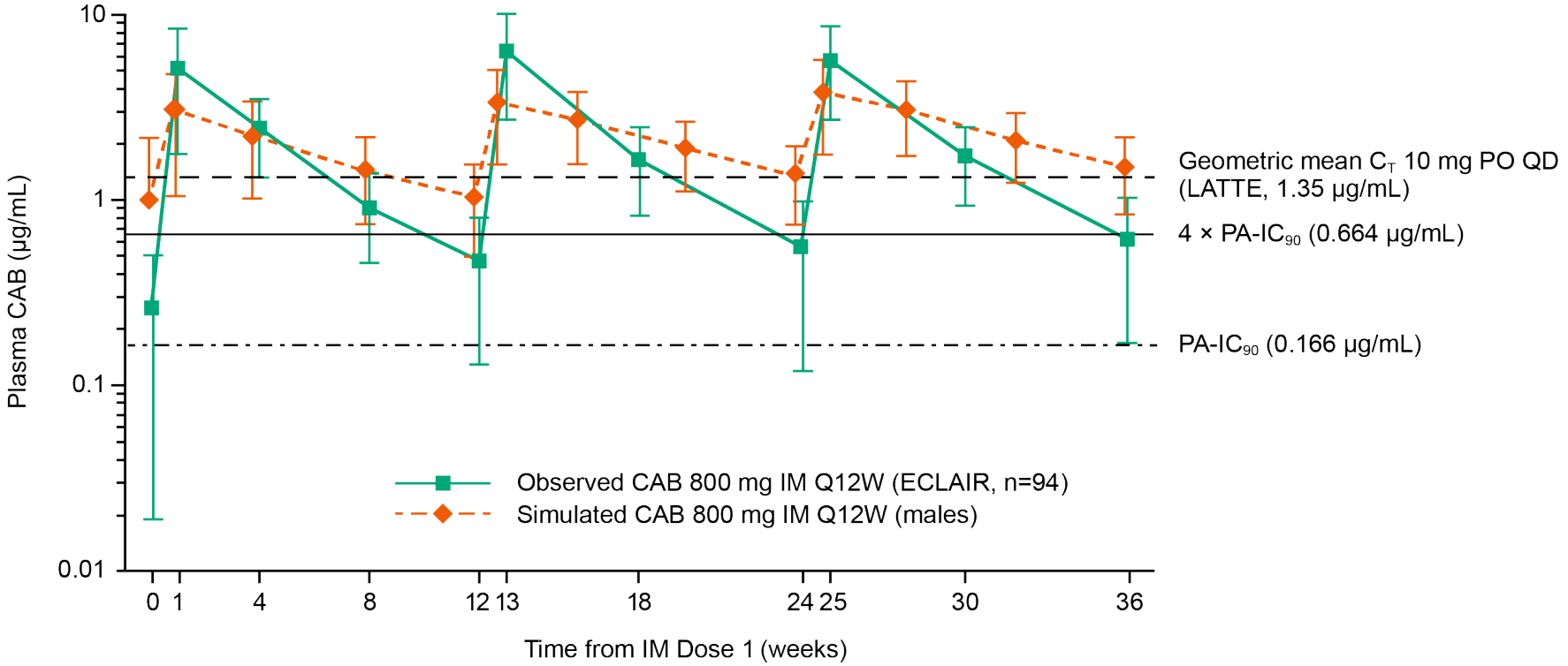
	PBO (N=21) n (%)		CAB (N=94) n (%)	
Subjects with any ISR event	12 (57)		87 (93)	
Total number of injections	62		272	
ISR events by maximum toxicity[a]	**Number of events (%)**	**Mean duration (days)**	**Number of events (%)**	**Mean duration (days)**
Pain	17/62 (27)	2.0	250/272 (92)	5.4
Grade 1	16 (26)		122 (45)	
Grade 2	1 (2)[b]		101 (37)	
Grade 3	0		27 (10)	
Pruritus	4 (6)	1.8	26 (10)	2.5
Swelling	0		22 (8)	3.8
Nodule/Bump	0		21 (8)	9.7
Warm to touch	0		19 (7)	3.2
Bruising	1 (2)	2.0	16 (6)	3.3
Induration	0		15 (6)	4.3

- No subjects discontinued due to AEs during the injection phase; 4 subjects who withdrew consent cited injection tolerability as a reason

[a]Percentages are out of total number of injections. With the exception of Grade 3 pain, all ISRs listed were Grade 1-2.
[b]Subject was misdosed with CAB on third injection.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

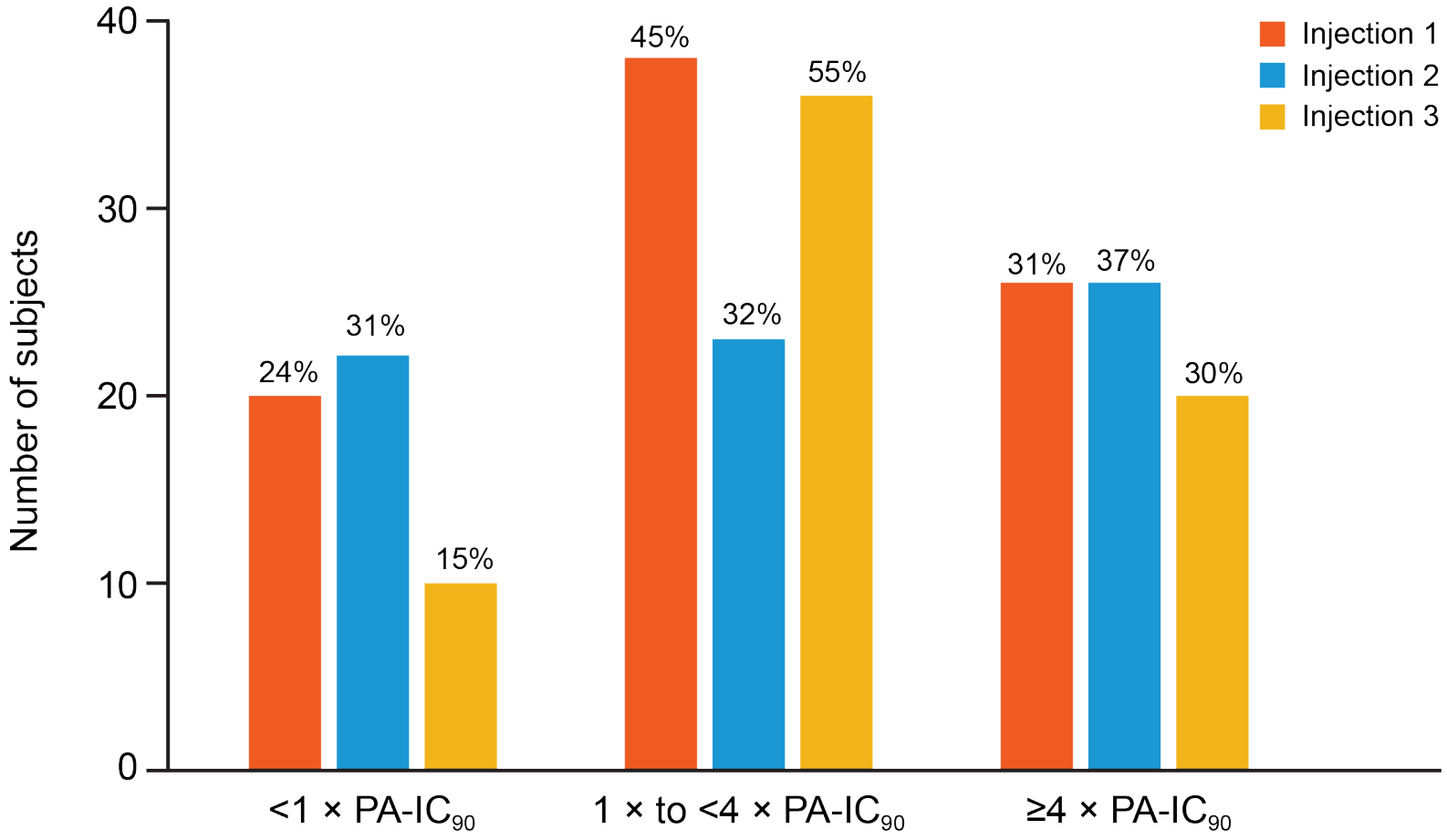
Predicted and Observed Mean (SD) CAB Concentration



C_T, concentration at the end of the dosing interval; PA-IC_{90}, protein binding–adjusted 90% inhibitory concentration; SD, standard deviation.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

Numbers of Subjects in CAB Concentration Ranges by Injection Visit (ECLAIR)



Percentages shown as percentage of reportable troughs at each injection visit within window.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

HIV Seroconversions

Case 1: 24-year-old man, PBO arm, HIV seroconversion at Week 23; referred to ID provider

Case 2: 22-year-old man, CAB LA injection arm, HIV seroconversion at Week 53 (24 weeks after final injection)

Study week	HIV rapid test result	HIV-1 RNA (c/mL)	PK value (µg/mL)
29 (pre-dose, final injection)	Negative	<50	0.038
41	Negative	<50	0.122
53	Negative	3,820,820	NQ
65	Positive	4142	NQ

- Subject reported unprotected sex with a casual partner between the visits at Weeks 41 and 53
- Concomitant transaminitis at Week 53 (Grade 3 ALT/Grade 2 AST)
- No pheno/genotype resistance mutations to INIs (DTG, RAL, EVG, or CAB), NNRTIs, or NRTIs for samples collected at Weeks 53 and 65
- Subject was referred to ID provider, and initiated on darunavir+ritonavir, emtricitabine/tenofovir

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DTG, dolutegravir; EVG, elvitegravir; ID, infectious disease; INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NQ, not quantifiable; PK, pharmacokinetic; RAL, raltegravir.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

ECLAIR Conclusions

- Both CAB oral and LA were well tolerated, permitting continued development of CAB for PrEP
- The absorption rate following CAB LA injection was faster than predicted by early PK population models, leading to higher peak and lower trough exposures
- 15% to 31% of trough concentrations were <PA-IC_{90}, whereas 30% to 37% were ≥4 × PA-IC_{90} across injection visits, below initial predictions
- Given observed trough levels, an 8-week dosing interval is currently under evaluation
- Participant satisfaction with IM CAB LA injections was high, including a preference for injections Q12W compared with oral CAB once-daily tablets

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

Long-Acting Antiretroviral Agents Potential Use

- Can we move away from daily oral therapy for HIV?
  - Are long-acting therapies as effective as oral therapies?
  - What about toxicity?
- Potential challenges with long-acting CAB + RPV IM:
  - What dosing interval might be approved: Q4W or Q8W?
  - Oral induction phase
  - IM dose volume/ISRs
  - What if a dose is missed?
- What pts might be ideal candidates for long-acting therapy?
  - Pts with chaotic lifestyles?
  - Pts with good clinic attendance who dislike daily pills?
- How can resistance be prevented if pts miss doses?