New drugs and formulations: pharmacology of the pipeline

Charles Flexner, MD

Johns Hopkins University

DIVISION OF CLINICAL PHARMACOLOGY

HIV Pipeline 2014

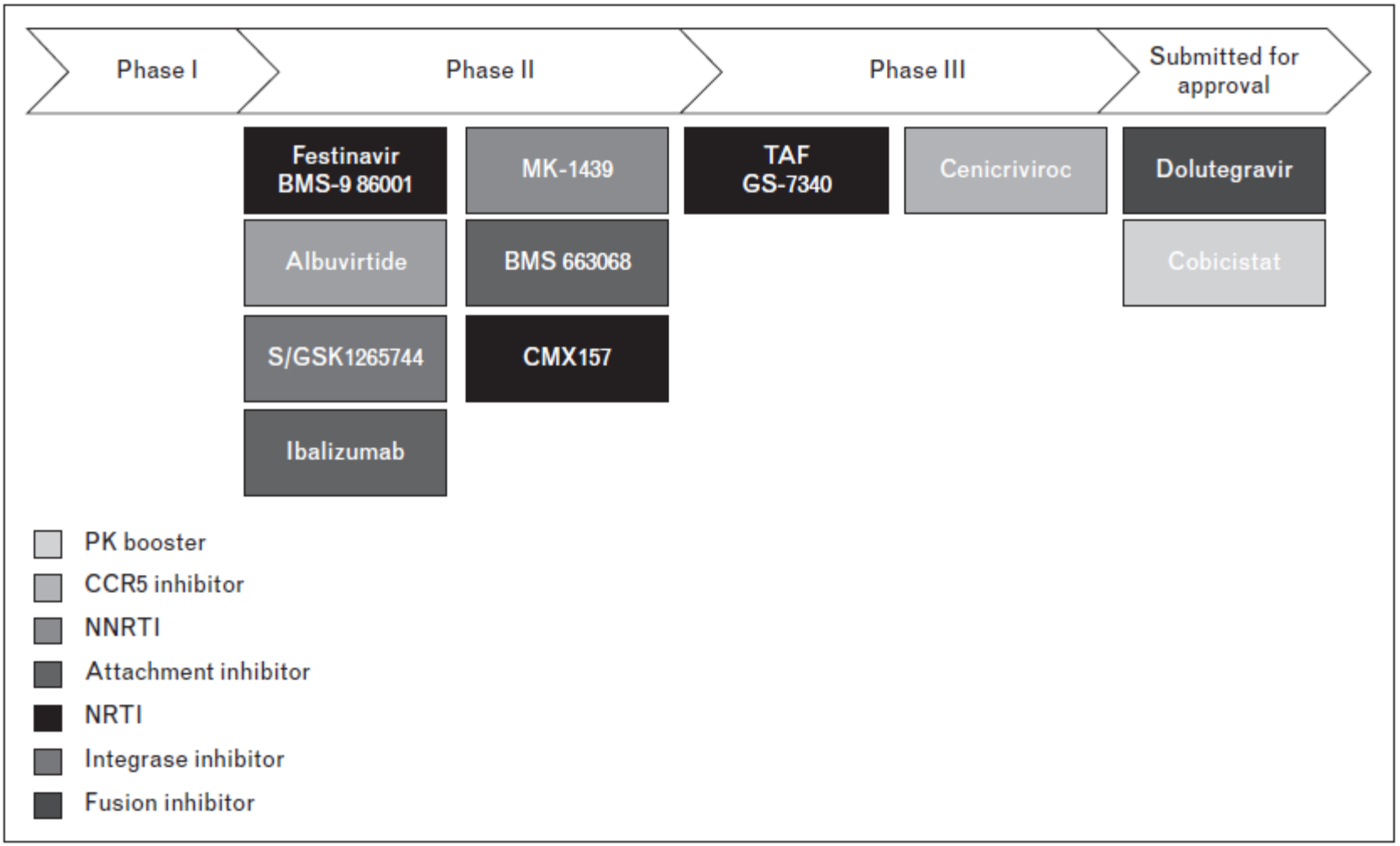


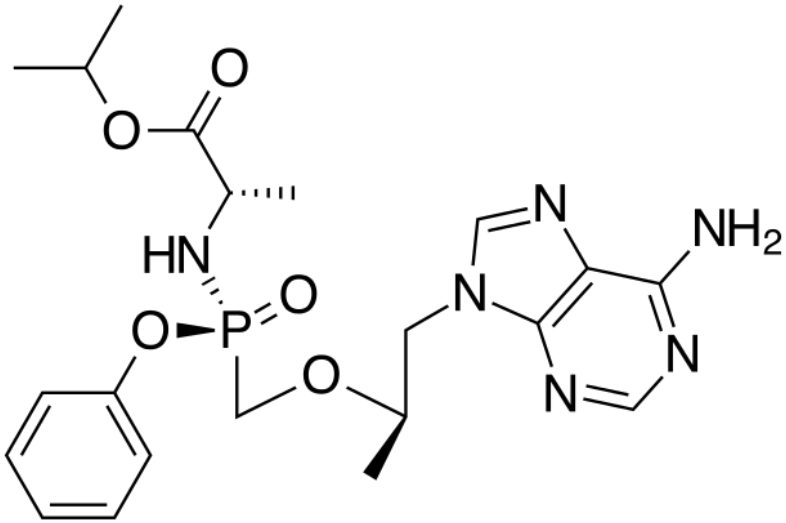
FIGURE 1. Investigational antiretroviral drugs in clinical development, 2013. Data from [1]. Note added in proof: Dolutegravir was granted regulatory approval in the USA on 12 August 2013.

Flexner and Saag, *Current Opin HIV AIDS* 2013

What we are going to discuss:

1. New NRTI's: Tenofovir alafenamide
2. New NNRTI's: Doravirine
3. New entry inhibitors: Cenicriviroc
4. New formulations: Does co-formulation matter?

How close are we to having a universally perfect antiretroviral regimen?



New NRTI's: Tenofovir alafenamide

New NRTI's: Why?

TAF Dose-Response

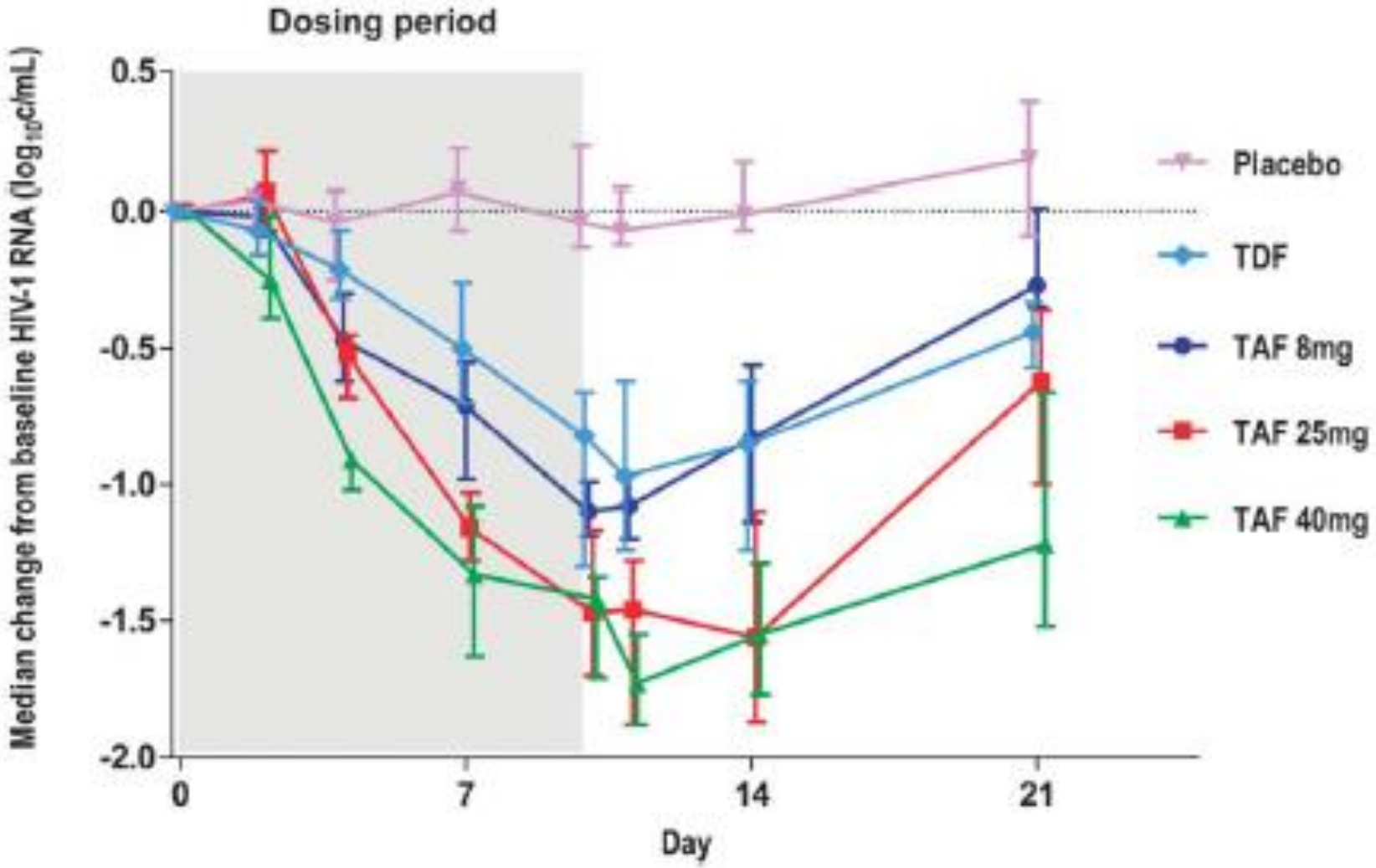


FIGURE 1. Median change from baseline in HIV-1 RNA.

Ruane et al., *JAIDS* 2013;63:449

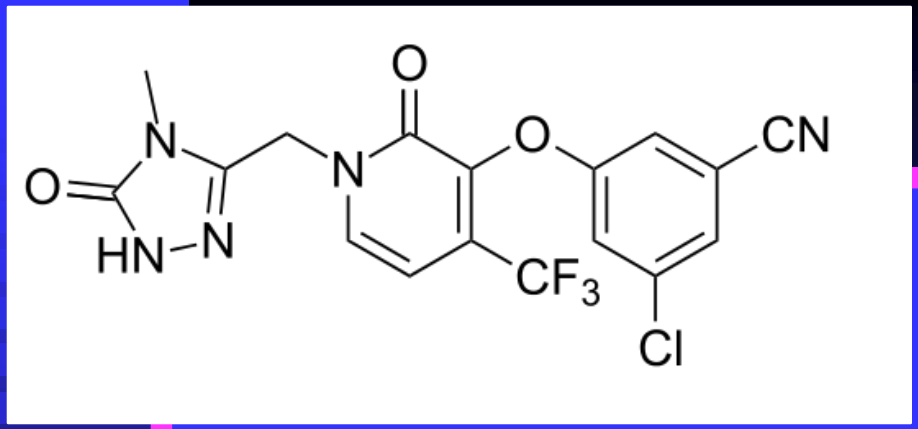
TAF Toxicity

- Data from two Phase 3 trials shows that TAF is less renal- and bone-toxic than TDF.
- Median change in estimated glomerular filtration rate (eGFR) from baseline to week 48:
  - -6.8 mL/min for E/C/F/TAF vs. -10.4 mL/min for Stribild in Study 104 ($p<0.001$)
  - -5.7 mL/min for E/C/F/TAF vs. -11.9 mL/min for Stribild in Study 111 ($p<0.001$)
- Median percentage decrease in lumbar spine bone mineral density:
  - -1.19 vs. -2.67 in Study 104 ($p<0.001$)
  - -1.11 vs. -2.81 in Study 111 ($p<0.001$)
- Median percentage decrease in hip bone mineral density:
  - -0.77 vs. -3.24 in Study 104 ($p<0.001$)
  - -0.74 vs. -2.78 in Study 111 ($p<0.001$)

Data from http://www.gilead.com/news/press-releases/2014/9/

Future Directions for TAF

- Two different doses being used in different FDC's:
  - 25 mg without cobicistat
  - 10 mg with cobicistat
- New FDC's in development
  - Includes TAF/FTC
- No plans for a TAF stand-alone formulation
- Use in PrEP?
- Use in hepatitis B virus treatment?
- Studies in patients at higher risk for renal and bone disease?



New NNRTI's: Doravirine

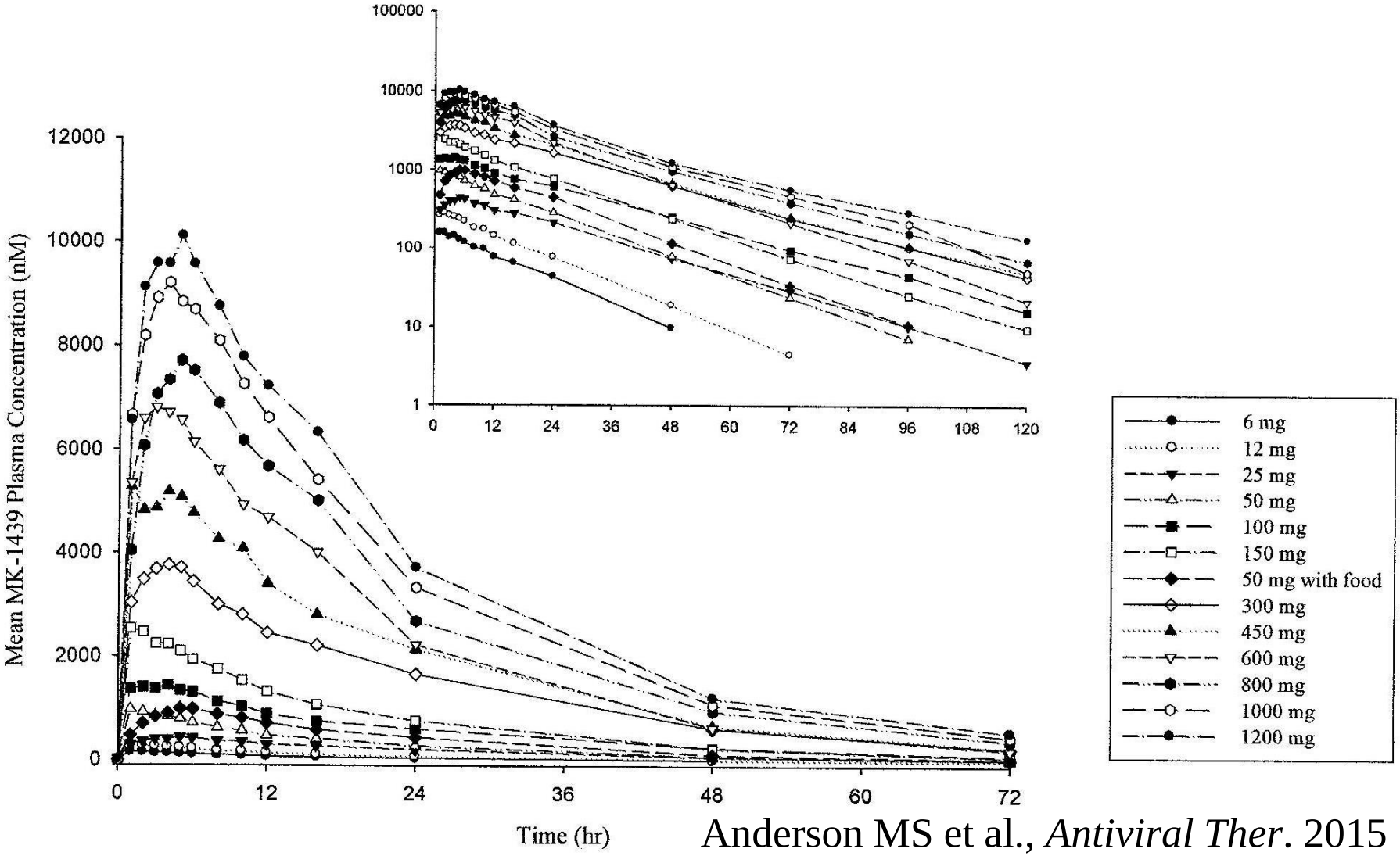
New NNRTI's: Why?

Doravirine Pharmacology

- Once-daily dosing
  - Plasma $t_{½}$ 11-16 hours
- Drug–drug interaction potential:
  - Metabolized via CYP3A4
  - Not a known CYP inducer or inhibitor
- No significant food effect
- Well-tolerated (no apparent CNS toxicity)
- No QTc prolongation seen

Anderson MS et al., *Antiviral Ther*. 2015: in press

Figure 2. Mean Doravirine Plasma Concentration versus Time Profile Following Single Doses of Doravirine, 6 to 1200 mg, in Healthy Male Subjects (Linear scale, first 72 hour postdose) (inset; semi-log scale)



Anderson MS et al., *Antiviral Ther*. 2015

48-Week Efficacy and Safety and Early CNS Tolerability of Doravirine, a Novel NNRTI, with TDF/FTC in ART-Naïve HIV-Infected Patients

Josep M. Gatell[1], Javier O. Morales-Ramirez[2], Debbie P. Hagins[3], Melanie Thompson[4], Keikawus Arasteh[5], Christian Hoffmann[6], Sorin Rugina[7], Olayemi Osiyemi[8], Simona Erscoiu[9], Robin Dretler[10], Charlotte Harvey[11], Xia Xu[11], Hedy Teppler[11] for the P007 Study Team

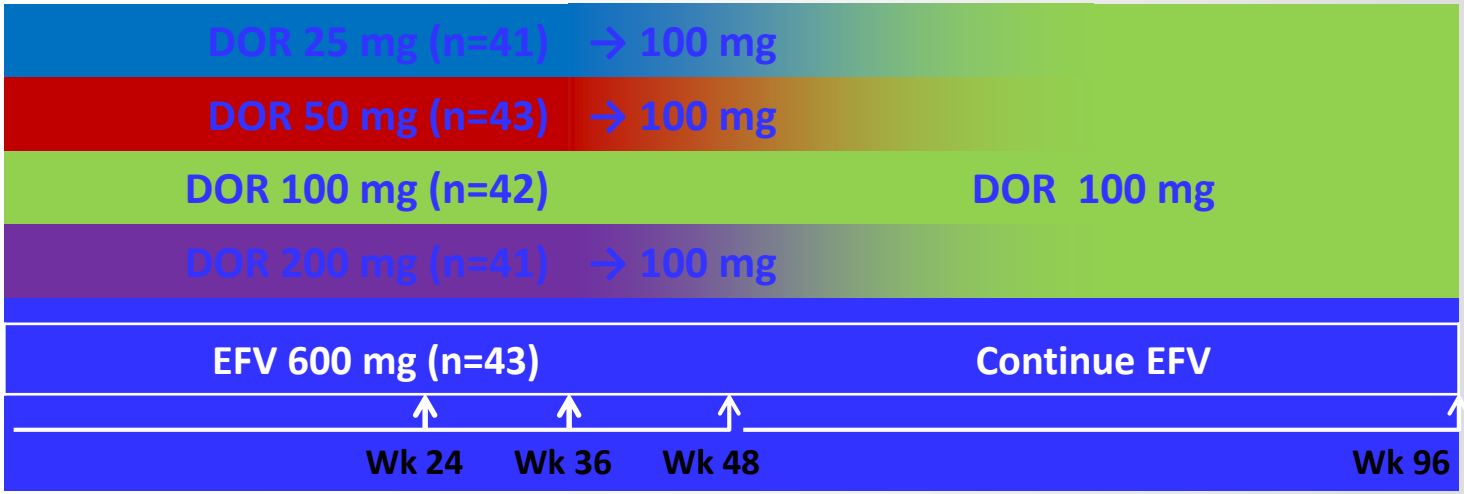
[1]Hospital Clinic/IDIBAPS. Univ of Barcelona, Spain; [2]Clinical Research Puerto Rico, San Juan, PR; [3]Chatham County Health Dept, Savannah, GA, USA; [4]AIDS Research Consortium of Atlanta, Atlanta, GA, USA; [5]EPIMED/Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany; [6]ICH Study Center, Hamburg, Germany; [7]Spitalul Clinic de Boli Infectioase, Constanta, Romania; [8]Triple O Research Institute PA, West Palm Beach, FL, USA; [9]Spitalul Clinic de Boli Infectioase si Tropicale "Dr. Victor Babes," Bucharest, Romania; [10]Infectious Disease Specialists of Atlanta, Decatur, GA, USA; [11]Merck & Co., Inc., Whitehouse Station, NJ, USA

Protocol 007: Study Schema

Patients:
HIV-1+
ART-naïve

HIV RNA ≥ 1,000 c/ml;

CD4 count ≥ 100 cells/µL



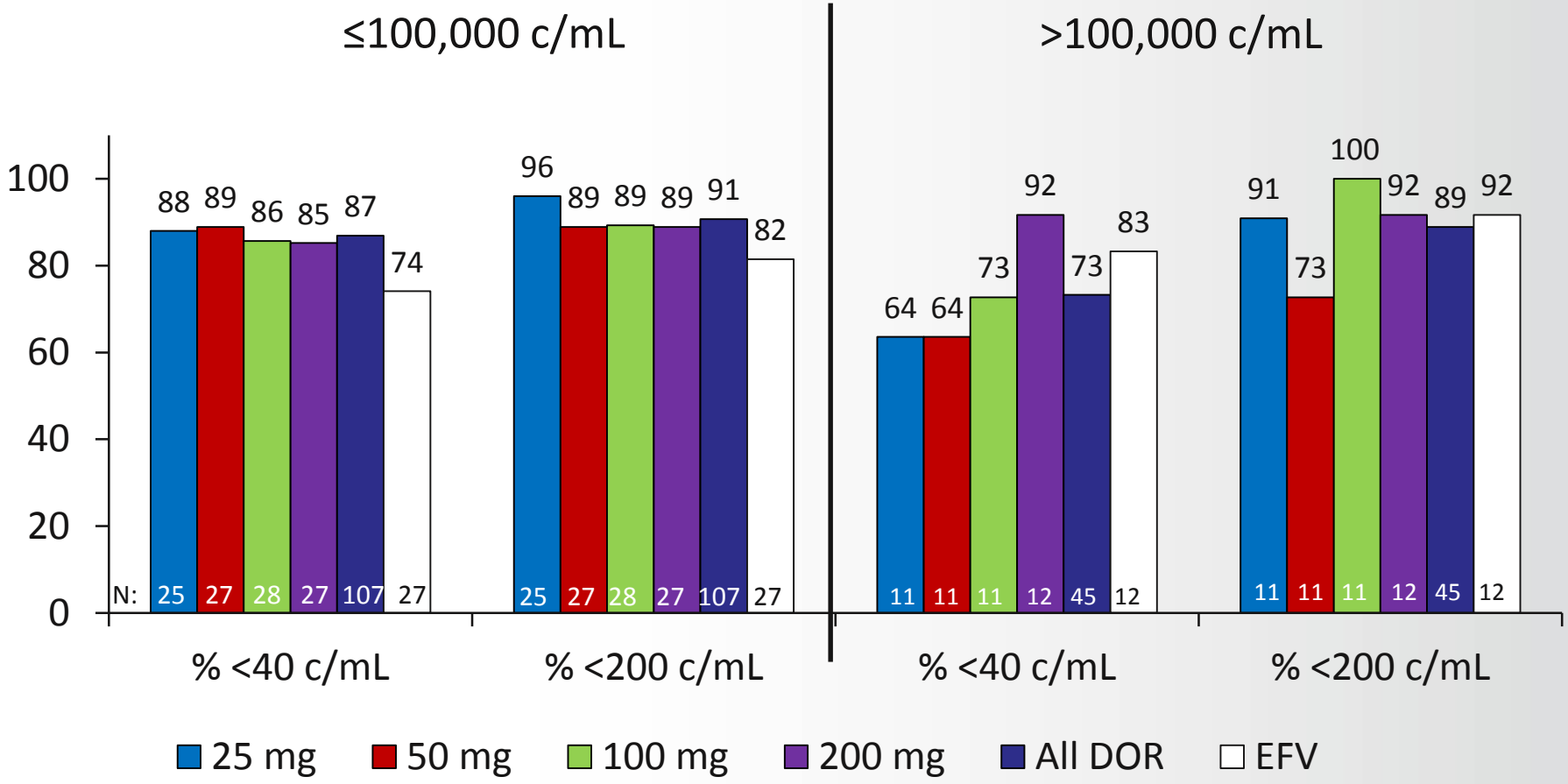
P007 Week 24 Analysis for Dose Selection[6]

- Antiretroviral activity of DOR comparable to EFV
- Favorable safety profile at all doses
- Doravirine 100 mg selected for further development
- Part 1 DOR patients began switch to 100 mg at Week 36

6. J Morales-Ramirez, et al. CROI 2014 [Abstr 92LB].

Virologic Response by Screening RNA

Ad hoc analysis, Week 48 (Observed Failure)



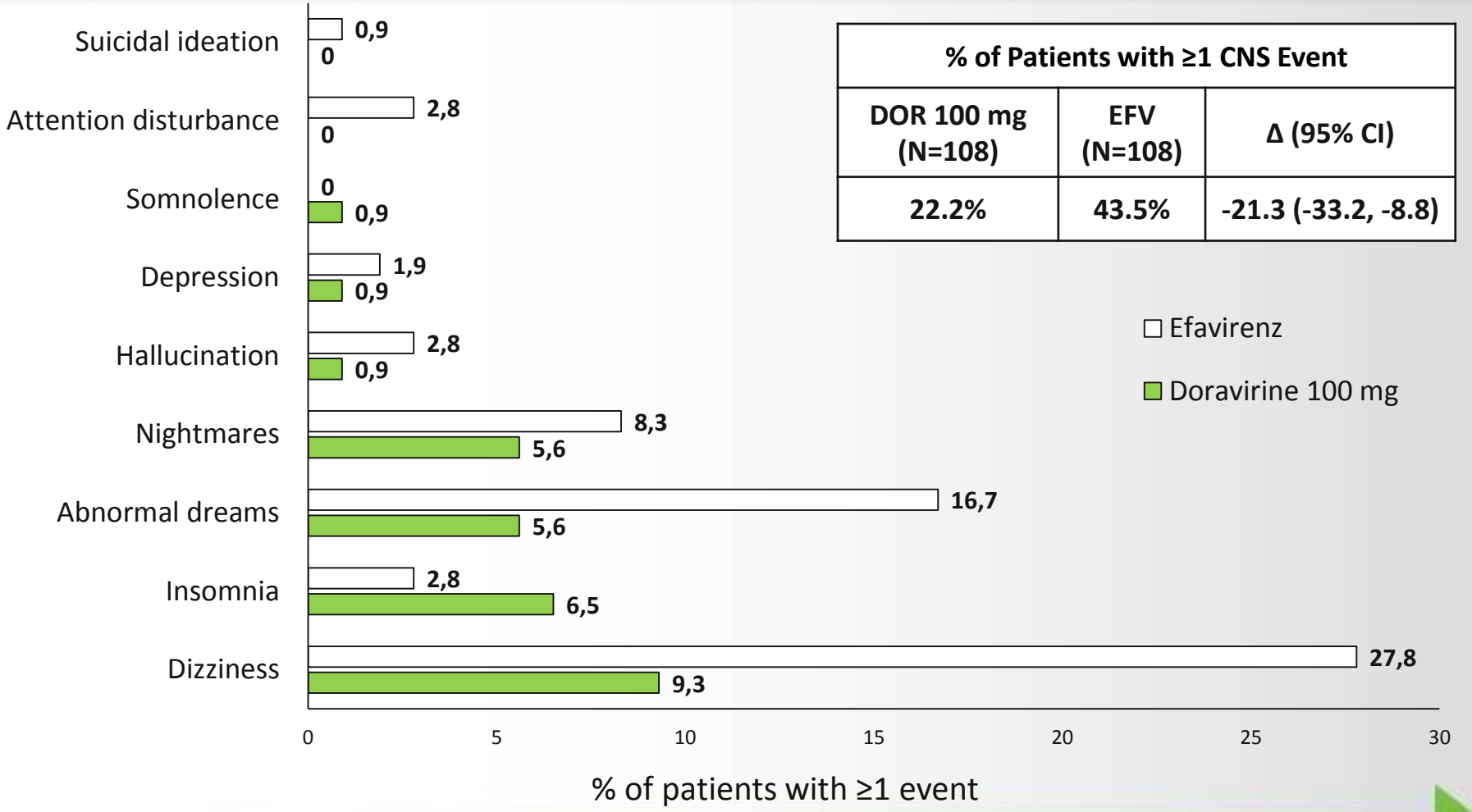
Gatell et al., Glasgow 2014

Primary Safety Comparison: CNS Events, All Causality

Parts 1 & 2 Combined, Week 8

Significantly fewer patients on DOR had ≥1 CNS event by week 8 (p<0.001)

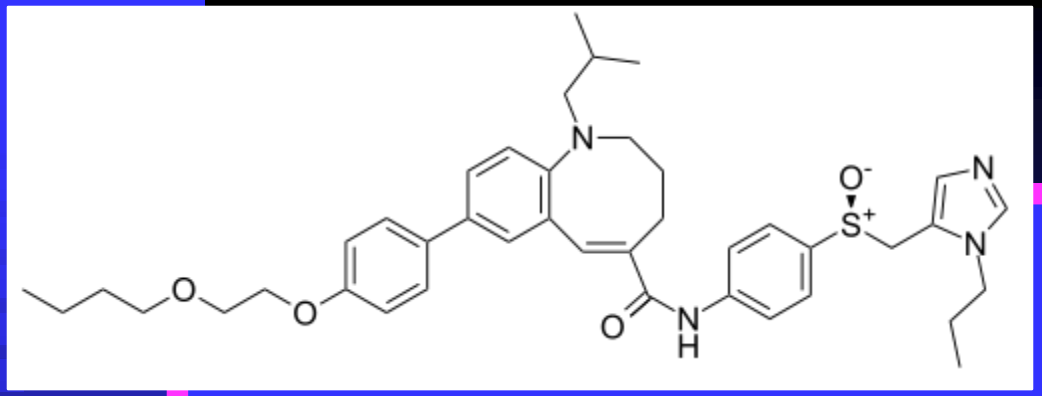
% of Patients with ≥1 CNS Event		
DOR 100 mg (N=108)	EFV (N=108)	Δ (95% CI)
22.2%	43.5%	-21.3 (-33.2, -8.8)



Gatell et al., Glasgow 2014

Future Directions for Doravirine

- 100 mg daily dose selected for future study
- Phase 3 trials underway
- New FDC's in development
- Positioning:
  - First-line?
  - Second-line?
  - Something else?



New entry inhibitors: Cenicriviroc

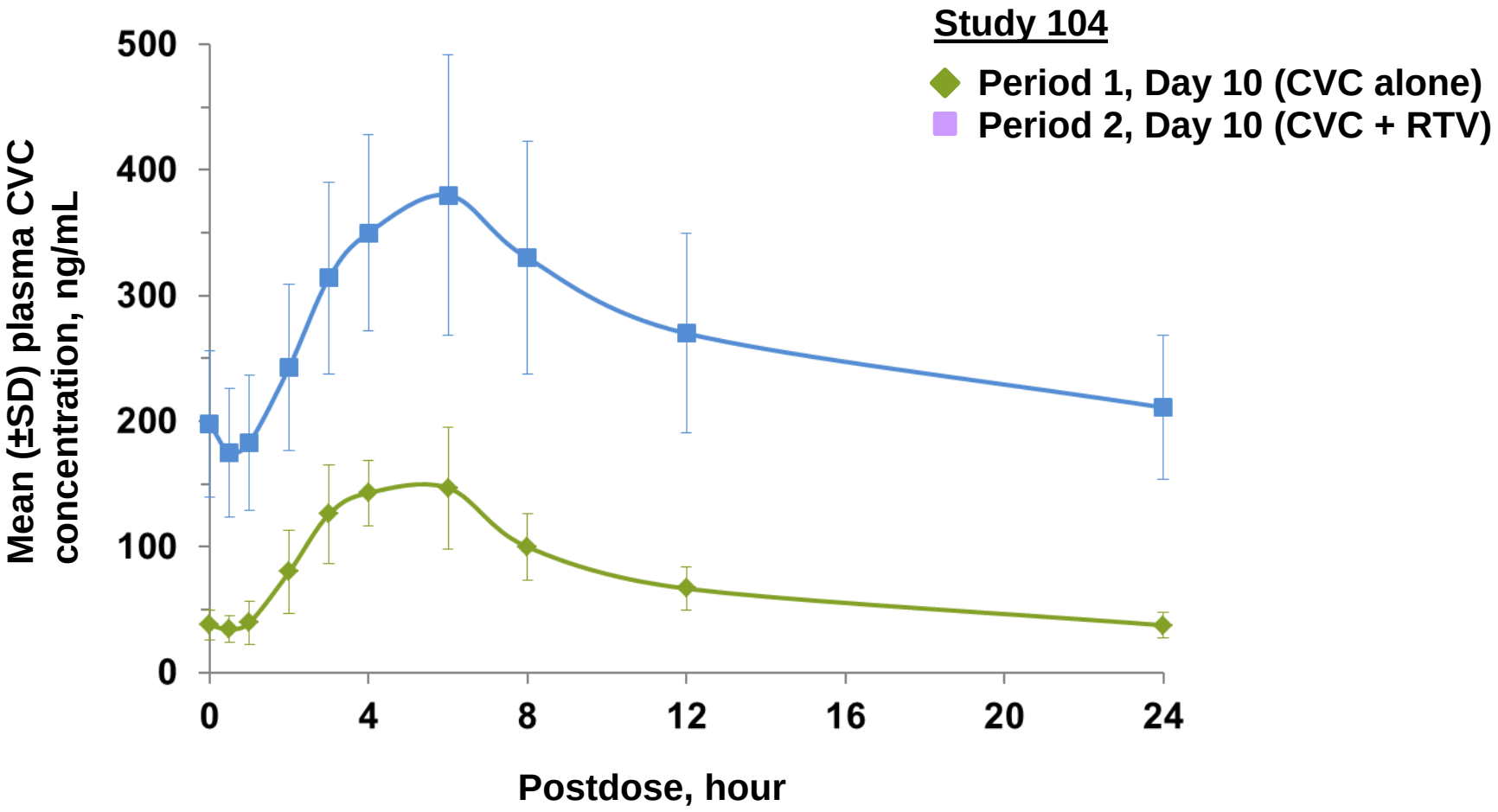
New entry inhibitors: Why?

Cenicriviroc Pharmacology

- Oral CCR5/CCR2 receptor antagonist about to enter Phase 3
- Once-daily dosing
  - Plasma $t_{½}$ (30–40 hours)
- Drug–drug interaction potential:
  - Metabolized via CYP3A4 and CYP2C8
  - Not a known CYP inducer or inhibitor
  - Substrate and inhibitor of P-gp
- Well-tolerated (no orthostatic hypotension)

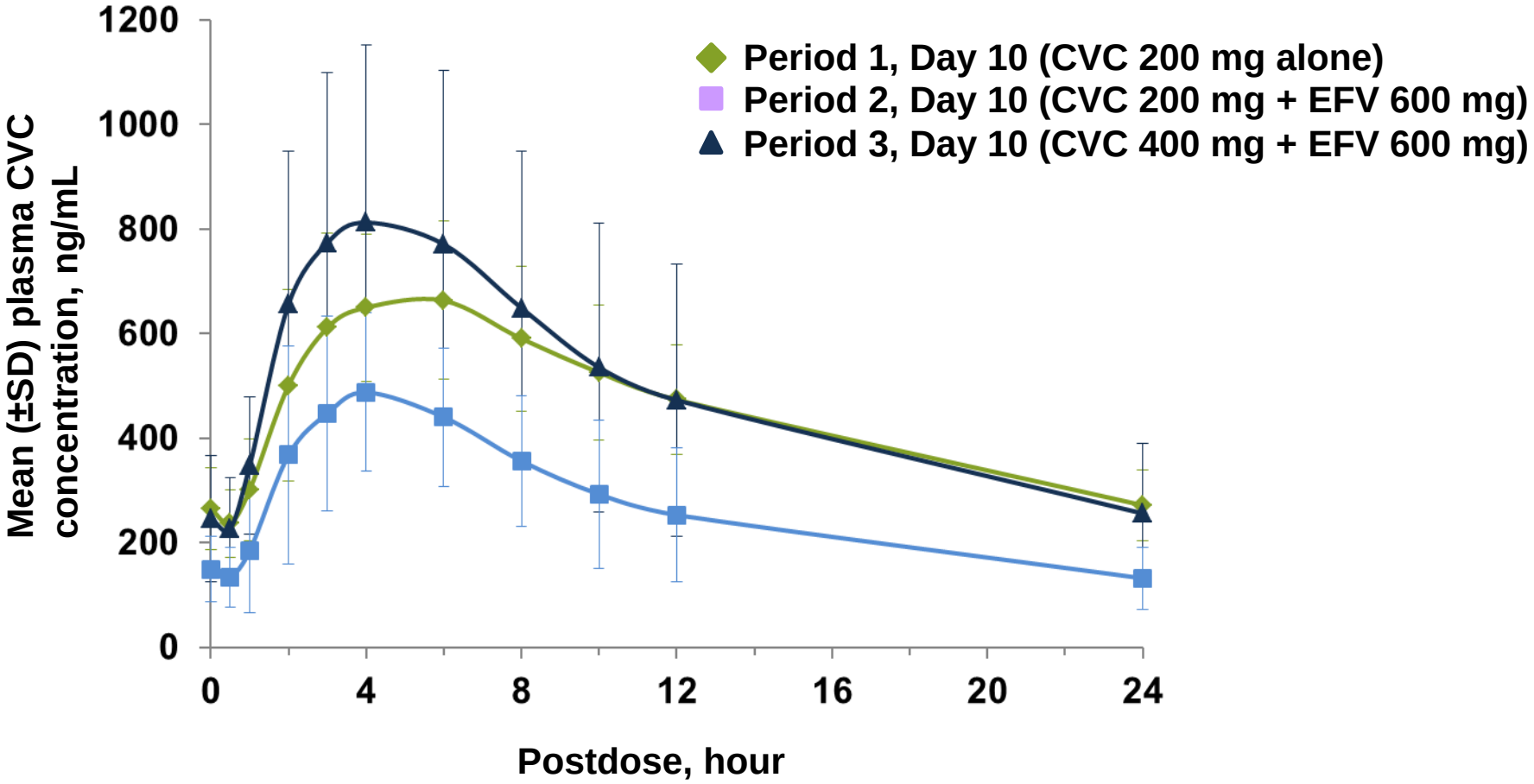
Lefebvre et al., 14th IWCPHT 2013, Abstract O-09

CVC boosting with ritonavir



Lefebvre et al., 14th IWCPHT 2013, Abstract O-09

Reduction in CVC concentrations with EFV



Lefebvre et al., 14th IWCPHT 2013, Abstract O-09

Week 24 Primary Analysis of Cenicriviroc vs Efavirenz, in Combination with FTC/TDF, in Treatment-naïve HIV-1 Infected Adults with CCR5-tropic virus (Study 652-2-202; NCT01338883)

- Joseph Gathe[1], Jerry Cade[2], Edwin DeJesus[3], Judith Feinberg[4], Jay Lalezari[5], Javier O. Morales-Ramírez[6], Anthony Scarsella[7], Michael Saag[8], Melanie Thompson[9], Eric Lefebvre[10]

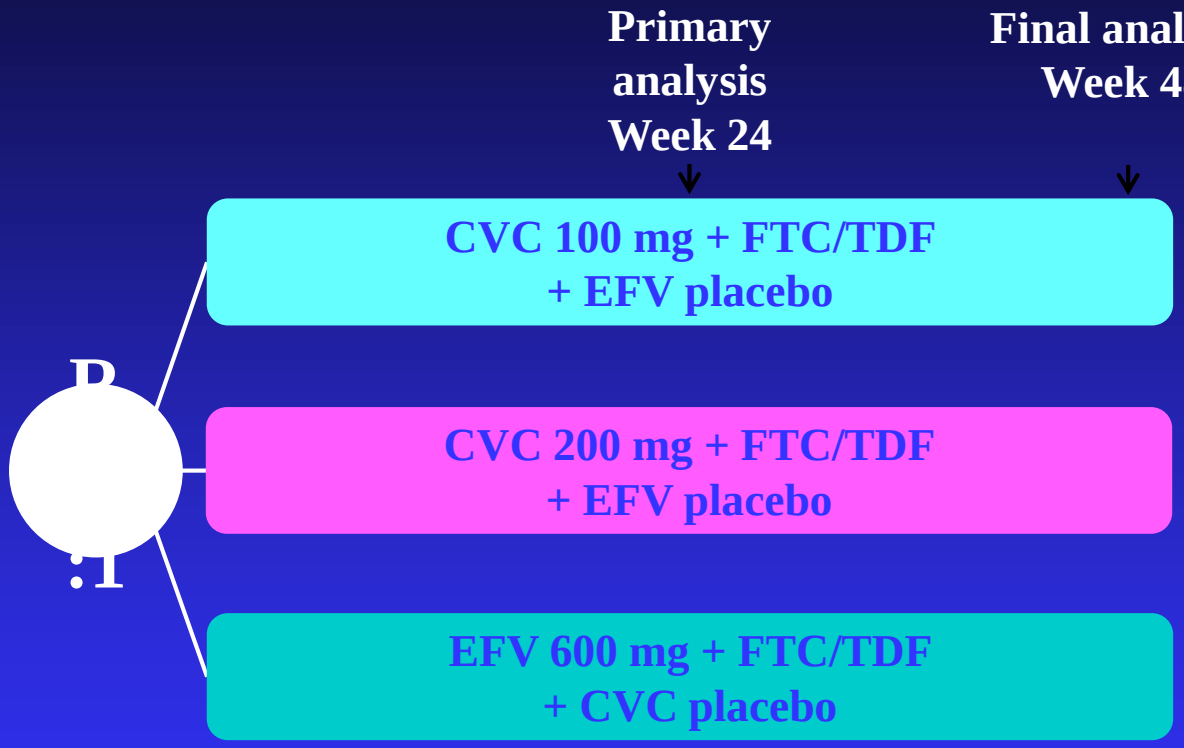
[1]Therapeutic Concepts, Houston, TX, US; [2]Nevada AIDS Res Ed Society, Las Vegas, NV, US; [3]Orlando Immunology Ctr, Orlando, FL, US; [4]Univ Cincinnati, Cincinnati, OH, US; [5]Quest Clin Res, San Francisco, CA, US; [6]Clin Res P.R., Inc., San Juan, Puerto Rico; [7]Pacific Oaks Med Grp, Beverly Hills, CA, US; [8]Univ Alabama at Birmingham, Birmingham, AL, US; [9]AIDS Res Consortium of Atlanta, Atlanta, GA, US; [10]Tobira Therapeutics Inc., San Francisco, CA, US

CROI 2013, Abstract 106LB

Design: Phase 2b, Randomized, Double-Blind, Double-Dummy, Dose-Finding Study

Subjects (N=143)

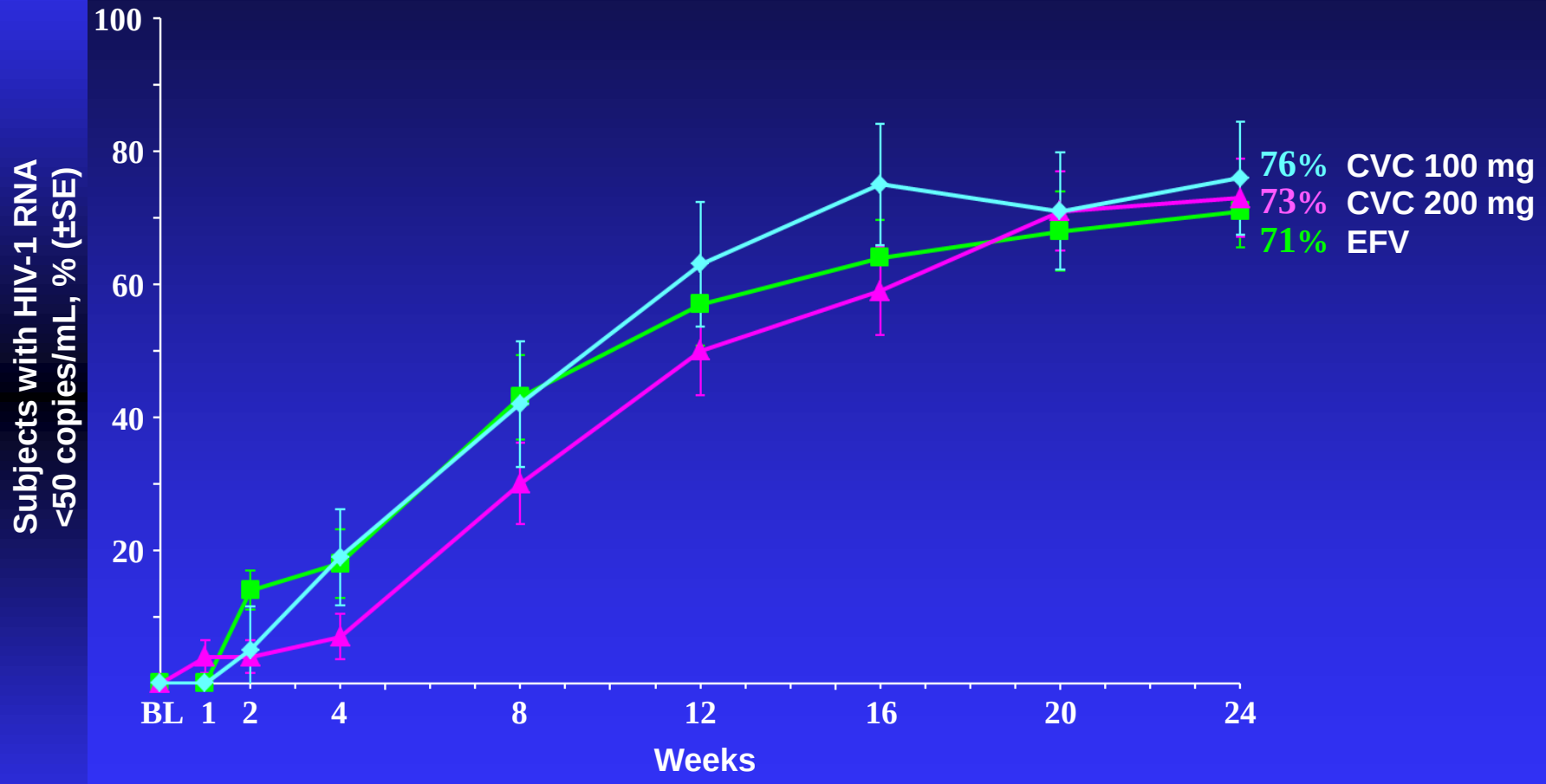
- Tx-naïve adults
- CCR5-tropic only HIV (genotype and phenotype)
- HIV RNA ≥1000 copies/mL
- CD4+ cell count ≥200 c/mm^3
- No primary NRTI/NNRTI resistance
- Stratified by baseline viral load (< or ≥100 000 copies/mL)



Primary endpoint: Subjects (%) with HIV-1 RNA <50 copies/mL at Week 24 in the ITT population (FDA Snapshot algorithm)

Gathe J. et al, CROI 2013; Abstract 106LB

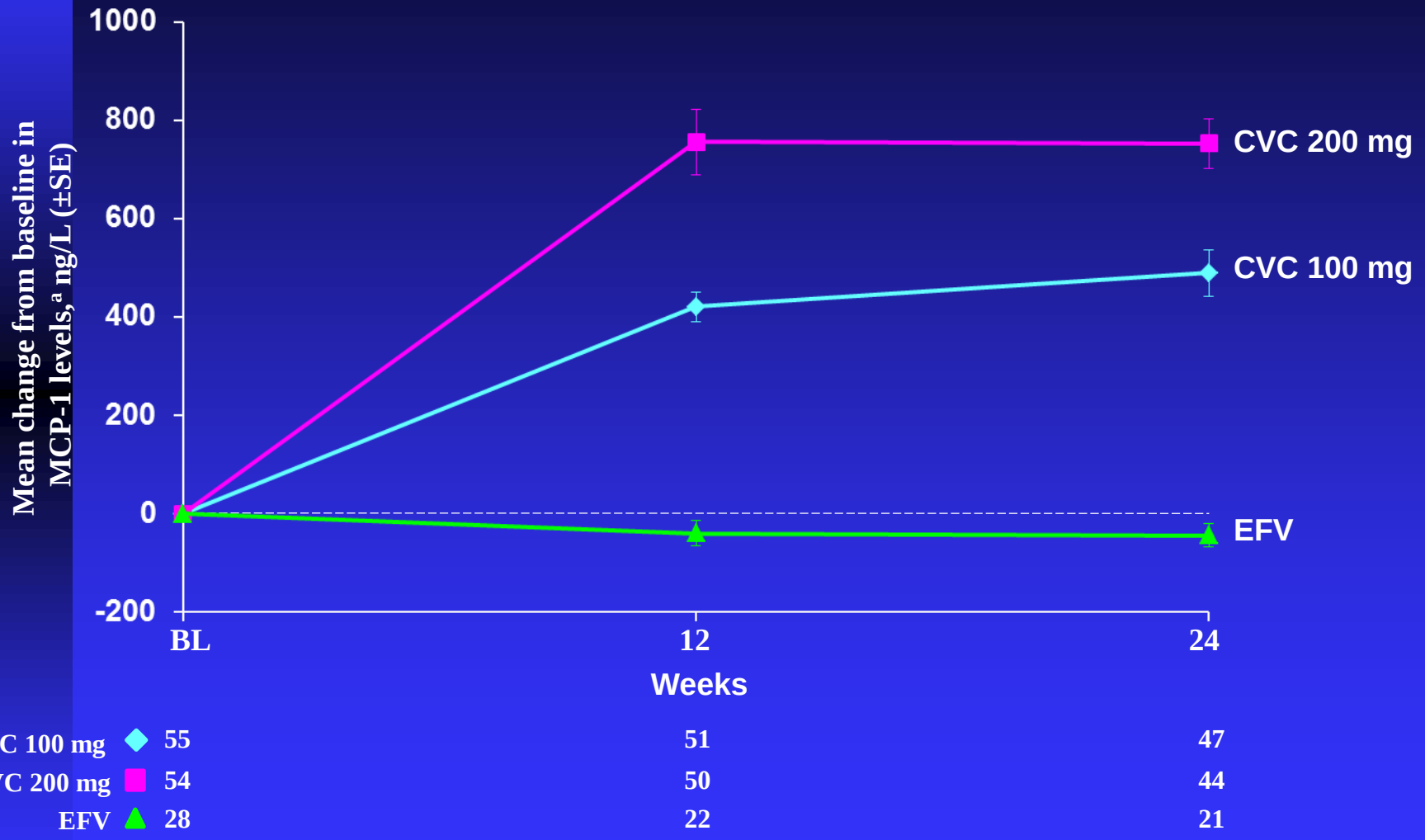
HIV-1 RNA <50 copies/mL (ITT-FDA Snapshot)



CVC 100 mg (N=59)	0	3	11	25	37	44	42	45
CVC 200 mg (N=56)	2	2	4	17	28	33	40	41
EFV (N=28)	0	4	5	12	16	18	19	20

Gathe J. et al, CROI 2013; Abstract 106LB

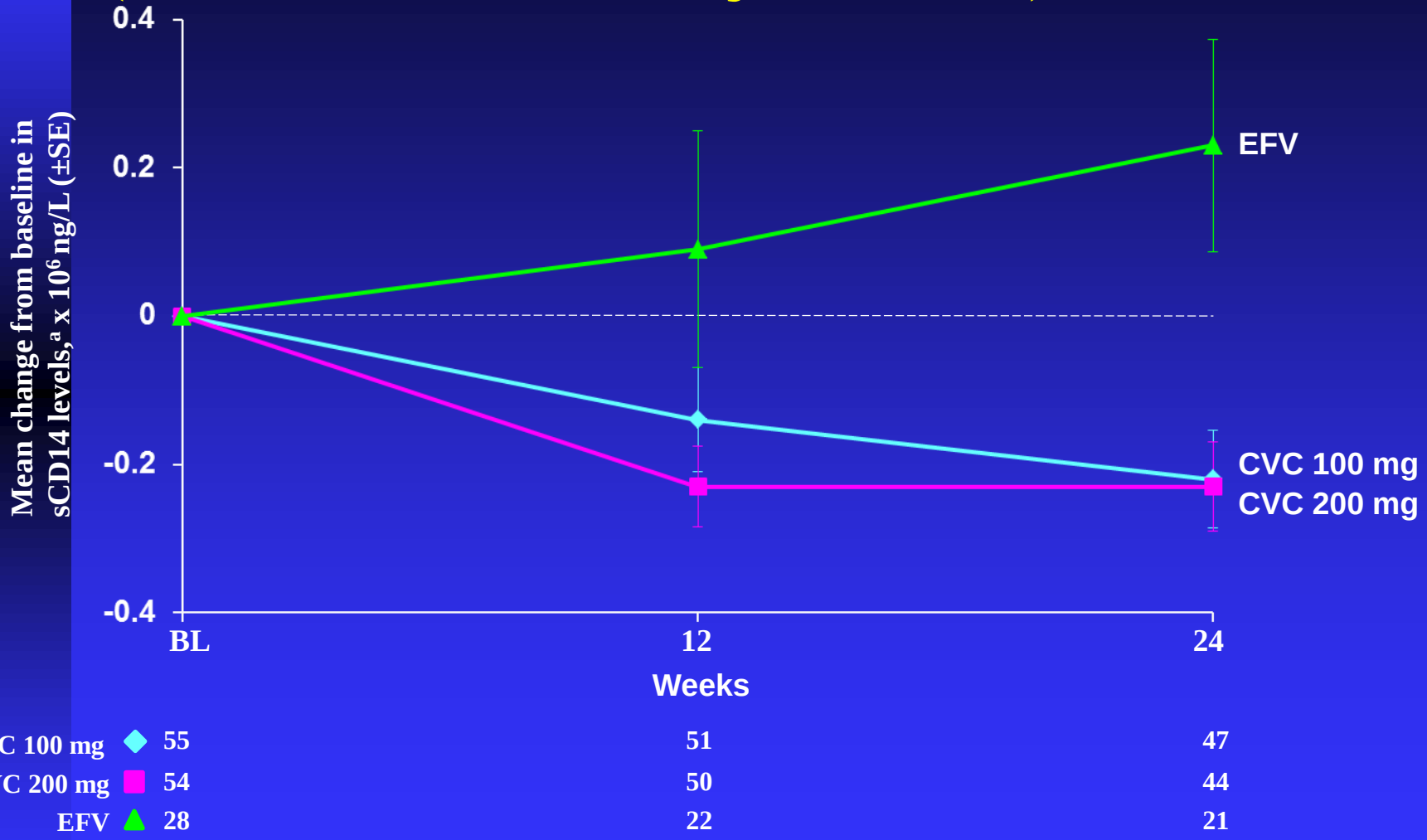
MCP-1 Changes from Baseline (Reflects CCR2 Blockade)



[a]Results are based on the number of subjects with available data for a given laboratory assessment

Gathe J. et al, CROI 2013; Abstract 106LB

sCD14 Changes from Baseline (anti-inflammatory effects)



[a]Results are based on the number of subjects with available data for a given laboratory assessment

Gathe J. et al, CROI 2013; Abstract 106LB

Future Directions for CVC

- CVC formulation optimised[1]
  - New single tablet of CVC with improved bioavailability
  - New fixed-dose combination (FDC) of CVC/3TC
  - Single-tablet regimens under development

- Phase 3 trials will evaluate CVC/3TC FDC as a novel backbone compared to TDF/FTC, co-administered with preferred third agents[2]

1. Menning and Dalziel. *Mol Pharm* 2013
2. Feinberg et al., EACS 2013

Does co-formulation matter?

Virologic outcomes in those taking an STR versus generic single tablets (TTR)

Caveats:

- Non-randomizeed
- Small Danish popl'n

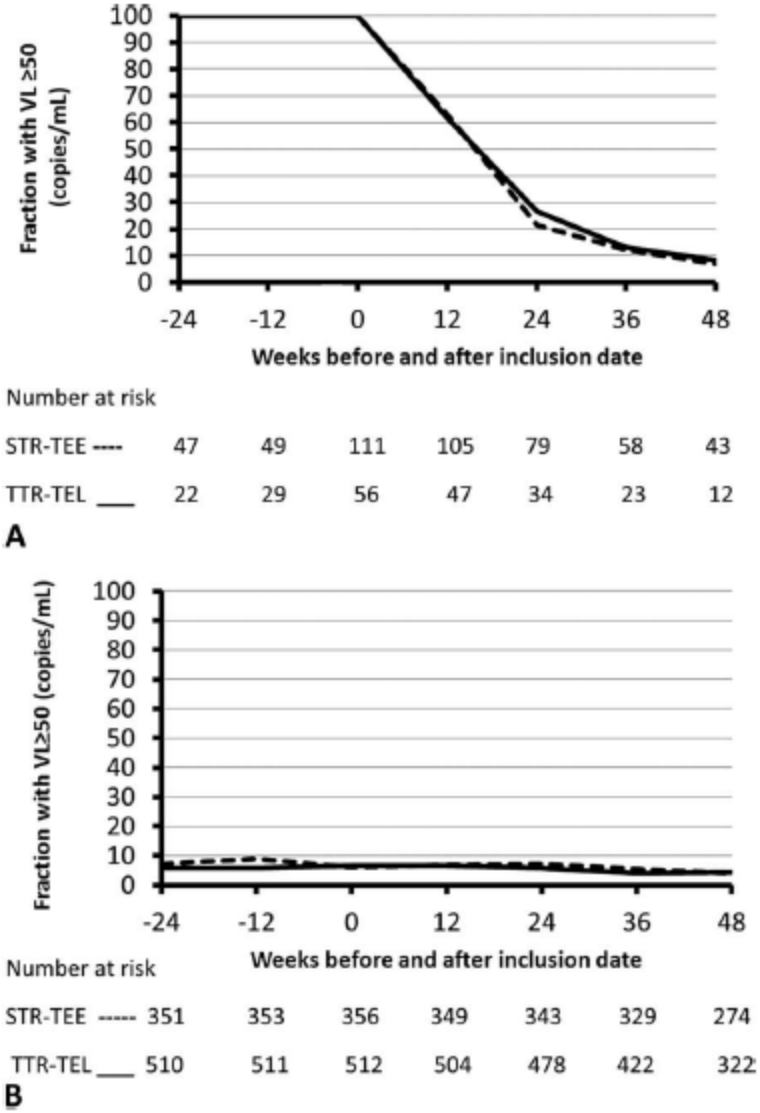


FIGURE 3. Fraction of HIV patients with VL ≥50 copies per milliliter. A, cART-naive HIV patients who in the period April 1, 2010 to March 31, 2011 initiated STR-TEE (broken line) and cART-naive HIV patients who in the period April 1, 2011 to March 31, 2012 initiated TTR-TEE (full line). B, HIV patients on STR-TEE April 1, 2010 who continued STR-TEE (broken line) and HIV patients, who were who were switched from STR-TEE to TTR-TEL after April 1, 2011 (full line).

Engsig et al, *JAIDS* 2014;66:407

The future of co-formulations?

- *All* oral ARV's in the pipeline are being developed for co-formulation.
- Patients and providers greatly prefer co-formulated drugs.
- Payers prefer less expensive drugs.
  - Who will prevail?

How close are we to having a universally perfect antiretroviral regimen?

A universal low-cost ARV regimen?

- Dolutegravir 50 mg
- Tenofovir alafenamide 25 mg
- 3TC/FTC 300 or 200 mg

→ 275-375 mg vs. 1100 mg QD