Safety and Efficacy of TBR-652, a Chemokine Receptor 5 (CCR5) Antagonist, in HIV-1-Infected, Antiretroviral (ARV) Treatment-Experienced, CCR5 Antagonist-Naïve Patients

Calvin Cohen, MD*

Research Director
Community Research Initiative of New England
Harvard Medical School

***On behalf of TBR-652-2-201 Study Team**

Abstract K-111, 17th CROI, San Francisco, February 16-19, 2010

TBR-652: Characteristics

- Oral CCR5 receptor antagonist
  - *In vitro* protein-adjusted EC50 = 0.29 nM (clinical isolates)
- Plasma T ½ = 35-40 hours
- Once-daily dosing
- Neither CYP inducer or inhibitor
- Additive to synergistic activity with other ART classes *in vitro*
- Oral bioavailability of current formulation enhanced with food
- Structure:

TBR-652: CCR2 Characteristics

- CCR2 activity: IC50 = 5.9 nM
- CCR2 is a chemokine receptor found on the cell surface of monocytes, dendritic cells (immature), and memory T cells
- Monocyte chemoattractant protein-1 (MCP-1) is the primary ligand for CCR2
- CCR2 has been associated with and studied in a variety of inflammation-associated diseases:
  - Atherosclerosis
  - Metabolic Syndrome/Insulin Resistance
- To date no significant safety signals have been identified with CCR2 antagonists

Protocol Design TBR-652-2-201

Evaluate antiviral potency, safety, tolerability, PK, and CCR2 activity

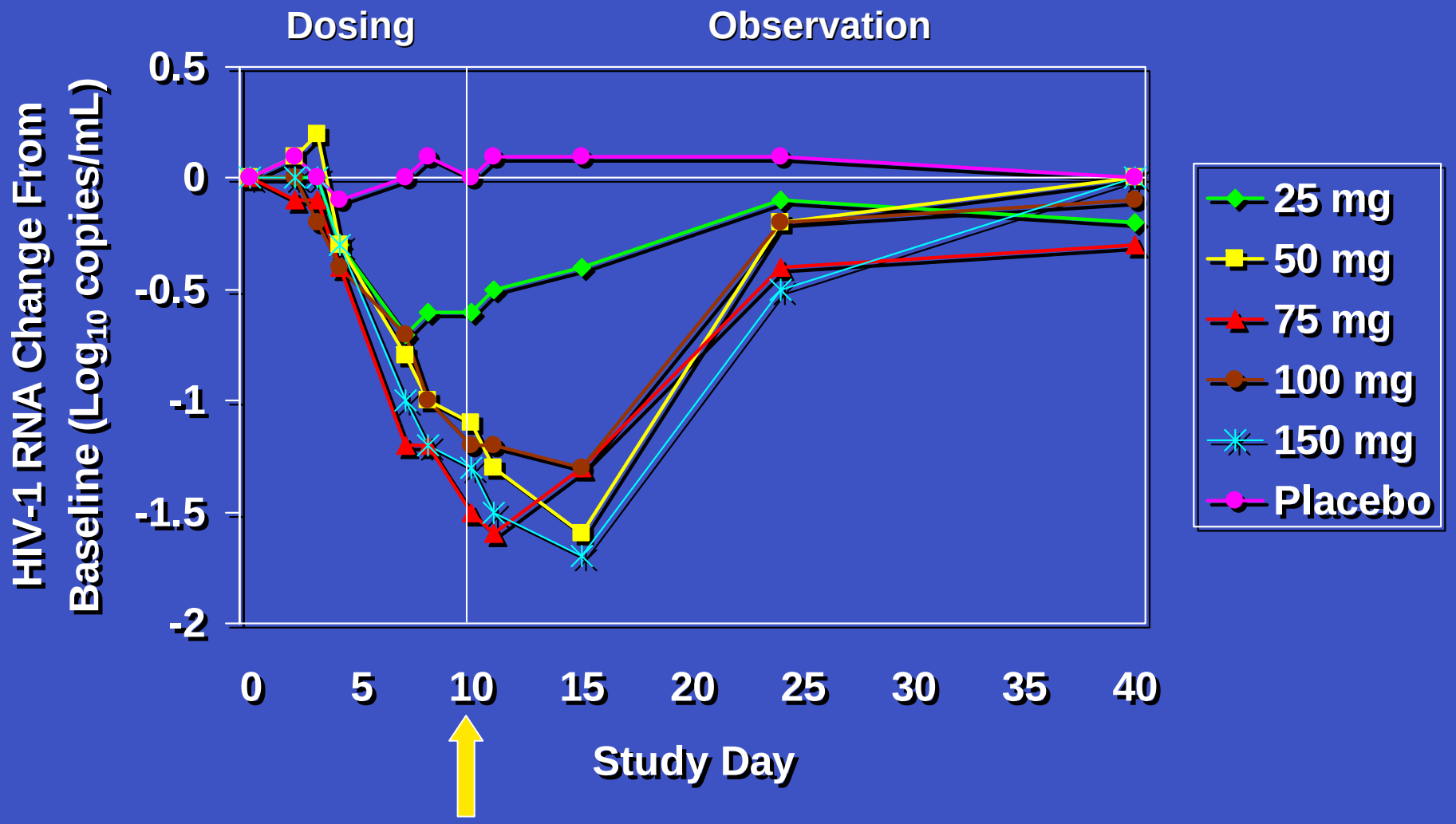
- Randomized, double-blind, placebo-controlled, dose- escalating study in HIV-infected subjects with:
  - CD4 ≥250 cells/mm^3
  - HIV-1 RNA ≥5000 copies/mL
  - CCR5-tropic virus by Trofile-ES assay
  - Treatment-experienced, no HIV treatment for ≥6 weeks
- 5 dose cohorts
  - TBR-652 (n≥8): 25, 50, 75, and 150 mg (F1 formulation)
  - TBR-652 (n=10): 100 mg (F2 formulation)
  - PBO (n=2)
- 10-day monotherapy
- MCP-1 measured on Day 1 and Day 10

TBR-652 Demographics and Baseline Patient Characteristics

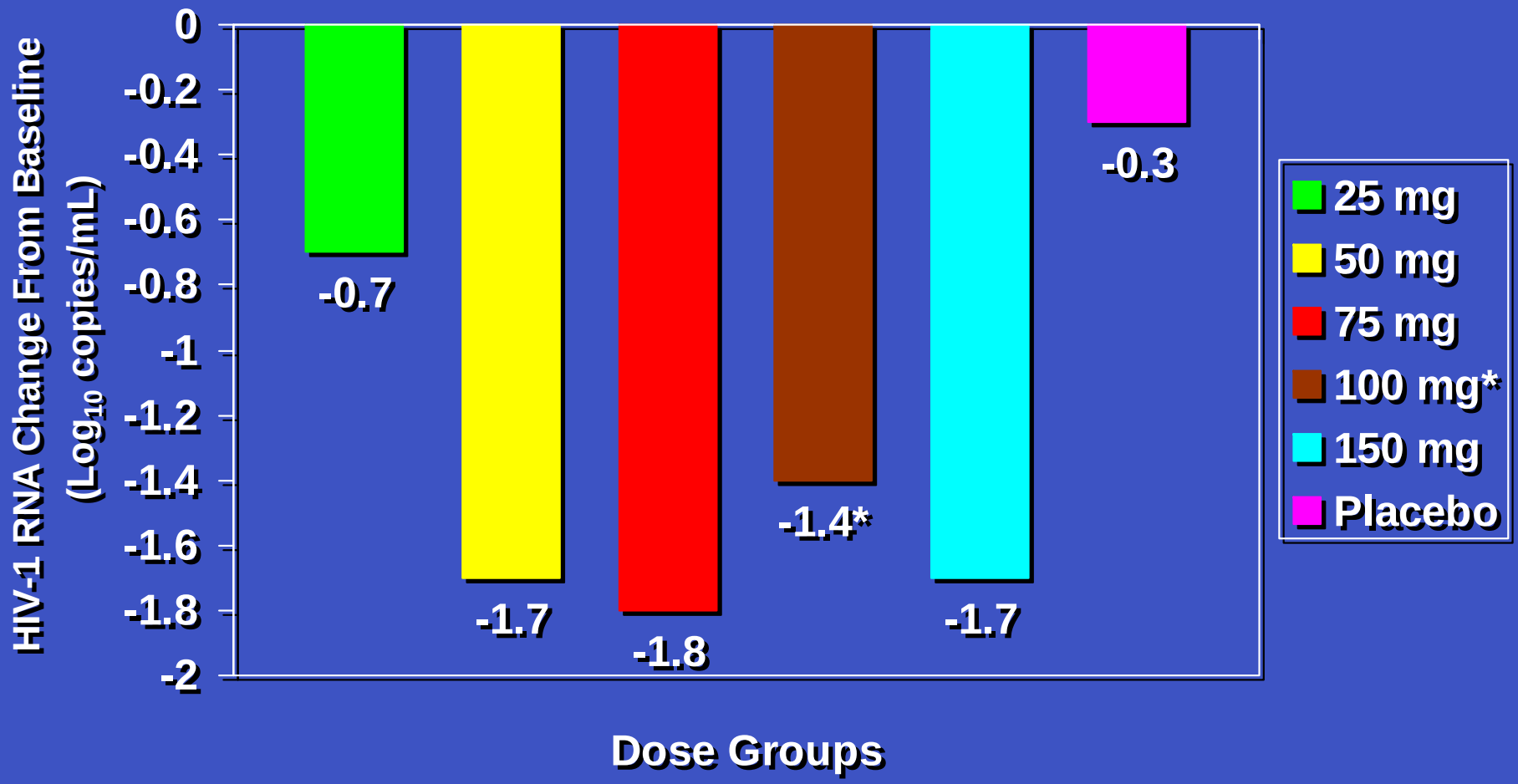
	TBR-652 QD Doses Evaluated					
	25 mg (n=8)	50 mg (n=8)	75 mg (n=9)	100 mg (n=10)	150 mg (n=9)	Placebo (n=10)
Gender (M/F)	8/0	7/1	9/0	8/2	6/3	9/1
Age (mean)	41	41	41	38	40	34
Median HIV-1 RNA (log_{10} copies/mL), (min-max)	4.2 (3.1-6.0)	4.5 (3.9-4.7)	4.6 (4.3-5.3)	4.4 (3.9-5.7)	4.0 (3.6-4.9)	4.2 (3.2-5.1)
Mean CD4 (cells/mm^3)	415	456	442	449	503	495

54 patients randomized.
1 early discontinuation during dosing period, not adverse event (AE)-related.

TBR-652 Viral Dynamics: Median Antiviral Response

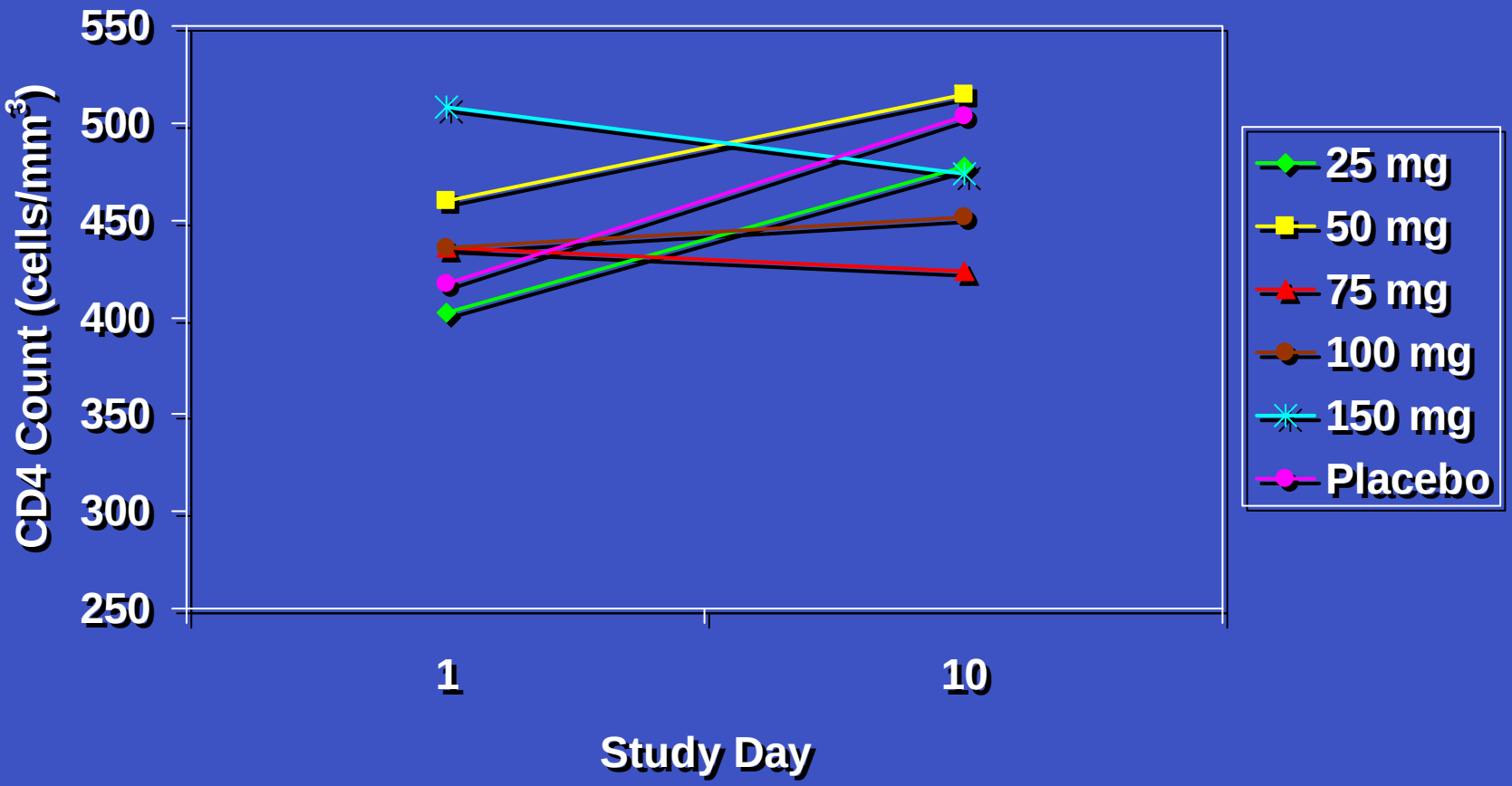


TBR-652: Median Change From Baseline: Nadir

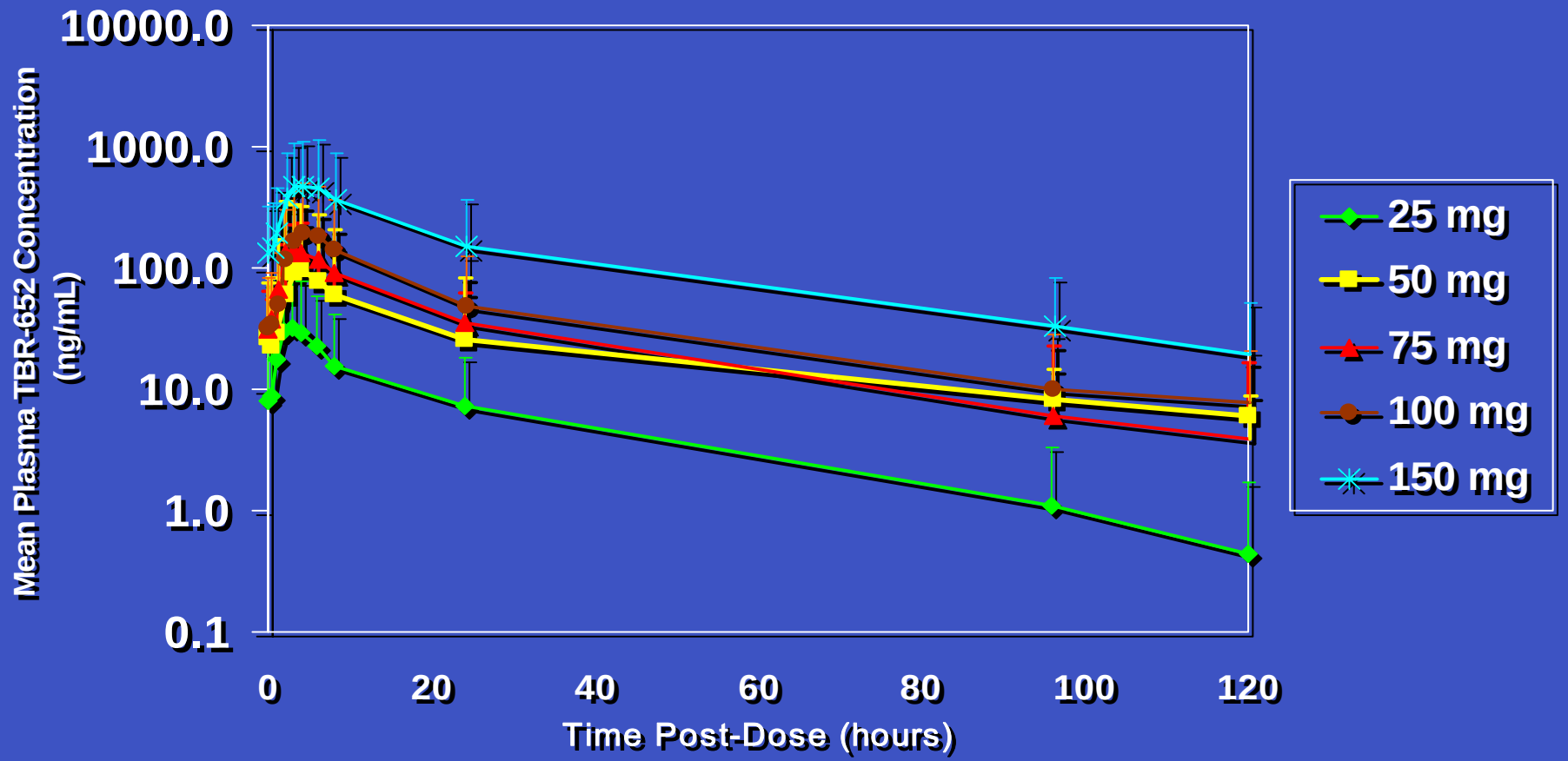


* 100 mg F2 formulation

TBR-652: Median CD4+ Count



TBR-652: Day-10 (Steady State) Pharmacokinetics



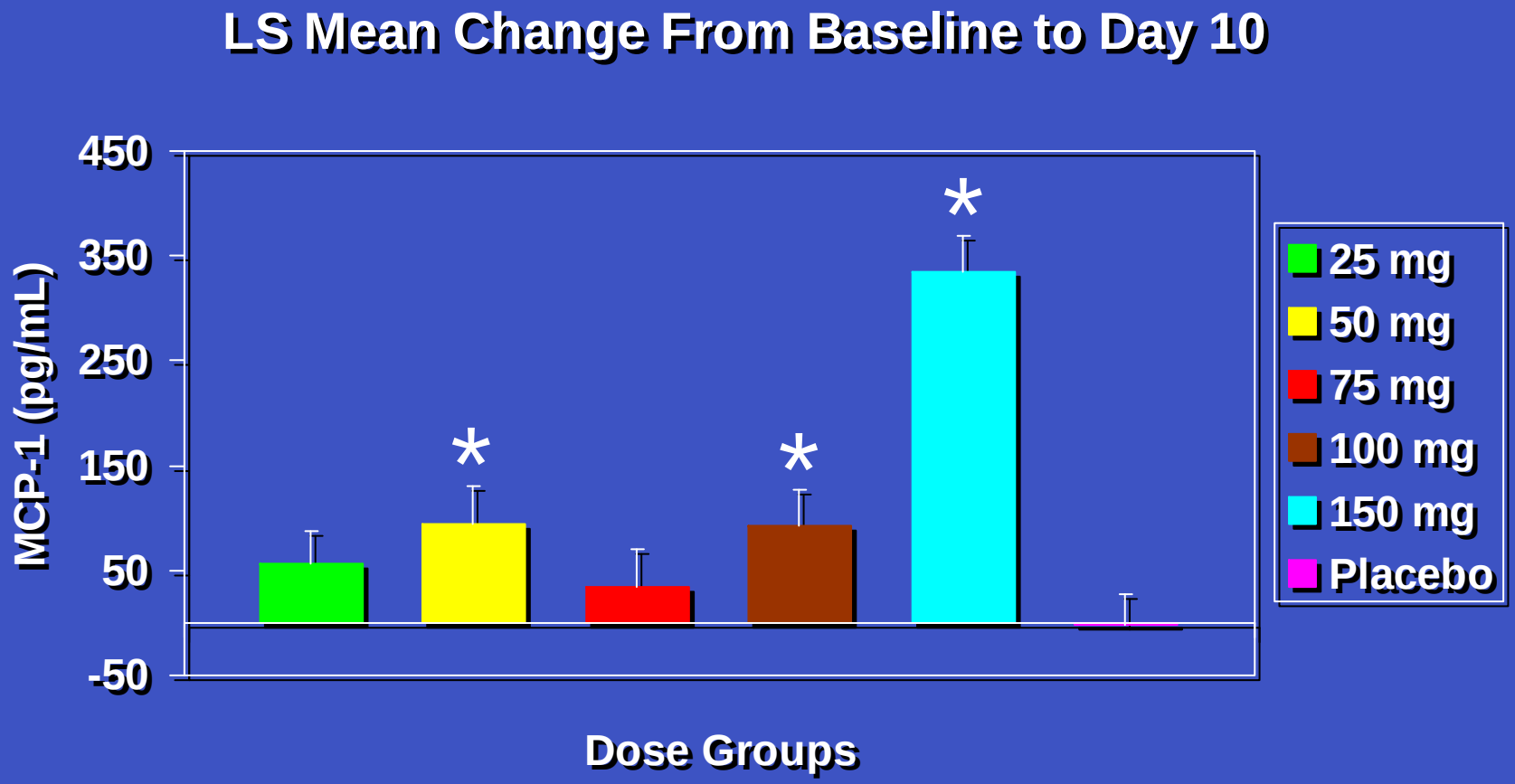
T ½ ranged from 23 to 48 hours.

TBR-652–Related Adverse Events*

	TBR-652 Dose Cohort					Placebo
	25 mg (n=9)	50 mg (n=7)	75 mg (n=9)	100 mg (n=10)	150 mg (n=9)	(n=10)
Any SAE	0	0	0	0	0	0
Any AE	4	3	0	5	8	3
Headache	0	1	0	0	2	0
Diarrhea	0	0	0	3	2	0
Abdominal discomfort	2	0	0	0	1	1
Fatigue	2	0	0	1	3	0
Nausea	1	1	0	1	3	1
Pyrexia	0	0	0	0	2	0

*AEs in 2 patients or more per cohort judged at least possibly related to study drug.

TBR-652: Dose-Dependent MCP-1 Binding Inhibition



*$P \leq 0.02$ versus placebo

Conclusions

- TBR-652 is a potent inhibitor of CCR5-tropic, HIV-1 replication
  - Median nadir response up to -1.8 $\log_{10}$
- TBR-652 demonstrated potent CCR2 activity
- Generally safe and well tolerated during short-term use
  - No study drug–related discontinuations, SAEs or deaths
  - No clinically significant trends in AEs, laboratory, vital signs, or ECGs
- Favorable and predictable pharmacokinetic profile*
- TBR-652 warrants further investigation as an unboosted, once-daily, oral CCR5 antagonist with potentially important anti-inflammatory effects

*Poster #598, Session 118, Wednesday, 2 PM-4 PM: PK/PD of TBR-652.

Acknowledgements

- All patients who participated
- Investigators and study coordinators
  - US sites
    Cynthia Brinson
    Calvin Cohen
    Edwin DeJesus
    Richard Elion
    Jerome Ernst
    Joseph Gathe
    Jacob Lalezari
    Peter Ruane
    Melanie Thompson
  - Argentina sites
    Javier Altclas
    Pedro Cahn
    Juan Carlos Cha Torea
    Fabian Fay
    Jorge Galindez
    Jose Luis Ippolito
    Carlos Zala
  - Tobira Study Team
    Sandra Palleja
    David Martin
    Reynold Driz
    Richard Ogden
    James Sapirstein
  - Tobira Consultants
    Richard Pollard, MD, UC-Davis
    Robert Grosso
    Sally Snyder
  - Collaborators
    ICON
    Monogram Biosciences
    Pharsight