The Single-Tablet, Fixed-Dose Regimen of Elvitegravir/GS-9350/Emtricitabine/Tenofovir DF (Quad) Achieves a High Rate of Virologic Suppression and GS-9350 is an Effective Booster

Calvin Cohen[1], David Shamblaw[2], Peter Ruane[3], Richard Elion[4], Edwin DeJesus[5], Hui C. Liu[6], Lijie Zhong[6], David Warren[6], Brian P. Kearney[6], and Steven L. Chuck[6]

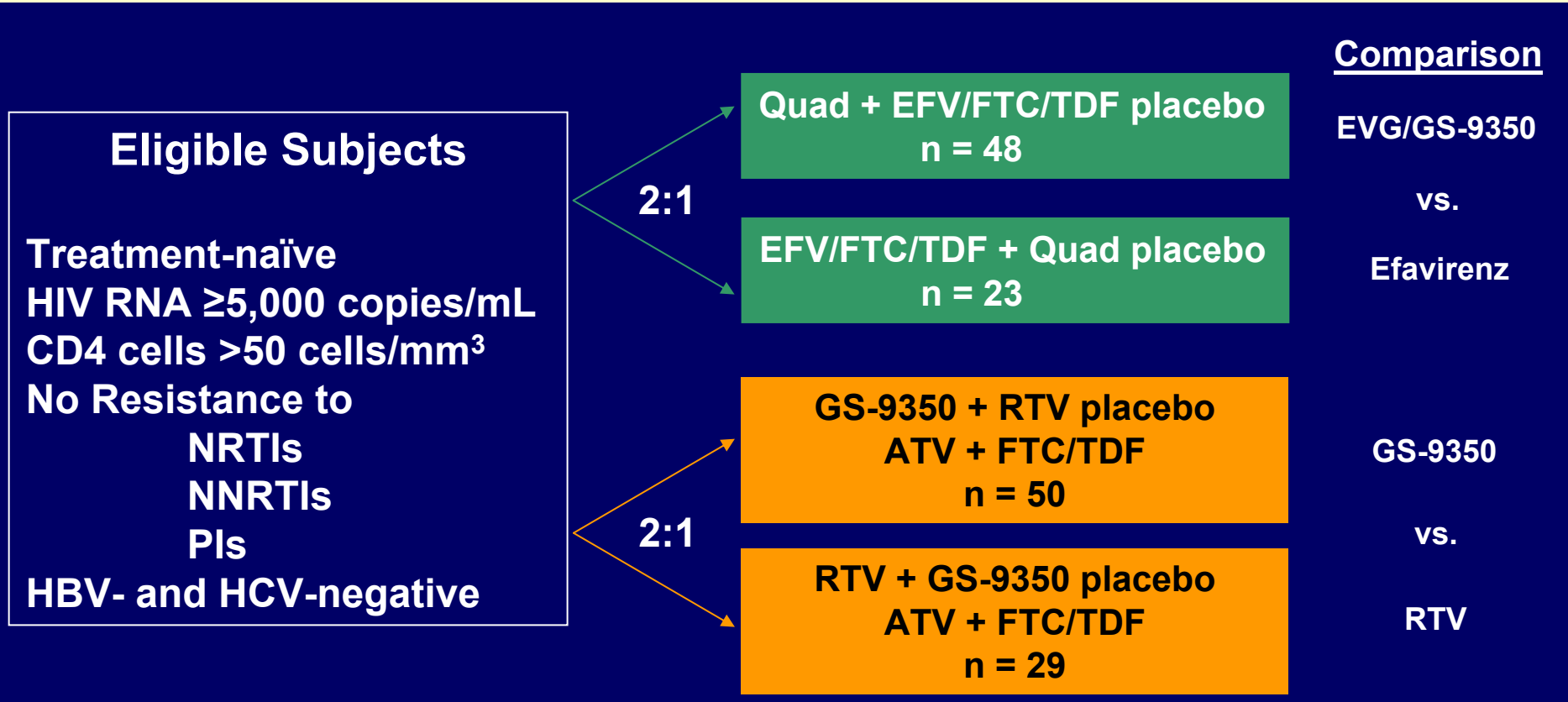
[1]Community Research Initiative of New England, Boston, MA; [2]San Diego, CA; [3]Los Angeles, CA; [4]Whitman Walker Clinic, Washington, D.C.; [5]Orlando Immunology Center, Orlando, FL; and [6]Gilead Sciences, Foster City, CA

CROI 2010

Background

- **Boosted elvitegravir 150 mg is a potent, once-daily HIV integrase inhibitor**
- **GS-9350 is a CYP3A inhibitor that lacks anti-HIV activity**
- **GS-9350 150 mg boosts EVG or atazanavir (ATV) equivalently to ritonavir 100 mg**
- **Elvitegravir (EVG)/GS-9350/Emtricitabine (FTC)/Tenofovir Disoproxil Fumarate (TDF) has been co-formulated in one tablet ("Quad")**

Design of the Two Phase 2 Studies



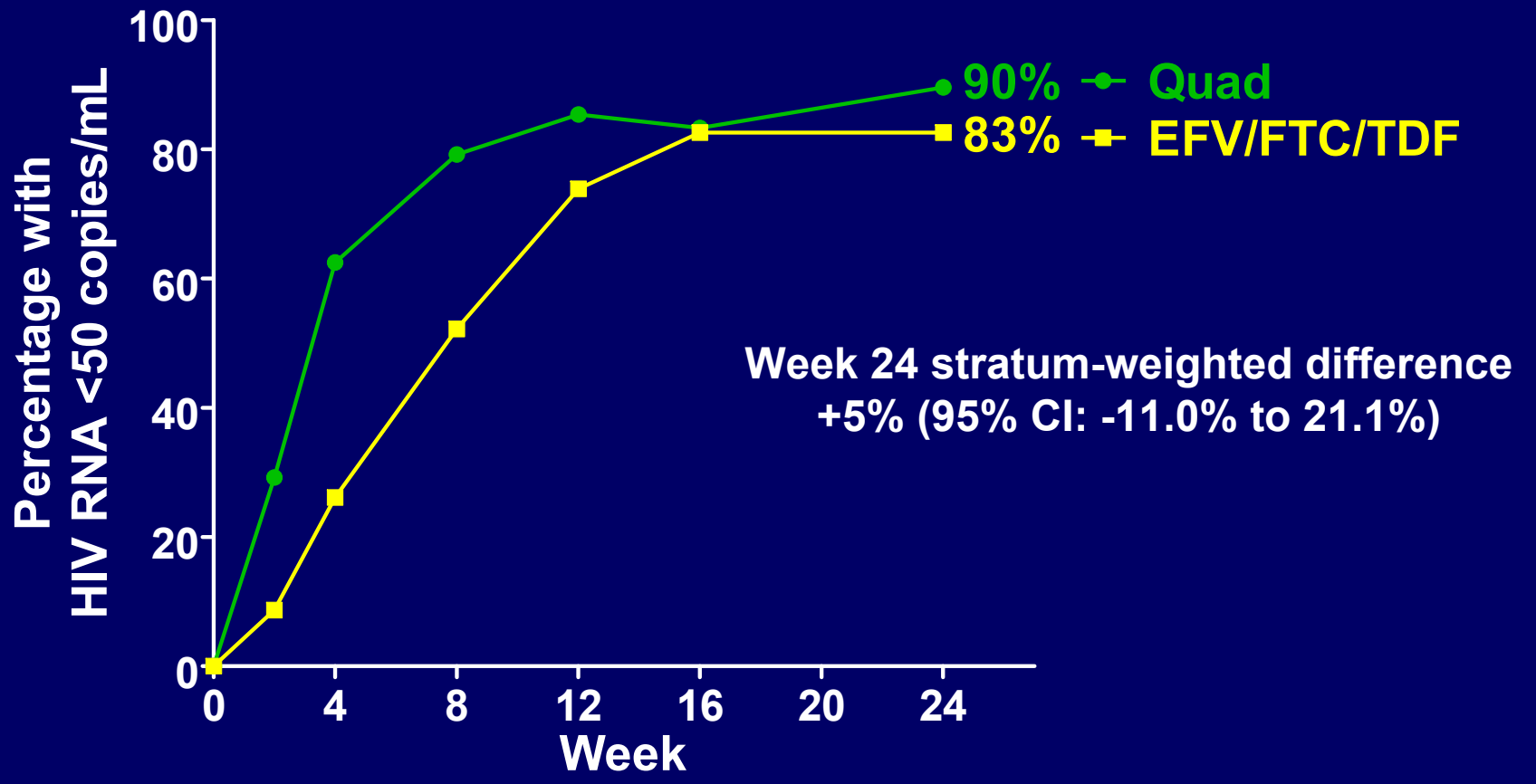
- Randomization was stratified by HIV RNA (≤ or > 100,000 copies/mL)
- Primary Endpoint: Proportions with HIV RNA < 50 copies/mL at Week 24
- 48-week trials

Baseline Characteristics

	Quad n=48	EFV/FTC/TDF n=23	GS-9350 n=50	RTV n=29
Age, mean years	36	35	37	34
Male	92%	91%	94%	86%
Race				
White	69%	78%	62%	55%
Black	25%	22%	36%	28%
HIV RNA				
Mean, $\log_{10}$ copies/mL	4.59	4.58	4.56	4.69
>100,000 copies/mL	23%	22%	24%	38%
CD4 cells/mm^3, median	354	436	341	367
AIDS	6%	4%	16%	10%

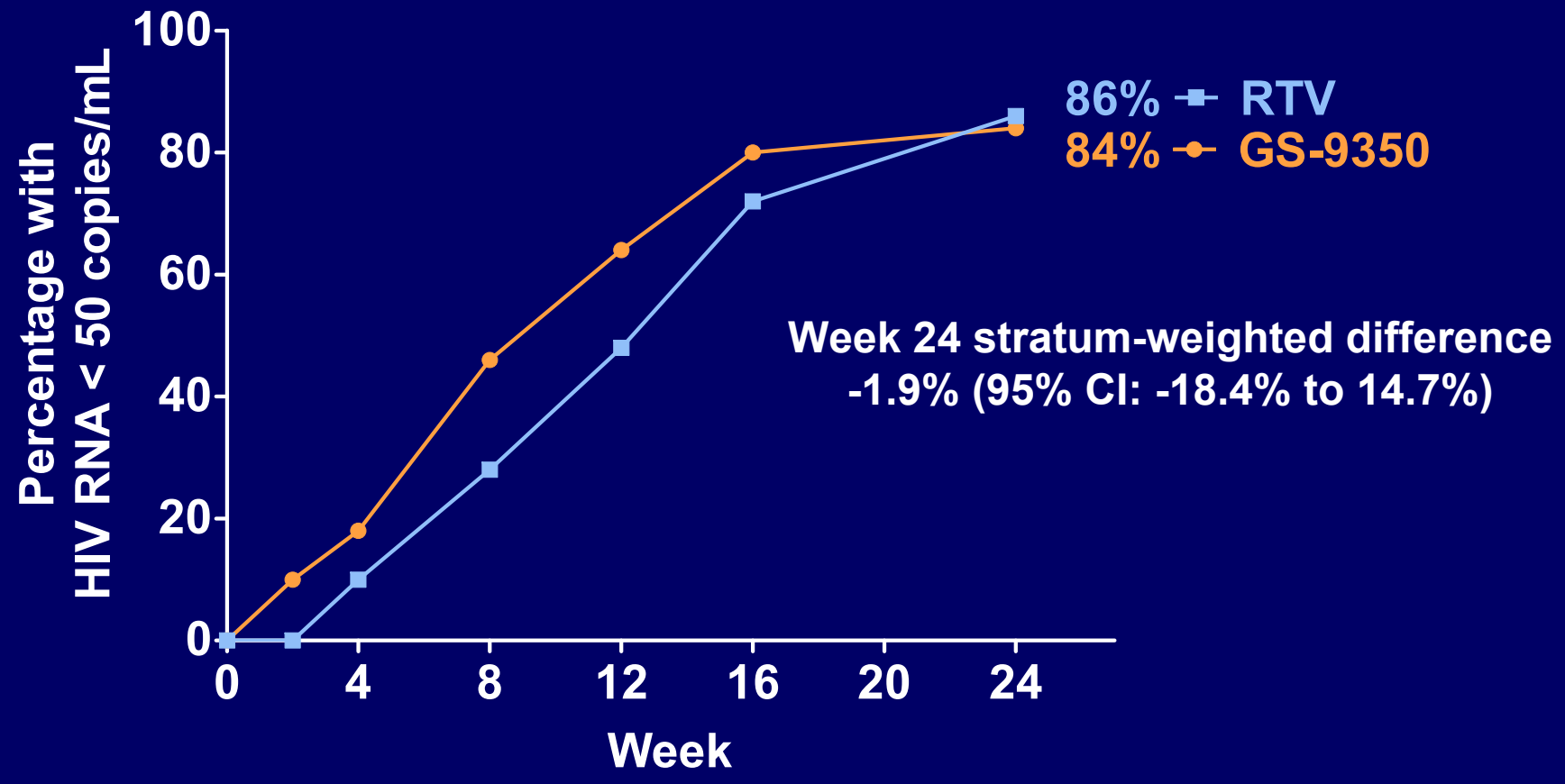
Quad vs. EFV/FTC/TDF

Primary Endpoint: Percentage with HIV RNA < 50 copies/mL (ITT M=F)



GS-9350 vs. RTV with ATV + FTC/TDF

Primary Endpoint: Percentage with HIV RNA < 50 copies/mL (ITT M=F)



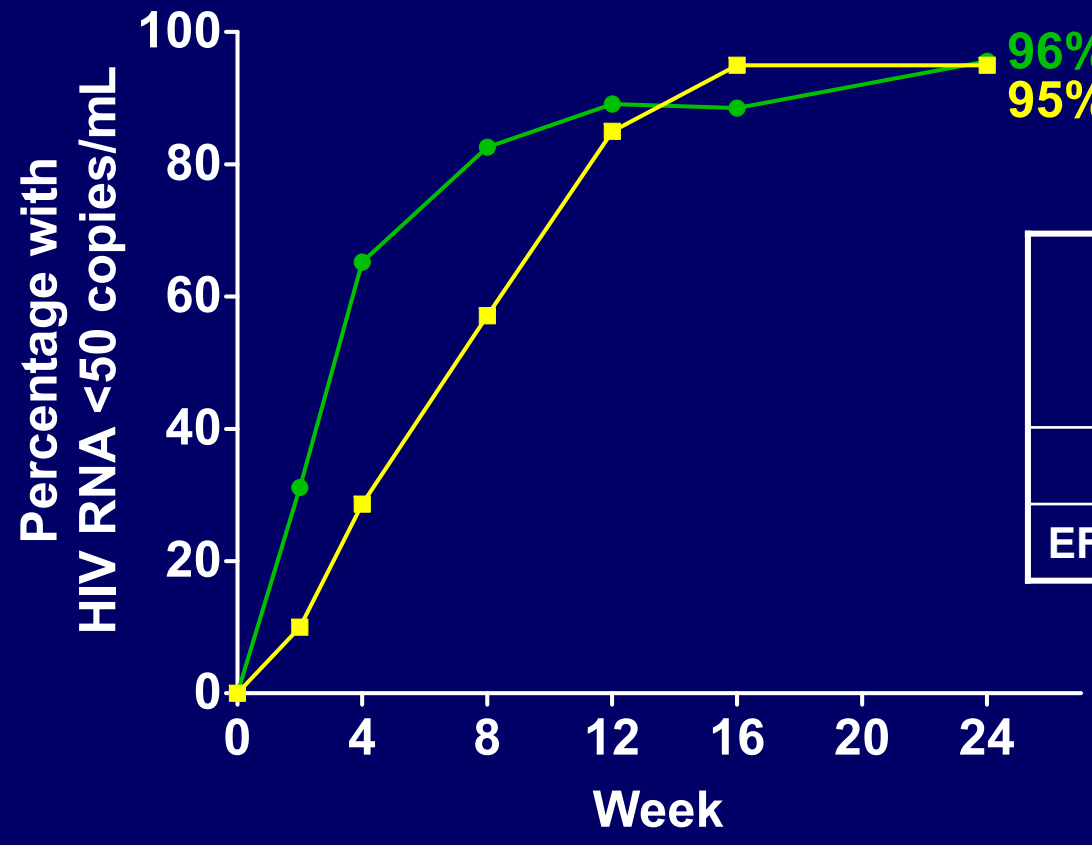
Disposition of Subjects

	Quad	EFV/FTC/TDF	GS-9350	RTV
Randomized	48	23	56	29
Never dosed			6[a]	
Discontinued Study Drugs before Week 24	3 (6%)	3 (13%)	4 (8%)	3 (10%)
Adverse Event	0	1	2	1
Lost to Follow up	2	1	1	1
Investigator's Discretion	1	0	1	0
Withdrew Consent	0	1	0	1
Subjects on Study Drugs through Week 24	45 (94%)	20 (87%)	46 (92%)	26 (90%)

[a]Protocol violation (n=4); withdrew consent (n=2); these 6 subjects are excluded from all ITT analyses

Quad vs. EFV/FTC/TDF

Percentage with HIV RNA < 50 copies/mL (ITT M=E)

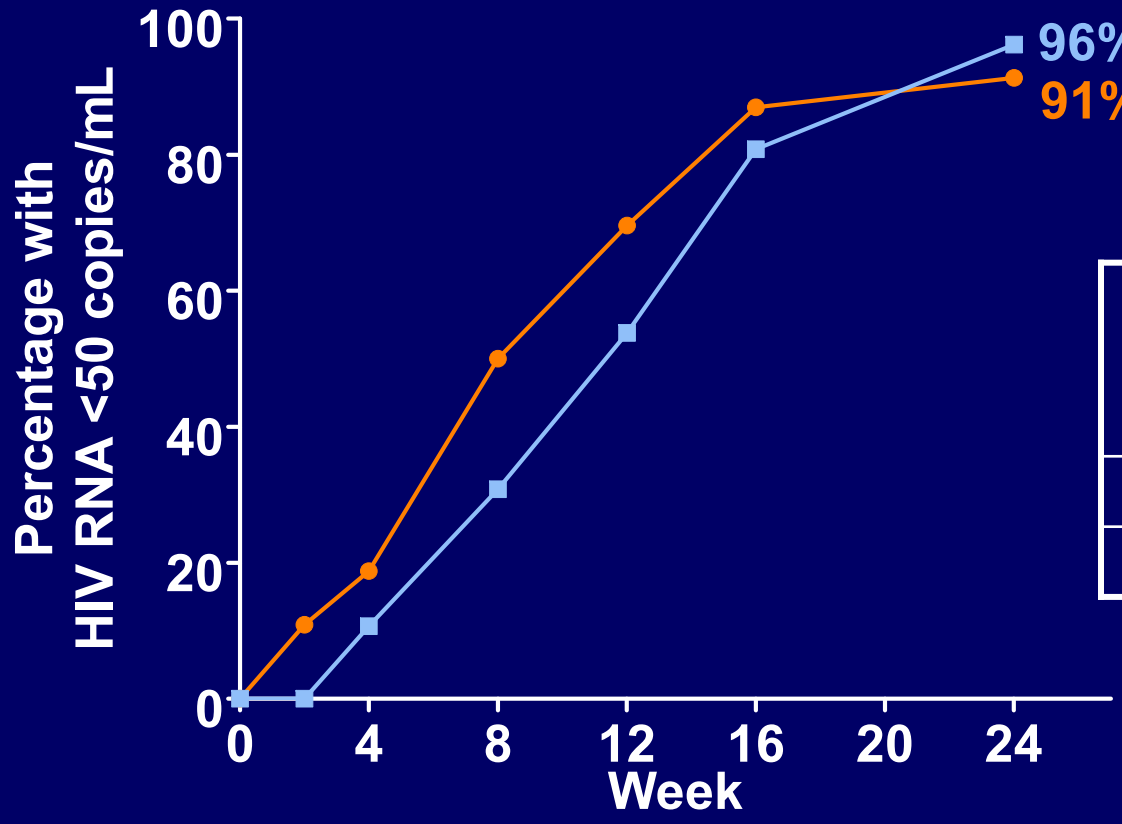


	Week 24 Median Δ CD4 cells
Quad	+123
EFV/FTC/TDF	+124

At Week 24: 3 subjects had HIV RNA > 50 copies/mL but < 400 copies/mL
At Week 32: 3 of the 3 subjects had HIV RNA <50 copies/mL

GS-9350 vs. RTV with ATV + FTC/TDF

Percentage with HIV RNA < 50 copies/mL (ITT M=E)



	Week 24 Median Δ CD4 cells
GS-9350	+206
RTV	+190

At Week 24: 5 subjects had HIV RNA > 50 copies/mL

At Week 32: 3 of the 5 had HIV RNA < 50 and 1 had 59 copies/mL; 1 virologic failure

Summary of Treatment-Emergent Adverse Events

	Quad n=48	EFV/FTC/TDF n=23	GS-9350 n=50	RTV n=29
Adverse Events related to Randomized Drug, Grades 1-4	**17 (35%)**	**13 (57%)**	**10 (20%)**	**7 (24%)**
Grade 3/4 Adverse Events	**0**	**2 (9%)**	**2 (4%)**	**0**
Adverse Events leading to discontinuation of study drug	**0**	**1 (4%)**	**2 (4%)**	**1 (3%)**
Serious Adverse Events (none related to study drugs)	**1 (2%)**	**1 (4%)**	**0**	**1 (3%)**

Adverse Events >5% Related to Randomized Drug in Any Treatment Group

	Quad n=48	EFV/FTC/TDF n=23	GS-9350 n=50	RTV n=29
Abnormal Dreams, Nightmares	5 (10%)	8 (35%)	0	0
Dizziness	0	3 (13%)	0	0
Fatigue	4 (8%)	3 (13%)	1 (2%)	2 (7%)
Somnolence	2 (4%)	2 (9%)	0	0
Headache	2 (4%)	2 (9%)	1 (2%)	0
Diarrhea	4 (8%)	1 (4%)	3 (6%)	3 (10%)
Nausea	2 (4%)	1 (4%)	5 (10%)	1 (3%)

Treatment-Emergent Laboratory Abnormalities Grades 2-4 Occurring in >5% of Any Treatment Arm

	Quad n=48	EFV/FTC/TDF n=23	GS-9350 n=50	RTV n=29
Bilirubin, total	0	0	40/49 (82%)	25 (86%)
Amylase	2 (4%)	2 (10%)	6 (12%)	2 (7%)
Neutrophils, decreased	3 (7%)	2 (10%)	1 (2%)	1 (3%)
Cholesterol*, total	4 (9%)	2 (10%)	3 (6%)	0
Proteinuria	1 (2%)	2 (10%)	2 (4%)	0

*Similar small median increases in cholesterol, LDL, HDL, triglycerides between arms in each study

Other Treatment-Emergent Laboratory Abnormalities

	Quad n=48	EFV/FTC/TDF n=23	GS-9350 n=50	RTV n=29
ALT Grades 2-4	0	0	1 (2%)	1 (3%)
AST Grades 2-4	0	0	0	1 (3%)
Hypophosphatemia (All were Grade 1)	0	0	1 (2%)	1 (3%)
Creatinine (All were Grade 1)	1 (2%)	0	6 (12%)	0

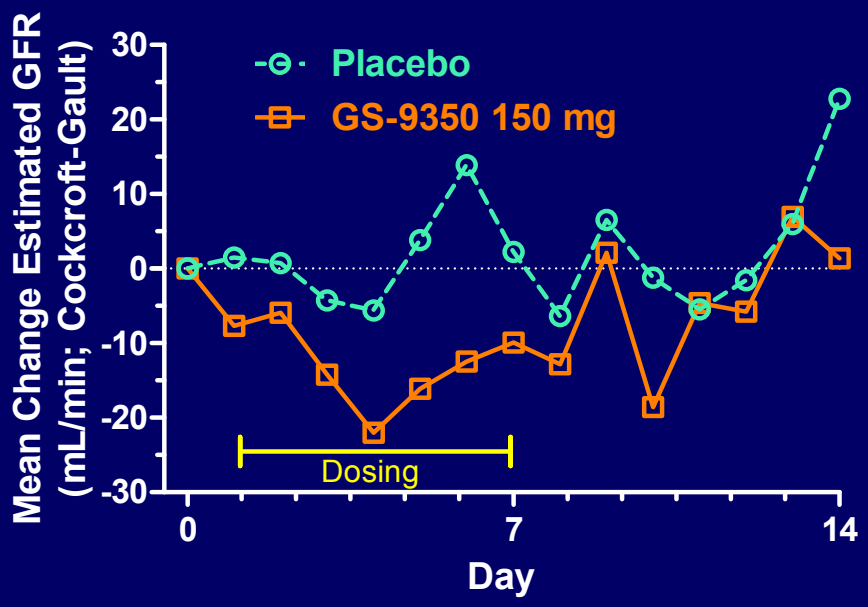
Small Increases in Serum Creatinine Affected Estimated GFR (Cockcroft-Gault)

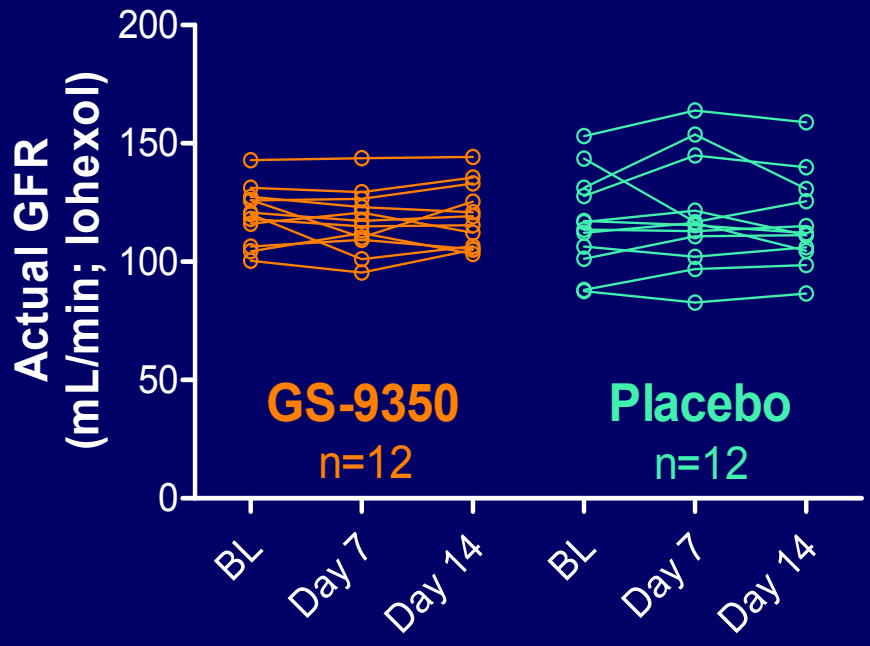
	Quad n=48	EFV/FTC/TDF n=23	GS-9350 n=50	RTV n=29
Δ Mean Serum Creatinine Baseline to Week 24	+0.14 mg/dL	+0.04 mg/dL	+0.18 mg/dL	+0.14 mg/dL
Δ Mean eGFR* Baseline to Week 24	-18 mL/min	-7 mL/min	-15 mL/min	-14 mL/min
Mean eGFR* At Week 24	111 mL/min	126 mL/min	102 mL/min	111 mL/min

*Estimated GFR by Cockcroft-Gault

Renal Study of GS-9350 Without ARVs in Healthy Volunteers

GS-9350 Alters Estimated GFR—Not Actual GFR





- **Study of GS-9350 (no ARVs) in healthy volunteers**
  - **Administered GS-9350 or placebo for 7 days**
  - **Measured serum creatinine and iohexol clearance concurrently**
- **GS-9350 is associated with lower estimated GFR**
  - **Onset in days, reversible in days**
- **GS-9350 has no effect on actual GFR**

GS-9350 Does Not Affect Actual GFR But Can Increase Serum Creatinine

- **Creatinine is excreted primarily by glomerular filtration but ~10-15% by active tubular secretion**
- **GS-9350 may inhibit tubular secretion of creatinine**
  - **Similar to the over-the-counter medicine, Cimetidine**

Conclusions from Phase 2 Studies

- **Quad (vs. EFV/FTC/TDF)**
  - **Efficacy met criteria for non-inferiority (90% vs. 83%)**
  - **Fewer study drug-related adverse events (particularly CNS)**
- **GS-9350-boosted ATV (vs. RTV-boosted ATV) + FTC/TDF**
  - **Similar efficacy**
  - **Similar safety and tolerability**
- **Results support proceeding to Phase 3 studies**

The generic name of GS-9350 is cobicistat

Thanks to the Investigators, Study Staff, and Subjects of Studies 236-0104 and 216-0105

B. Akil
N. Bellos
P. Benson
F. Bredeek
J. Burack
C. Cohen
R. Corales
G. Crofoot
F. Cruickshank
E. DeJesus
R. Dretler
R. Elion
J. Gathe, Jr.
T. Hawkins
R. Hsu
T. Jefferson
P. Kadlecik
H. Khanlou
C. Kinder
A. LaMarca
C. Mayer
D. Parks
G. Pierone
D. Prelutsky
B. Rashbaum
K. Rawlings
G. Richmond
W. Robbins
J. Rodriguez
P. Ruane
S. Schneider
M. Sension
P. Shalit
D. Shamblaw
J. Slim
K. Staszkow
M. Thompson
L. Waldman
D. Ward
D. Wheeler
M. Wohlfeiler
B. Young