Poster Number

H-938B

50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
September 12-15, 2010
Boston, MA USA

The Single-Tablet Regimen Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF; "QUAD") Maintains a High Rate of Virologic Suppression, and Cobicistat (COBI) is an Effective Pharmacoenhancer Through 48 Weeks

R Elion,[1] J Gathe,[2] B Rashbaum,[3] P Shalit,[4] T Hawkins,[5] HC Liu,[6] L Zhong,[6] DR Warren,[6] BP Kearnery,[6] and SL Chuck[6]

[1]Whitman Walker Clinic, Washington, D.C.; [2]Houston, TX; [3]Washington, D.C.; [4]Seattle, WA; [5]Santa Fe, NM; [6]Gilead Sciences, Inc., Foster City, CA

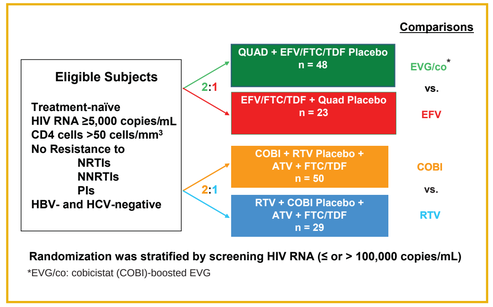
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650)574-5056
Fax: (650)578-5595
email: david.warren@gilead.com

Background

- COBI boosts the integrase inhibitor EVG and atazanavir (ATV) equivalent to ritonavir (RTV), but is devoid of HIV activity
- Once-daily highly active antiretroviral therapy (HAART), especially a single tablet HAART, encourages adherence which directly affects durable HIV suppression

Methods

Figure 1. Design of the Two Phase 2 Studies



Randomization was stratified by screening HIV RNA (≤ or > 100,000 copies/mL)

*EVG/co: cobicistat (COBI)-boosted EVG

Results

Table 1. Baseline Characteristics

QUAD n=48	EFV/FTC/TDF n=23		COBI n=50	RTV n=29
36	35	Age, mean years	37	34
92%	91%	Male	94%	86%
		Race		
69%	78%	White	62%	55%
25%	22%	Black	36%	28%
		HIV RNA		
4.59	4.58	Mean, $\log_{10}$ copies/mL	4.56	4.69
23%	22%	>100,000 copies/mL	24%	38%
354	436	CD4 cells/mm³, median	341	367
6%	4%	AIDS	16%	10%

Results (cont'd)

Table 2. Disposition of Subjects

QUAD	EFV/FTC/TDF		COBI	RTV
48	23	Randomized	56	29
0	0	Never dosed	6	0
3 (6%)	3 (13%)	Discontinued Study Drugs*	5 (10%)	3 (10%)
0	1	Adverse Event	2	1
2	1	Lost to Follow up	1	1
1	0	Investigator's Discretion	1	0
0	1	Withdrew Consent	1	0
0	0	Protocol Violation	0	1
45 (94%)	20 (87%)	Subjects on Study Drugs through Week 48	45 (90%)	26 (90%)

*No subject on any treatment arm developed genotypic or phenotypic resistance

Figure 2. QUAD is Non-inferior to EFV/FTC/TDF
Percentage with HIV RNA < 50 copies/mL (ITT M=F)

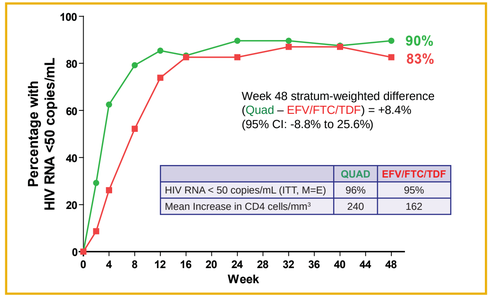


Figure 3. Percentage with HIV RNA < 50 copies/mL (ITT M=F), COBI vs. RTV

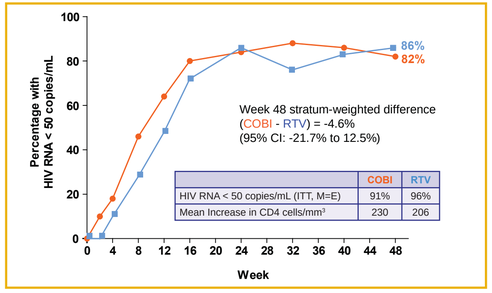


Table 3. Summary of Treatment-Emergent Adverse Events

QUAD n=48	EFV/FTC/TDF n=23		COBI n=50	RTV n=29
22 (46%)	13 (57%)	Adverse Events related to Any Study Drug, Grades 1-4	18(36%)	14(48%)
2[a] (4%)	2[b] (9%)	Grade 3/4 Adverse Events	2[f] (4%)	0
0	1[c] (4%)	Grade 3/4 Adverse Events Adverse Events leading to discontinuation of study drug	2[g] (4%)	1[h] (3%)
1[d] (2%)	1[e] (4%)	Serious Adverse Events (none related to study drugs)	2 (4%)[i]	1[e, j] (3%)

a. pneumonia; anogenital warts
b. B-cell lymphoma with lymphadenopathy; neutropenia
c. Suicidal ideation (Wk 9)
d. Cellulitis
e. B-cell lymphoma and injection site reaction
f. Rash; Hyperbilirubinemia
g. Vomiting (Wk 1); rash (Wk 2)
h. Ocular icterus (Wk 3)
i. Pneumonia; cellulitis
j. Pneumonia

Table 4. Adverse Events >5% Related to Randomized Drug

QUAD n=48	EFV/FTC/TDF n=23		COBI n=50	RTV n=29
6 (12%)	8 (35%)	Abnormal Dreams/Nightmares	0	0
4 (8%)	3 (13%)	Fatigue	1 (2%)	3 (10%)
0	3 (13%)	Dizziness	0	0
4 (8%)	2 (9%)	Diarrhea	3 (6%)	3 (10%)
2 (4%)	2 (9%)	Somnolence	0	0
2 (4%)	2 (9%)	Headache	0	0
0	2 (9%)	Anxiety/Anxiety Disorder	0	0
3 (6%)	1 (4%)	Nausea	5 (10%)	1 (3%)
3 (6%)	1 (4%)	Abdominal Distension	0	0
0	0	Flatulence	0	2 (7%)
3 (6%)	0	Rash	0	0

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

QUAD n=46	EFV/FTC/TDF n=21		COBI n=49	RTV n=29
0	0	Hyperbilirubinemia	43 (87.8%)	25 (86.2%)
4 (8.7%)	2 (9.5%)	Hyperamylasemia	6 (12.2%)	3 (10. 3%)
4 (8.9%)	5 (25.0%)	Hypercholesterolemia	3 (6.5%)	1 (3.8%)
5 (10.9%)	3 (14.3%)	Creatine Kinase	4 (8.1%)	2 (6.8%)
3 (6.5%)	4 (19.0%)	Neutropenia	0	0
1 (2.2%)	3 (14.3%)	Proteinuria	0	0
0	0	Hypophosphatemia	1 (2.0%)	2 (6.9%)
0	0	Hematuria	3 (6.1%)	2 (6.8%)

n= subjects with at least one postbaseline data

Table 6. Mean Change from Baseline to Week 48 in Fasting Lipids (mg/dL)

QUAD n=41	EFV/FTC/TDF n=18		COBI n=41	RTV n=24
20	30	Total Cholesterol	4	4
12	22	LDL Cholesterol	7	1
3	8	HDL Cholesterol	1	5
31	20	Triglycerides	-1	7

n= subjects with both baseline and Week 48 measurements

Table 7. Rates of Total Bilirubin Elevation, Jaundice, and Ocular Icterus over 48 Weeks

Toxicity Grade	ATV + COBI n=49	ATV + RTV n=29
1	4 (8%)	4 (14%)
2	12 (25%)	12 (41%)
3	22 (45%)	8 (28%)
4	9 (18%)	5 (17%)

n= subjects with at least one postbaseline data

Jaundice[a]	2 (4%)	1 (3%)
Ocular icterus[a]	6 (12%)	4 (14%)

a. Atazanavir-related

Table 8. Mean Change in Serum Creatinine (mg/dL) and e-GFR* (Cockcroft-Gault, mL/min)

QUAD n=48	EFV/FTC/TDF n=23		COBI n=50	RTV n=29
		SCr Mean Δ from Baseline		
+0.10	+0.01	Week 2	+0.11	+0.04
+0.14	+0.04	Week 24	+0.18	+0.14
+0.17	+0.06	Week 48	+0.15	+0.13
		e-GFR Mean Δ (Mean % Δ)		
-13.1 (-9%)	-1.1 (-1%)	Week 2	-9.3 (-8%)	-4.3 (-3%)
-18.0 (-13%)	-6.6 (-5%)	Week 24	-15.2 (-13%)	-14.1 (-11%)
-19.7 (-14%)	-5.5 (-4%)	Week 48	-13.3 (-12%)	-13.8 (-11%)
		Mean e-GFR		
131	131	Baseline	117	122
116	128	Week 2	108	117
111	126	Week 24	102	111
109	127	Week 48	104	111

*estimated glomerular filtration rate

Conclusions

- **QUAD efficacy was non-inferior to EFV/FTC/TDF**
  - **Safety and tolerability were similar, although QUAD had fewer NSS-related AEs compared to EFV/FTC/TDF**
  - **QUAD may be an alternative once-daily fixed-dose regimen tablet**
- **COBI-boosted ATV (ATV/co) + FTC/TDF had similar efficacy, safety, and tolerability vs. RTV-boosted ATV (ATV/r) + FTC/TDF**
- **In treatment arms receiving COBI, changes in e-GFR occurred early, remained stable through Week 48, and were similar to that seen in the arm receiving RTV**
- **Three Multi-center International Phase 3 Studies are in progress:**
  - **QUAD vs EFV/FTC/TDF (n=700)**
  - **QUAD vs ATV/r + FTC/TDF (n=700)**
  - **(ATV/co vs. ATV/r) + FTC/TDF (n=700)**

Acknowledgements

- Thanks to the Investigators, Study Staff, and Subjects of Studies 236-0104 (QUAD vs. EVF/FTC/TDF) and 216-0105 (COBI vs RTV) + ATV + FTC/TDF

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