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Week 144 Resistance Analyses of the Phase 3 EVG/COBI/FTC/TDF Studies

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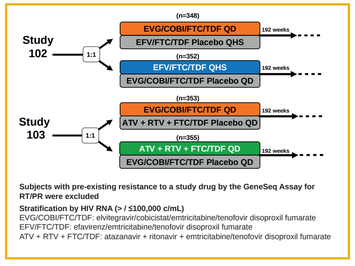
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Introduction

- Elvitegravir (EVG)/cobicistat (COBI)/emtricitabine (FTC)/tenofovir DF (TDF) has been co-formulated as the first integrase strand transfer inhibitor-containing single-tablet regimen Stribild™ (STB, EVG/COBI/FTC/TDF)
  - EVG is a once-daily HIV integrase strand transfer inhibitor (150 mg)
  - COBI is a pharmacoenhancer of EVG (150 mg)
  - FTC/TDF (TVD) is a preferred first line NRTI combination (200 mg/300 mg)[1-3]
- Two phase 3 studies of the EVG/COBI/FTC/TDF single-tablet regimen in treatment-naïve subjects are ongoing (Figure 1)
  - High and comparable efficacy of EVG/COBI/FTC/TDF vs. EFV/FTC/TDF (Study GS-US-236-0102)[4] and EVG/COBI/FTC/TDF vs. ATV + RTV + FTC/TDF (Study GS-US-236-0103)[5] through Week 144
  - High virologic suppression rates in all subgroups, including those with baseline HIV-1 RNA >100,000 c/mL or CD4 < 200 cells/µL
  - EVG/COBI/FTC/TDF was well-tolerated
- This poster describes the resistance analyses at baseline and through Week 144

Figure 1. Design of the Phase 3 Studies 102 and 103 in Treatment-Naïve Subjects



Subjects with pre-existing resistance to a study drug by the GeneSeq Assay for RT/PR were excluded

Stratification by HIV RNA (> / ≤100,000 c/mL)

EVG/COBI/FTC/TDF: elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
EFV/FTC/TDF: efavirenz/emtricitabine/tenofovir disoproxil fumarate
ATV + RTV + FTC/TDF: atazanavir + ritonavir + emtricitabine/tenofovir disoproxil fumarate

Key Entry Criteria

- Treatment-naïve adult subjects
- Genotypic sensitivity to study drugs by the GeneSeq Assay (PR/RT; Monogram Biosciences):
  - EFV, FTC, and TDF in Study 102
  - ATV, FTC, and TDF in Study 103
- Plasma HIV-1 RNA ≥5000 c/mL
- Screening estimated glomerular filtration rate (eGFR) ≥70 mL/min by Cockcroft-Gault (CG)

Figure 2. Primary Drug Resistance Mutations for EVG, FTC, and TDF[6]

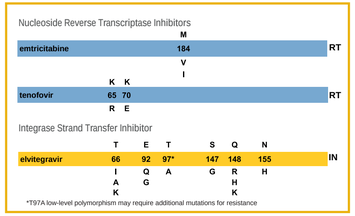


Figure 3. HIV-1 RNA < 50 c/mL through Week 144 (Missing=Failure) Study 102

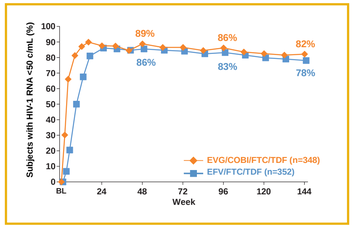
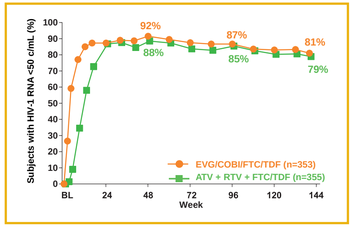


Figure 4. HIV-1 RNA < 50 c/mL through Week 144 (Missing=Failure) Study 103



Objectives

- Determine the impact of pre-existing HIV-1 drug resistance on treatment outcome through Week 144
- Describe the HIV-1 drug resistance mutations that developed through Week 144
- Determine the frequency and order of mutation development using the first failure samples for the EVG/COBI/FTC/TDF subjects with emergent resistance

Methods

- **Screening Genotypic Analysis:** Genotypic analyses of HIV-1 protease (PR) and reverse transcriptase (RT) were performed at screening (GeneSeq, Monogram Biosciences). Subjects with resistance to study drugs were excluded. No genotyping of integrase (IN) was conducted at screening
  - A retrospective IN genotyping substudy was conducted post-week 48 on baseline samples from patients in the EVG/COBI/FTC/TDF group. Specifically, these were from all patients from Study 102 and non-B subtype samples from Study 103
- **Resistance Analysis Population:**
  - Suboptimal virologic response
    - <1 $\log_{10}$ below baseline at Week 8 and HIV-1 RNA ≥50 c/mL, confirmed at Week 12
  - Virologic rebound: two consecutive visits with HIV-1 RNA
    - ≥400 c/mL after achieving HIV-1 RNA <50 c/mL (or at a single visit if at Week 48, Week 96, or Week 144)
    - >1 $\log_{10}$ increase from nadir
  - Early Discontinuation
    - HIV-1 RNA ≥400 c/mL at last visit, at or after Week 8

Methods (cont'd)

- **Post-Baseline Resistance Analyses:** Subjects in the post-baseline resistance analysis population had genotypic and phenotypic analyses of the PR and RT genes (PhenoSense GT, Monogram Biosciences) and the IN gene (IN GeneSeq and IN PhenoSense assays, Monogram Biosciences) at the confirmation of failure visit or last visit.
  - If the IN GeneSeq or PhenoSense assays failed to amplify, the IN genotype was determined using the IN GenoSure assay (Labcorp). If genotypic or phenotypic resistance was detected, retrospective genotypic and phenotypic analyses of PR, RT, and IN were conducted on stored baseline samples.
- **First Failure Resistance Analyses:** Subjects from the EVG/COBI/FTC/TDF group with documented emergent resistance mutations were further analyzed. The first failure analysis consisted of genotyping of samples from the first time point of virologic failure with HIV-1 RNA ≥400 copies/mL. The PRIme assay (Monogram Biosciences) was the primary assay used, but GeneSeq IN and GenoSure MG were used in the case of an assay failure.

Results

Table 1. Baseline HIV-1 Primary Drug Resistance Mutations in These Studies had No Impact on Treatment Response and Resistance to EVG/COBI/FTC/TDF through Week 144

Resistance Mutation	Number of Subjects n (%)	Week 144 Snapshot			Week 144 Resistance Analysis (Analyzed/ Resistant)
		Success	Failure	No Data in Window	
Any Primary INSTI Mutation[a]	**4/363 (1.1%)**	**4 (100%)**	**0 (0%)**	**0 (0%)**	**0/0**
T97A	3 (0.8%)	3 (100%)	0	0	0/0
Y143H	1 (0.3%)	1 (100%)	0	0	0/0
Any Primary NNRTI Mutation[b]	**95/701 (13.6%)**	**75 (78.9%)**	**8 (8.4%)**	**12 (12.6%)**	**8/1[c]**
V90I	14 (2.0%)	9 (64.3%)	2 (14.3%)	3 (21.4%)	1/0 (also had K103N at BL)
A98G	3 (0.4%)	3 (100%)	0	0	1/0
K103N	27 (3.9%)	22 (81.5%)	2 (7.4%)	3 (11.1%)	3/0
V106I	17 (2.4%)	16 (94.1%)	1 (5.9%)	0	1/1
V108I	3 (0.4%)	2 (66.7%)	1 (33.3%)	0	1/0
V179D/F/T	19 (2.7%)	15 (78.9%)	2 (10.5%)	2 (10.5%)	1/0
Y181C/I/V	4 (0.6%)	4 (100%)	0	0	0/0
G190A/S	2 (0.3%)	1 (50.0%)	1 (50.0%)	0	1/0
Any Primary NRTI Mutation[d]	**52/701 (7.4%)**	**41 (78.8%)**	**4 (7.7%)**	**7 (13.5%)**	**5/2[c]**
Any TAM[e]	17 (2.4%)	13 (76.5%)	0	4 (23.5%)	1/0
2 TAMs	6 (0.9%)	3 (50.0%)	0	3 (50.0%)	0/0
M41L	9 (1.3%)	8 (88.9%)	0	1 (11.1%)	1/0
D67N	7 (1.0%)	4 (57.1%)	0	3 (42.9%)	0/0
K219E/N/Q/R	7 (1.0%)	4 (57.1%)	0	3 (42.9%)	0/0
A62V	3 (0.4%)	2 (66.7%)	1 (33.3%)	0	1/0
T69D	4 (0.6%)	3 (75.0%)	1 (25.0%)	0	1/1
F77L	1 (0.1%)	1 (100%)	0	0	0/0
V118I	31 (4.4%)	25 (80.6%)	2 (6.5%)	4 (12.9%)	2/1
Any Primary PI Mutation[f]	**18/701 (2.6%)**	**14 (77.8%)**	**2 (11.1%)**	**2 (11.1%)**	**1/0[c]**

a. No EVG/COBI/FTC/TDF subjects with IN data (n=363) had HIV-1 with T66I/A/K, E92G/Q, Y143C/R, S147G, Q148H/K/R, or N155H/S in IN at baseline.
b. No EVG/COBI/FTC/TDF subjects had HIV-1 with L100I, K101E/H/P, or M230L in RT at baseline.
c. Samples not analyzed were either due to HIV-1 RNA < 400 copies/mL or treatment discontinuation prior to Week 8.
d. No EVG/COBI/FTC/TDF subjects had HIV-1 with E44D, K65R, T69 insertions, K70E/R, L74V/I, V75I, Y115F, F116Y, Q151M, M184V/I, L210W, or T215F/Y in RT at baseline.
e. Thymidine-analog resistance associated mutations (TAMs) are M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R.
f. No EVG/COBI/FTC/TDF subjects had HIV-1 with V32I, I47A/V, G48V, I50V/L, I54L/M, T74P, L76V, V82A/F/L/S/T, I84V, or N88S in PR at baseline.

Results (cont'd)

Figure 5. HIV-1 RNA through Week 144 for Subjects with Primary INSTI Mutations at Baseline and Treated with EVG/COBI/FTC/TDF

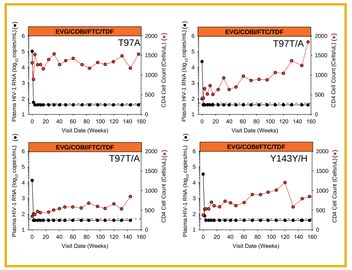


Table 2. Emergent Drug Resistance in Subjects with Virologic Failure Through Week 144 (Integrated Analysis of Studies 102 and 103)

		EVG/COBI/FTC/TDF (n = 701)	EFV/FTC/TDF (n = 352)	ATV + RTV + FTC/TDF (n = 355)
Resistance Analysis Population[a] % (n)		6.0% (42)	8.0% (28)	5.4% (19)
Developed Any Primary Resistance to Study Drugs % (n)		2.6% (18)	4.0% (14)	0.6% (2)
Baseline to Week 48		1.9% (13)	2.3% (8)	0% (0)
>Week 48 to Week 96		0.4% (3)	0.6% (2)	0% (0)
>Week 96 to Week 144		0.3% (2)	1.1% (4)	0.6% (2)
Emergent Primary Resistance Mutations % (n)	NRTI-R	FTC/TDF 2.4% (17)	FTC/TDF 1.1% (4)	FTC/TDF 0.6% (2)
		M184V/I 2.4% (17) K65R 0.7% (5)	M184V/I 1.1% (4) K65R 0.9% (3)	M184V/I 0.6% (2) K65R 0
	3rd agent	EVG (INSTI) 2.1% (15)	EFV (NNRTI) 4.0% (14)	ATV + RTV (PI/r) 0% (0)
		E92Q 1.3% (9) N155H 0.7% (5) Q148R 0.4% (3) T66I 0.3% (2) T97A 0.1% (1)	K103N 3.7% (13) K101E 1.4% (5) V108I 1.1% (4) Y188F/H/L 0.9% (3) M230L 0.6% (2) V90I 0.3% (1) G190A 0.3% (1) P225H 0.3% (1)	I50L 0 I84V 0 N88S 0
	Primary PI-R	0.1% (1)[b]	0.6% (2)[c]	0% (0)

a. Resistance Analysis Population: Subjects who experience either suboptimal virologic response (<1 $\log_{10}$ below baseline at/after Week 8, confirmed at next visit and ≥400 c/mL), virologic rebound (two consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving HIV-1 RNA <50, or >1 $\log_{10}$ increase from nadir), or had HIV-1 RNA ≥400 c/mL at Week 48, Week 96, Week 144, or their last visit.
b. One subject had emergent M46I/L in protease.
c. One subject had emergent I50I/L and one subject had emergent Q58E in protease.

Table 3. Genotypic and Phenotypic Analysis of the EVG/COBI/FTC/TDF Virologic Failures with Emergent Resistance Through Week 144 (Integrated Analysis of Studies 102 and 103, n=18/701)

Virology Subject (Study)	Time of Virology Analysis	Genotype														Phenotype[a] (Fold-Change vs WT)																	
		NRTI-R	INSTI-R													NRTIs									NNRTIs			PIs					INSTIs[f]
			Primary					Secondary								ABC	ddI	3TC	FTC	TFV	d4T	ZDV	EFV	ETR	NVP	AMP	ATV	DRV	IDV	LPV	TPV	EVG	RAL
Baseline to Week 48 ("Year 1")																																	
332 (103)	W12			M184V												2.8	1.3	>94	>40	0.44	0.60	0.18	0.44	0.49	0.16	0.44	0.33	0.71	0.59	0.46	0.52	1.0	1.1
503 (102)	W16		K65K/R	M184MI												1.9	1.5	>122	115	0.87	0.87	0.37	0.67	0.78	0.34	0.40	0.87	0.79	0.75	0.78	0.94	1.8	1.4
648 (102)	W16			M184V		E92Q										2.8	1.4	>70	>75	0.46	0.55	0.24	0.75	0.82	0.66	1.2	1.0	1.3	1.2	1.2	1.1	36	3.6
476 (103)	W16		ND		T66TI	E92E/Q			N155H/N						E157E/Q	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	58	6.6
562 (103)	W24			M184V					N155H							3.5	1.6	>134	>125	0.54	0.85	0.36	0.59	0.55	0.49	1.0	1.0	0.75	1.4	0.72	0.93	36	10.7
182 (102)	W24			M184I		E92Q										2.1	1.2	>74	>103	0.48	0.61	0.33	1.1	1.5	0.60	0.71	1.2	1.0	1.3	1.3	1.0	27	3.3
359 (103)	W24			M184V				Q148R								3.4	2.1	>120	>126	0.74	0.71	0.22	0.74	0.90	0.86	0.25	0.79	0.61	0.39	0.50	0.61	22	8.7
257 (102)	W32		K65K/R	M184V		E92Q								S153A		2.6	3.4	>102	>108	1.2	1.1	0.38	0.35	0.34	0.31	0.69	0.93	0.57	0.66	0.78	0.98	111	3.9
101 (102)	W32			M184V		E92E/Q		Q148Q/R	N155H/N							3.6	2.0	>94	>108	0.72	0.79	0.39	0.83	0.92	0.52	0.24	0.59	0.35	0.69	0.43	0.51	50	11.8
299 (103)	W32	A62A/V	K65R	M184V				Q148R				G140C				4.9	2.9	>85	>84	1.6	0.78	0.38	0.38	0.36	0.47	1.1	0.95	0.67	0.86	0.93	0.87	>188	28
012 (102)	W40	A62A/V	K65R	M184V		E92Q				H51H/Y	L68V					6.8	3.7	>90	>88	1.5	0.83	0.41	0.45	0.51	0.27	0.44	0.83	0.44	0.63	0.48	0.72	148	6.2
041 (102)	W40			M184V	T66TA	E92E/Q										3.9	1.7	>109	>152	0.64	0.55	0.49	1.4	1.7	1.5	1.1	1.2	0.77	1.8	0.91	1.4	5.6	1.9
667 (102)	W48			M184V		E92Q										3.2	1.1	>131	>120	0.46	0.69	0.36	0.72	0.57	0.33	0.96	1.3	0.69	1.0	0.90	0.88	44	3.6
Week 48 to Week 96 ("Year 2")																																	
425 (103)	W72			M184V		E92Q										3.2	1.4	>64	>63	0.39	0.65	0.20	0.40	0.35	0.27	0.27	0.55	0.29	0.34	0.52	0.49	42	2.2
322 (102)	W84			M184V					N155H							2.9	1.5	>72	>97	0.57	0.75	0.33	0.48	0.46	0.43	0.33	0.57	0.38	0.67	0.28	0.31	ND[c]	ND[c]
545 (102)	W96	A62V	K65R	M184V					N155H							6.2	3.7	>88	>89	1.2	0.96	0.46	0.49	0.50	0.39	0.34	0.58	0.83	0.63	0.63	0.75	55	15.3
Week 96 to Week 144 ("Year 3")																																	
516 (103)	W132			M184V			T97A[c]							G163G/R		3.6	1.5	>92	>65	0.55	0.70	0.29	1.1	1.4	1.4	0.44	0.61	0.40	0.56	0.63	0.48	ND[c]	ND
461 (103)	W144			M184MV		ND										2.2	1.8	>105	>94	0.63	0.80	0.32	0.35	0.39	0.28	0.42	0.56	0.47	0.50	0.52	0.53	ND	ND

a. PhenoSense PR/RT or IN (Monogram Biosciences). Phenotype above the defined assay cutoffs are colored red (FC above the biological or lower clinical cut-off) or green (at or below the cut-off).
ND= no data due to assay failure.
b. A62V is a fitness compensatory mutation for K65R and does not alter susceptibility to TFV (Svarovskaia et al., 2008, JAIDS 48:428-436).
c. Clonal sequencing of the HIV-1 from this subject showed linkage of M184V and E92Q on the same genome in 25 of 25 clones.
d. No phenotypic data was available, but N155H was present and has reduced susceptibility to EVG and RAL.
e. No phenotypic data was available, but the site-directed mutant virus containing T97A+G163R had 4.09-fold reduced susceptibility to EVG.
f. No genotypic cross-resistance to DTG based on United States Prescribing Information-defined list of Q148 substitution plus ≥2 of L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R.

All subjects with phenotypic resistance to a component of EVG/COBI/FTC/TDF had a primary resistance-associated mutation
The most common pattern was M184V in RT and E92Q in integrase

Table 4. First Failure Analysis of Subjects with Emergent EVG/COBI/FTC/TDF Resistance (Integrated Analysis of Studies 102 and 103)

- Subjects with drug resistance at confirmation visit assessed for resistance at first failure

		EVG/COBI/FTC/TDF (n = 701) Confirmation Sample Resistance	EVG/COBI/FTC/TDF (n = 701) Resistance at First Failure
Resistance Analysis Population % (n)		6.0% (42)	2.6% (18)
Subjects with Data for RT and/or IN		6.0% (42)	2.4% (17)
Developed Any Primary Resistance to Study Drugs % (n)		2.6% (18)	2.1% (15)
Baseline to Week 48		1.9% (13)	1.4% (10)
>Week 48 to Week 96		0.4% (3)	0.4% (3)
>Week 96 to Week 144		0.3% (2)	0.3% (2)
Emergent Primary Resistance Mutations % (n)	NRTI-R	FTC/TDF 2.4% (17)	FTC/TDF 2.0% (14)
		M184V/I 2.4% (17) K65R 0.7% (5)	M184V/I 2.0% (14) K65R 0.4% (3)
	INSTI-R	EVG 2.1% (15)	EVG 1.1% (8)
		E92Q 1.3% (9) N155H 0.7% (5) Q148R 0.4% (3) T66I 0.3% (2) T97A 0.1% (1)	E92Q 0.4% (3) N155H 0.3% (2) Q148R 0.1% (1) T66I/A/V 0.1% (1) T97A 0.1% (1)

Figure 6A. Clinical Case where M184I/V in RT is the First Mutation to Develop

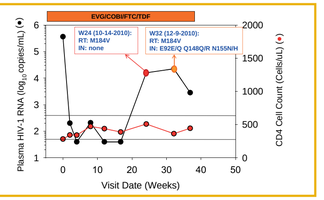
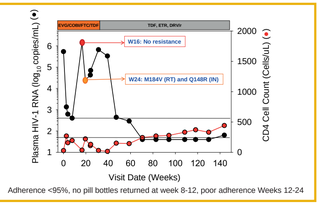


Figure 6B. Clinical Case where the First Failure Timepoint Failed to Detect Resistance



- Adherence <95%, no pill bottles returned at week 8-12, poor adherence Weeks 12-24

Table 5. Detailed Longitudinal Analysis of Resistance Analysis Population at First Failure and Failure Confirmation (EVG/COBI/FTC/TDF Group, n=18; see Table 4)

Virology Subject (Study)	First Failure			Failure Confirmation		
	Analysis Window (W)	NRTI-R	INSTI-R	Analysis Window (W)	NRTI-R	INSTI-R
359 (103)	16	none	none	24	M184V	Q148R
425 (103)	40	none	none	72	M184V	E92Q
503 (102)	12	M184MI	none	16	K65K/R M184MI	***none
332 (103)	8	M184V	none	12	M184V	***none
101 (102)	24	M184V	none	32	M184V	E92E/Q Q148Q/R N155H/N
667 (102)	40	***M184V	***none	48+etest	***M184V	***E92Q
012 (102)	24	***K65R M184V	***E92Q	40	A62A/V K65R M184V	E92Q H51H/Y L68V
516 (103)	120	M184MI/V	T97A	132	M184V	***T97A G163G/R
476 (103)	12	***/***	***T66TI/AV	16	***/***	T66TI/ E92E/Q N155N/H E157E/Q
648 (102)	12	M184V	E92Q	16	M184V	E92Q
562 (103)	24	M184V	N155H	24+etest	M184V	***N155H
299 (103)	24	***K65R/I M184MI/V	Q148R G140A/S	32	A62A/V K65R M184V	Q148R G140C
545 (102)	84	***A62V K65R M184V	N155H	96	A62V K65R M184V	N155H
182 (102)	24	***M184MI	***E92Q	32	M184I	***E92Q
461 (103)	144	***M184V/I	***/***	144+etest	M184MI/V	***/***
257 (102)	32	***/***	***/***	32+etest	***K65R/I M184V	***E92Q S153A
322 (102)	84	***M184V	***/***	84+etest	M184V	***N155H T66TI
041 (102)	32	***M184V	***/***	40	M184V	E92E/Q

*** genotypic assay failure and retest result; ***/*** denotes multiple assay failures

First Failure Samples found that M184V/I frequently emerges prior to INSTI-R. First Failure Samples detected 27 of 51 mutations found at failure confirmation in RT and IN

Conclusions

- **High and durable efficacy was observed in subjects treated with EVG/COBI/FTC/TDF, EFV/FTC/TDF and ATV + RTV + FTC/TDF at Week 48, Week 96, and Week 144**
- **EVG/COBI/FTC/TDF had high efficacy in subjects with pre-existing primary drug resistance mutations (e.g. K103N in RT or T97A in IN)**
- **The rate of resistance development to EVG/COBI/FTC/TDF was low (2.6% of treated subjects)**
  - **The most common pattern of resistance was M184V in RT and E92Q in IN**
    - **Linkage of integrase resistance mutations and M184V/I also observed with RAL studies STARTMRK and QDMRK[6,7,8]**
  - **All subjects with phenotypic resistance had a primary resistance mutation; these mutations were consistent with the known resistance profile of EVG, FTC, and TDF**
  - **Evidence of EVG cross-resistance to RAL; no cross-resistance to DTG detected by genotype**
- **Longitudinal analyses of resistance at the first failure timepoint**
  - **M184V/I often develops first**
  - **First failure analysis can fail to detect resistance in some cases**
    - **Failed to detect mutations in RT (4/18 subjects) and in IN (10/18 subjects) by standard population sequencing**
  - **Possible role for deep sequencing at early failure timepoints**

References & Acknowledgments

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