Table 1. Reasons for Drug Discontinuation

	COBI, n = 344		RTV, n = 348	
	Week 96	Week 144, Δ	Week 96	Week 144, Δ
Study drug DC due to AEs, n (%)	35 (10.2)	+3 (+1)	35 (10.1)	+4 (+1.1)
Hepatobiliary AEs, n (%)	18 (5.2)	0	11 (3.2)	+1 (+0.3)
Renal AEs, n (%)	8 (2.3)	+2 (+0.6)	10 (2.9)	+1 (+0.3)
Proximal renal tubulopathy, n	6	0	6	1
Isolated creatinine increase, n	2	2	4	0
Rash, n (%)	1 (0.3)	0	2 (0.6)	0
Dermatitis allergic, n (%)	2 (0.6)	0	0	0

AEs, adverse events; DC, discontinued.

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Noninferiority of COBI versus RTV came with infrequent nucleotide and nucleoside reverse transcriptase inhibitor resistance and no protease inhibitor resistance. These data, and the recent approval of cobicistat by the FDA, will lead to coformulations with ATV and DRV.

Safety and Efficacy of DTG Plus ABC/3TC for Treatment-Naïve Patients With HIV

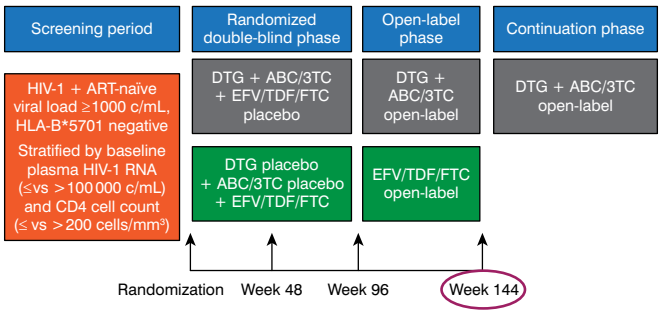
Written by Brian Hoyle

Results from a 48-week, open-label extension of A Trial Comparing GSK1349572 50mg Plus Abacavir/Lamivudine Once Daily to Atripla [SINGLE, NCT01263015], a phase 3, randomized, double-blind trial, have reaffirmed week 48 and week 96 results [Walmsley SL et al. *N Engl J Med.* 2013] of the superiority of once-daily dolutegravir (DTG) 50 mg used with abacavir/lamivudine (ABC/3TC) compared with efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in treatment-naïve patients with HIV-1. The latest findings were reported by Keith Pappa, PharmD, GlaxoSmithKline, Research Triangle Park, North Carolina, USA.

Prior to week 96, the study had been conducted in a double-blind fashion. From weeks 96 to 144, patients were free to remain on the therapy they had been randomized to with knowledge of the drug being used (Figure 1).

In the SINGLE study, 833 patients were randomized to receive daily DTG+ABC/3TC (n=414) or EFV/TDF/FTC (n=419). The primary end point at week 48 utilized the US Food and Drug Administration snapshot analysis, which is the proportion of patients with a last available HIV-1 RNA within the visit of <50 copies/mL. Secondary end points included the proportion of patients with decreased HIV-1 RNA to <50 copies/mL at week 144, the change from baseline in the CD4⁺ T cell count, long-term safety, immune response, health outcomes, and emergence of viral resistance. The study arms were comparable at baseline in terms of age, sex, race (African American), proportion of US Centers for Disease Control and Prevention class C, median HIV-1 RNA count, and median CD4⁺ count.

Figure 1. Design of the SINGLE Study



ABC/3TC, abacavir/lamivudine; ART, antiretroviral therapy; c/mL, copies per milliliter; DTG, dolutegravir; EFV/TDF/FTC, efavirenz/tenofovir/emtricitabine; HIV, human immunodeficiency virus; HLA-B, major histocompatibility complex, class 1, B57.1

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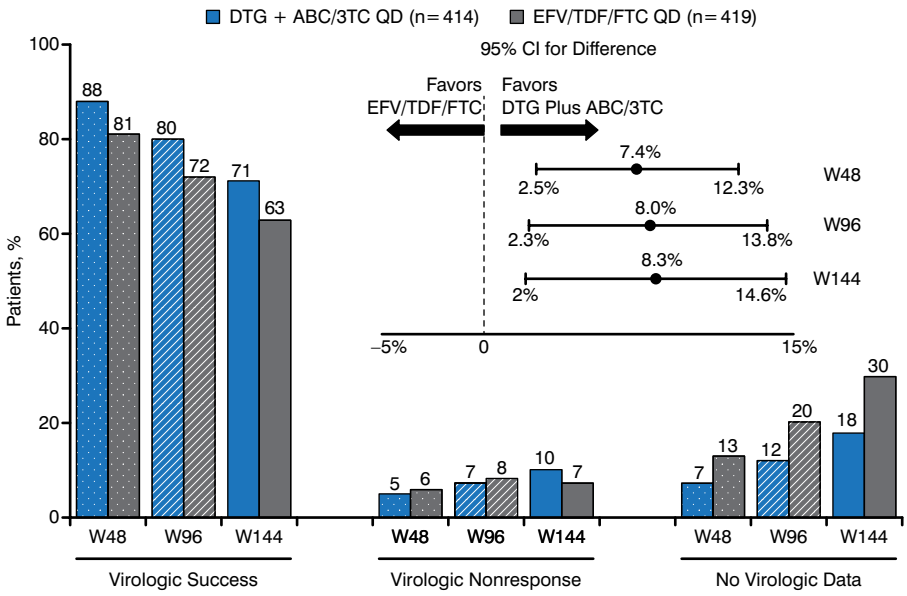
At week 144, the proportion of patients having HIV-1 RNA viral load <50 copies/mL was significantly higher in the DTG+ABC/3TC arm than in the EFV/TDF/FTC arm (71% versus 63%; adjusted treatment difference between groups: +8.3%; 95% CI, 2.0 to 14.6; $P=.010$). The change in CD4 count from baseline to week 144 was significantly greater in the DTG+ABC/3TC arm than in the EFV/TDF/FTC arm (adjusted mean ±SE, 378.5±11.0 versus 331.6±11.6; 95% CI, 15.6 to 78.1; $P=.003$).

Figure 2. HIV-1 RNA Results at Week 144



ABC/3TC, abacavir/lamivudine; DTG, dolutegravir; EFV/TDF/FTC, efavirenz/tenofovir/emtricitabine; HIV, human immunodeficiency virus; W48, week 48; W96, week 96; W144, week 144.
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Table 1. Change in Common Drug-Related Adverse Events, Week 96 to Week 144

Adverse Event	DTG + ABC/3TC QD, n = 414		EFV/TDF/FTC QD, n = 419	
	Week 96, %	Week 144, Δ	Week 96, %	Week 144, Δ
Any	44	+1	67	+1.2
Dizziness	7	+0	33	+0.2
Abnormal dreams	7	+0	16	+0.2
Nausea	11	+0.2	12	+0
Insomnia	10	+0	6	+0.7
Diarrhea	6	+0	8	+0
Fatigue	7	+0	7	+0
Headache	6	+0	7	+0
Rash	< 1	+0	8	+0

Reported in > 5% of patients in either treatment. There was an overall low rate of elevated liver chemistries in both treatment groups. ABC/3TC, abacavir/lamivudine; DTG, dolutegravir; EFV/TDF/FTC, efavirenz/tenofovir/emtricitabine.

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Figure 2 presents snapshot outcomes by analysis time points with virologic success significantly greater for the DTG regimen at each time point. The forest plot data demonstrate superiority at each time point.

Protocol-defined virologic failure (PDVF) was defined as confirmed HIV-1 RNA ≥ 50 copies/mL at or after week 24. Among patients taking DTG + ABC/3TC, PDVF was evident in 39 patients (9%), none due to identifiable mutations. In the EFV/TDF/FTC group, PDVF was evident in 33 patients (8%), 13 of which had identifiable non-nucleoside (in 6 patients) and nucleoside (in 1 patient) reverse transcriptase inhibitor mutations. At week 144, the difference between the DTG + ABC/3TC arm and the EFV/TDF/FTC arm for patients entering the trial with ≤ 100 000 copies/mL HIV-1 RNA (73% versus 64%, respectively), > 100 000 copies/mL HIV-1 RNA (69% versus 61%, respectively), ≤ 200 CD4 cells/μL (60% versus 56%, respectively), and > 200 CD4 cells/μL (73% versus 64%, respectively) was consistent with the overall treatment difference observed for the population studied.

The drug-related adverse effects profile evident at week 96 showed little change to week 144 (Table 1).

The number and proportion of serious adverse events through week 144 were similar in each arm. However, the number of serious drug-related adverse events was lower in the DTG + ABC/3TC group (n = 2 [< 1%]) compared with the EFV/TDF/FTC group (n = 9 [2%]). The same trend was evident for adverse events that led to withdrawal through week 144 (n = 16 [4%] versus n = 58 [14%]). As reported at weeks 48 and 96, the DTG group had small, nonclinically meaningful, nonprogressive changes in serum creatinine, due to known inhibition of creatinine tubular secretion by DTG.

The latest findings from this open-label extension of the SINGLE study reaffirm the earlier SINGLE findings that the DTG + ABC/3TC regimen is superior to EFV/TDF/FTC in treatment-naïve patients with HIV-1.

Doravirine 100 mg Dose Selected for Subsequent Studies Based on Exposure–Response Analysis

Written by Toni Rizzo

Commonly used nonnucleoside reverse transcriptase inhibitors (NNRTIs) are associated with suboptimal efficacy or safety profiles. Doravirine is a novel, next-generation NNRTI in development for the treatment of HIV-1 infection. It is dosed once daily and has a rapid onset with a median T_{max} of 1 to 5 hours and an apparent terminal half-life of 11 to 19 hours. Doravirine is not expected to interact with proton pump inhibitors (PPIs) and can be dosed without regard to food intake.

Part 1 of A Dose-Ranging Study to Compare MK-1439 Plus TRUVADA® Versus Efavirenz Plus TRUVADA® in Human Immunodeficiency Virus (HIV)-1 Infected Participants (MK-1439-007) [NCT01632345] examined the safety, tolerability, pharmacokinetics (PK), and efficacy of 4 doses of doravirine (25, 50, 100, and 200 mg once daily) versus efavirenz, both taken with emtricitabine–tenofovir. The Part 1 efficacy and safety results demonstrated that all 4 doses of doravirine had potent antiretroviral activity and fewer drug-related adverse events (AEs) than efavirenz [Morales-Ramirez et al. CROI 2014]. In this report, Matthew L. Rizk, PhD, Merck and Company, Inc., Whitehouse Station, New Jersey, USA, presented exposure–response analysis results from Part 1 of this dose-ranging study.

Sparse doravirine PK data, available from 167 of 208 enrolled patients, were pooled with densely sampled phase 1 PK data in a population PK model to obtain individual post-hoc estimates of steady-state PK parameters. Individual PK estimates and week 24 HIV-1 RNA (vRNA) were matched, and PK–pharmacodynamic (PD) trends were explored. Individual area under the curve (AUC) estimates were plotted against the predefined AE rate. Steady-state C_{trough} distributions were compared to in vitro C_{trough} targets for wild-type and various mutant HIV-1 strains.

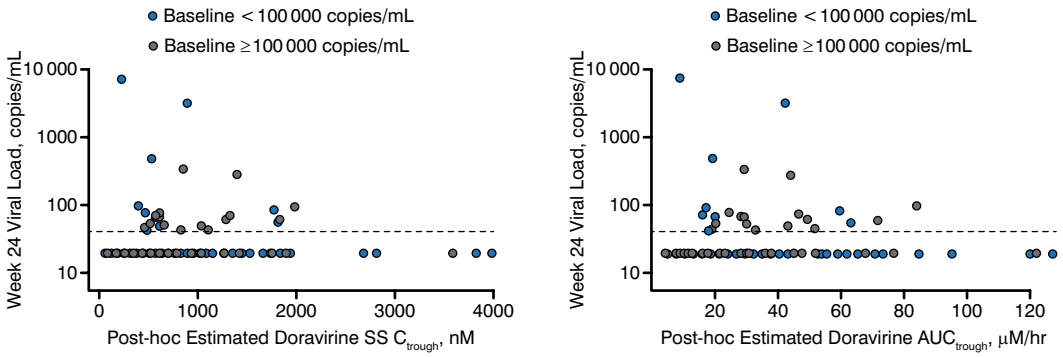
The exposure–response analysis of efficacy showed that there was no trend between C_{trough} or AUC and the proportion of patients with undetectable HIV-1 RNA at week 24 (Figure 1). No difference in the PK–PD relationship between high and low-viral-load patients was observed.

No apparent trend between AUC and the proportion of patients with central nervous system AEs, abnormal dreams, nausea, or diarrhea was observed. A logistic regression model found no significant relationship between AUC and nausea.

Comparison of steady-state C_{trough} distributions and in vitro C_{trough} targets for wild-type and mutant HIV-1 found that 25 mg through 200 mg doses of doravirine provided good coverage of wild-type virus, consistent with the clinical results (Table 1). The 100 mg dose provided better coverage (92.3%) of dual mutant strains [K103N/Y181C] compared with 50 mg, which provided 69.5% coverage.

The safety and efficacy results showed that all tested doses of doravirine were efficacious and safe and had numerically higher response rates and fewer drug-related AEs than efavirenz. Although all 4 doravirine doses underwent exposure–response analysis, the study primarily focused on the 50 mg and 100 mg doses. The

Figure 1. HIV RNA vs steady-state C_{trough} and $AUC_{0–24\ hr}$ by baseline HIV RNA



AUC, area under the curve; SS, steady-state.

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