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.

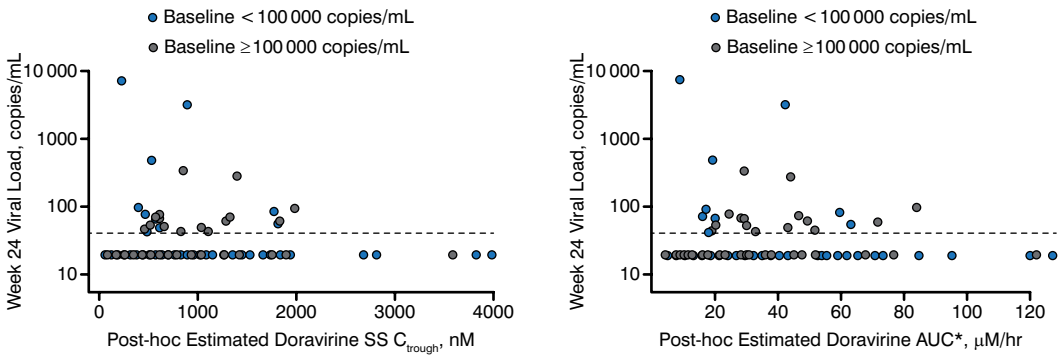
The exposure–response analysis of efficacy showed that there was no trend between C_{trough} or AUC and the proportion of patients with undetectable HIV-1 RNA at week 24 (Figure 1). No difference in the PK–PD relationship between high and low-viral-load patients was observed.

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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*On May 1, 2015, AUC_{trough} was changed to AUC.

Table 1. Simulated Percentage of Patients With Higher-Than-Target Steady-State C_{24} hr for a Representative HIV-1 Patient Population Assuming Full Compliance

Dose, mg QD	Concentration, nM Median (90% PI)	Wild Type 78 nM	K103N 117 nM	Y181C 195 nM	G190A 211 nM	K103N/ Y181C 335 nM
25	228 (77, 580)	94.9	86.9	61.8	56.2	26.6
50	453 (156, 1051)	99.3	97.7	90.5	88.5	69.5
100	831 (276, 1993)	99.9	99.7	98.2	97.5	92.3
200	1467 (479, 3442)	100	100	99.5	99.4	98.3

QD, once daily; 90% PI, 90% prediction interval.
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analysis confirmed that there is no relationship between doravirine plasma levels and both efficacy and AE rates. Based on these results and the superior coverage of dual mutant HIV-1 strains [K103N/Y181C], the 100 mg dose of doravirine was selected for Part 2 of the study (with additional enrollment at 100 mg doravirine vs efavirez) and for study in Phase 3.

No Resistance and Improved Renal and Bone Profiles With a Single-Table Regimen of D/C/F/TAF

Written by Toni Rizzo

Tenofovir disoproxil fumarate (TDF) is a safe and potent prodrug of the nucleotide reverse transcriptase inhibitor tenofovir; it is available as a single-tablet regimen; and it can be taken in combination with 3 of the 4 guideline-recommended third agents. Tenofovir alafenamide (TAF) is a novel tenofovir prodrug that provides higher intracellular tenofovir diphosphate levels and lower plasma tenofovir levels than TDF. Darunavir is a protease inhibitor (PI) dosed as a single daily tablet. PIs have a high genetic barrier to resistance, but a PI-based single-tablet regimen has not been available.

Anthony Mills, MD, Southern California Men's Medical Group, Los Angeles, California, USA, presented the results of the week 48 analysis of the Safety and Efficacy of Darunavir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Versus Cobicistat-Boosted Darunavir Plus Emtricitabine/Tenofovir Disoproxil Fumarate Fixed Dose Combination in HIV-1 Infected, Antiretroviral Treatment Naïve Adults [GS-US-299-0102; NCT01565850]. This phase 2 trial compared the combination of darunavir/cobicistat/emtricitabine/TAF (D/C/F/TAF) versus darunavir (DRV) boosted by cobicistat (COBI) and F/TDF in treatment-naïve HIV-infected adults.

A total of 150 treatment-naïve patients with HIV RNA ≥5000 copies/mL, CD4 >50, estimated glomerular filtration rate >70 mL/min, and a screening genotype with sensitivity to darunavir, TDF, and emtricitabine (F) were randomized to D/C/F/TAF (n=100) or DRV+COBI+F/TDF (n=50) once daily with matched placebos. The primary end point was HIV-1 RNA <50 copies/mL (virologic success) at week 24.

At week 24, there were similar proportions of patients in the D/C/F/TAF and DRV+COBI+F/TDF groups that achieved virologic success (75% vs 74%; weighted difference, 3.3; 95% CI, −11.4 to 18.1). At week 48, 77% of patients in the D/C/F/TAF group versus 84% in the DRV+COBI+F/TDF group had achieved virologic success (weighted difference −6.2; 95% CI, −19.9 to 7.4).

Of 8 patients meeting the criteria for resistance analysis due to virologic rebound, none tested resistant to TDF, emtricitabine, or darunavir. The study drug was discontinued by 18% of D/C/F/TAF patients and 16% of DRV+COBI+F/TDF patients, but none of the discontinuations were efficacy related. Two patients in each arm discontinued due to adverse events (AEs). AEs in the D/C/F/TAF versus the DRV+COBI+F/TDF group were as follows: diarrhea (21% vs 26%), upper respiratory tract infection (16% vs 14%), fatigue (14% vs 18%), nausea (13% vs 10%), and rash (12% vs 8%).

The mean change in serum creatinine at week 48 was +0.06 mg/dL in the D/C/F/TAF group and +0.09 mg/dL in the DRV+COBI+F/TDF group ($P=.053$). Renal tubular proteinuria rates were significantly lower in the D/C/F/TAF group (retinol binding protein:creatinine ratio, $P=.003$; β-2 microglobulin:creatinine ratio, $P=.002$).

At week 48, in the D/C/F/TAF group versus the DRV+COBI+F/TDF group, the median changes in fasting metabolic assessments were as follows: total cholesterol (40 vs 5 mg/dL, $P<.001$), low-density lipoprotein (26 vs 4 mg/dL, $P<.001$), high-density lipoprotein (7 vs 3 mg/dL, $P=.009$); total cholesterol:high-density lipoprotein ratio (0.0 vs −0.2, $P=.15$), triglycerides (29 vs −5 mg/dL, $P=.007$), and serum glucose (5 vs 2 mg/dL, $P=.33$). Patients in the D/C/F/TAF group had a significantly lower mean percentage change in bone mineral density of the hip ($P\leq.001$) and spine ($P=.003$) at week 48.

At week 48, viral suppression rates were the same in both study groups, and no patients had developed drug resistance. Both regimens were well tolerated, with similarly low rates of AE-related discontinuation. Dr Mills concluded that the improved renal and bone profiles of TAF and the high-resistance barrier of darunavir warrant a phase 3 study of a single-tablet regimen of D/C/F/TAF.