Efficacy and safety of doravirine 100mg QD vs efavirenz 600mg QD with TDF/FTC in ART-naive HIV-infected patients: week 24 results

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Background: Doravirine (DOR), an investigational NNRTI with a novel resistance profile, was compared with efavirenz (EFV) in a double-blind, randomized, 2-part study in ART-naïve HIV-infected patients who also received tenofovir/emtricitabine (TDF/FTC). In Part 1 (dose selection), DOR at 25, 50, 100 and 200mg QD showed rates of virologic suppression similar to EFV 600mg QD; DOR 100mg was selected for ongoing evaluation. Part 2 enrolled additional patients to receive DOR 100mg or EFV. Using data from Parts 1+2 combined, DOR 100mg showed significantly fewer CNS AEs than EFV at week 8.

Methods: Week 24 efficacy and safety results were analyzed for all patients who received DOR 100mg or EFV in Part 1 (n=42 per group) and Part 2 (n=66 per group) combined. Patients were stratified at randomization by screening RNA ≤ or >100,000 copies/mL. Primary endpoints were the proportion of patients with HIV RNA < 40 c/mL (efficacy) and the proportion of patients with pre-specified CNS events (safety).

Results: Of the 108 patients randomized and treated per group, mean baseline RNA was 4.6 $\log_{10}$ c/mL in both the DOR and EFV groups, and mean CD4 counts were 432 and 448 cells/mm^3, respectively. Discontinuations in the DOR and EFV groups, respectively, were 4.6% and 12.0%.

Week 24 Efficacy, including subgroup responses by screening RNA ≤ or >100,000 c/mL			
Endpoint	DOR† (N=108)	EFV† (N=108)	Difference [DOR-EFV] (95% CI)
HIV RNA <40 c/mL‡	72.2 %	73.1 %	-1.2 (-13.0, 10.5)
screening RNA ≤100K§ (n=66, 63)	83.3 %	85.7 %	-2.4 (-15.3, 10.6)
screening RNA >100K§ (n=38, 38)	60.5 %	65.8 %	-5.3 (-26.4, 16.4)
HIV RNA <200 c/mL‡	88.9 %	87.0 %	1.9 (-7.0, 11.0)
screening RNA ≤100K§ (n=66, 63)	92.4 %	92.1 %	0.4 (-9.8, 10.8)
screening RNA >100K§ (n=38, 38)	92.1 %	94.7 %	-2.6 (-16.5, 10.7)
Mean change in CD4 count§	154/mm³	146/mm³	8 (-37, 52)

† with TDF/FTC.
‡ Non-completer=Failure (NC=F) approach to missing data.
§ Observed Failure (OF) approach to missing data.

Week 24 Clinical Adverse Event (AE) Summary & Primary Safety Analysis (CNS AEs)			
Proportion of patients with:	DOR† (N=108)	EFV† (N=108)	Difference [DOR-EFV] (95% CI)
One or more AEs	75.9 %	84.3 %	-8.3 (-19.1, 2.4)
Drug-related AEs	27.8 %	55.6 %	-27.8 (-39.9, -14.8)
Serious AE	0.9 %	4.6 %	-3.7 (-9.6, 0.9)
Serious drug-related AEs	0 %	0.9 %	-0.9 (-5.1, 2.5)
Discontinued due to AEs	0.9 %	5.6 %	-4.6 (-10.8, 0.1)
One or more CNS AEs	26.9 %	46.3 %	-19.4 (-31.7, -6.6)*

† with TDF/FTC
* Prespecified safety hypothesis, p<0.001

[Tables]

The most common drug-related clinical AEs in the DOR and EFV groups, respectively, were nausea (7.4%; 5.6%), dizziness (6.5%; 25.0%), abnormal dreams (5.6%; 14.8%), nightmares (4.6%; 8.3%), and sleep disorder (3.7%; 6.5%). Drug-related AEs leading to discontinuation were hallucination for DOR (n=1) and dysesthesia, hallucination, drug eruption, dizziness, and disturbance in attention for EFV (n=5). The most common CNS AEs (all causality) were dizziness (DOR 9.3%; EFV 27.8%), insomnia (7.4%; 2.8%), abnormal dreams (6.5%; 17.6%), and nightmares (6.5%; 8.3%). Lab abnormalities of Grade 2 or greater were uncommon in both groups.

Conclusions: DOR 100mg qd demonstrated antiretroviral activity and immunological effect similar to EFV (each with TDF/FTC) and was generally safe and well tolerated during 24 weeks of treatment in ART-naïve, HIV-1 infected patients. Treatment-emergent CNS AEs through week 24 were significantly less common in the DOR group than in the EFV group.