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Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial.

Madruga JV, Cahn P, Grinsztejn B, Haubrich R, Lalezari J, Mills A, et al; DUET-1 study group.

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BACKGROUND: Antiretroviral agents active against drug-resistant HIV-1 are needed for treatment-experienced patients. The aim of this trial was to assess the efficacy, safety, and tolerability of TMC125 (etravirine), a non-nucleoside reverse transcriptase inhibitor (NNRTI).

METHODS: DUET-1 is a continuing, multinational randomised, double-blind, placebo-controlled, phase III trial. Treatment-experienced adult patients with virological failure on stable antiretroviral therapy, documented genotypic evidence of NNRTI resistance, viral load over 5,000 copies per mL, and three or more primary protease inhibitor mutations were randomly assigned to receive 200 mg TMC125 or placebo twice daily. All patients also received darunavir with low-dose ritonavir and investigator-selected nucleoside reverse transcriptase inhibitors. Enfuvirtide use was

optional. The primary endpoint was a confirmed viral load below 50 copies per mL at week 24 (FDA time-to-loss of virological response algorithm). Analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, with the number NCT00254046.

FINDINGS: 612 patients were randomised and treated (304 in the TMC125 group, 308 in the placebo group). By week 24, 42 (14%) patients in the TMC125 group and 56 (18%) in the placebo group had discontinued, mainly due to virological failure. At week 24, 170 (56%) patients in the TMC125 group and 119 (39%) patients in the placebo group achieved a confirmed viral load of less than 50 copies per mL (difference in response rates 17%; 95% CI 9-25; $p=0.005$). Most adverse events were mild or moderate in severity. The type and incidence of adverse events, including neuropsychiatric events, seen with TMC125 were generally comparable with placebo, with the exception of rash (61 [20%] patients on TMC125 vs 30 [10%] on placebo) and diarrhoea (36 [12%] patients on TMC125 vs 63 [20%] on placebo).

INTERPRETATION: In treatment-experienced patients with NNRTI resistance, treatment with TMC125 achieved better virological suppression at week 24 than did placebo. The safety and tolerability profile of TMC125 was generally comparable with placebo.

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Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial.

Lazzarin A, Campbell T, Clotet B, Johnson M, Katlama C, Moll A, et al; DUET-2 study group.

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BACKGROUND: TMC125 (etravirine) is a non-nucleoside reverse-transcriptase inhibitor (NNRTI) with activity against NNRTI-resistant HIV-1 in phase I trials. The aim of DUET-2 is to examine the efficacy, tolerability, and safety of TMC125 in treatment-experienced patients.

METHODS: In this continuing randomised, double-blind, placebo-controlled, phase III trial, HIV-1-infected patients on failing antiretroviral therapy with evidence of resistance to currently available NNRTIs and at least three primary protease inhibitor mutations were eligible for enrolment if on stable (8 weeks unchanged) antiretroviral therapy with plasma HIV-1 RNA greater than 5,000 copies per mL. Patients were randomly assigned to receive either TMC125 (200 mg) or placebo, each given twice daily with darunavir-ritonavir, investigator-selected nucleoside/nucleotide reverse transcriptase inhibitors, and optional enfuvirtide. The primary endpoint was the proportion of patients with confirmed viral load below 50 copies per mL at week 24 (FDA time-to-loss of virological response algorithm). Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00255099.

FINDINGS: 591 patients were randomised and treated (295 patients in the TMC125 group and 296 in the

placebo group). By week 24, 51 (17%) patients in the TMC125 group and 73 (25%) in the placebo group had discontinued, mainly because of virological failure. 183 (62%) patients in the TMC125 group and 129 (44%) in the placebo group achieved confirmed viral load below 50 copies per mL at week 24 (difference 18%, 95% CI 11-26; $p=0.0003$). The type and frequency of adverse events were much the same in the two groups.

INTERPRETATION: In treatment-experienced patients, treatment with TMC125 led to better virological suppression at week 24 than did placebo. The safety and tolerability profile of TMC125 was generally comparable with placebo.

DISCUSSION

The DUET-1 and -2 studies are a pair of randomized, placebo-controlled, double-blind, phase III trials evaluating the efficacy and tolerability of TMC125 (etravirine), a novel non-nucleoside reverse transcriptase inhibitor (NNRTI), in highly treatment-experienced HIV-infected patients. The DUET-1 trial was conducted in Argentina, Brazil, Chile, France, Mexico, Panama, Puerto Rico, Thailand, and the United States, whereas DUET-2 was conducted in Australia, Belgium, Canada, France, Germany, Italy, the Netherlands, Poland, Portugal, Spain, the United Kingdom, and the United States. Both studies enrolled patients experiencing virologic failure with evidence of ≥ 1 NNRTI resistance mutations and ≥ 3 primary PI resistance mutations. A total of 1,203 participants in both DUET studies received ritonavir-boosted darunavir, a new protease inhibitor (PI) with a good efficacy in patients harboring PI-resistant HIV-1, as part of their optimized background regimen. The participants in both DUET studies were randomized to receive TMC125 or placebo, each combined with darunavir/ritonavir-containing

optimized background regimen.

The 24-week result of both studies revealed that there was a benefit of adding TMC125 to darunavir/ritonavir-containing optimized background regimen. In DUET-1, the patients in the TMC125 arm also had a greater increase in CD4 cell count from baseline, compared with the patients in the placebo arm. However, the efficacy of TMC125 was found to be dependent on the number of the 13 TMC125 resistance mutations including V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, and G190A/S. Interestingly, K103N mutation is not listed among the 13 TMC125 resistance mutations since it does not affect the susceptibility to TMC125.

TMC125 was well tolerated, with a toxicity profile comparable to that of the placebo arm.

However, rash was reported to be more common in the TMC125 arm, and ranged from 14 percent to 29 percent. This finding addresses the common adverse effect which is similar to other NNRTIs.

In summary, TMC125 is the first NNRTI in the second generation showing the efficacy in highly treatment-experienced HIV-infected patients with NNRTI resistance. Ritonavir-boosted darunavir also plays an important part in these two studies. Implication for using TMC125 with other PIs may be possible but clinical trials are needed to confirm this implication. Since the efficacy of TMC125 directly depends on the number of TMC125 resistance mutations, late detection of NNRTI failure may accumulate the number of these mutations and compromised the efficacy to TMC125.