Impact of TMC125, a next-generation NNRTI, on clinical outcomes (AIDS-defining illnesses and deaths): 24-week findings from a planned pooled analysis of the DUET studies

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Abstract

Objectives: To evaluate, at 24 weeks, differences in clinical outcomes (i.e., AIDS-defining illnesses and deaths) between TMC125 (etravirine; ETR) plus background regimen (BR; darunavir/ritonavir, NRTIs) and optional enfuvirtide (ENF) and placebo plus BR in a pooled analysis of DUET-1 and DUET-2. These are two identical, ongoing, randomized, double-blind, placebo-controlled, Phase III trials, aiming to show superiority of TMC125 over placebo in HIV-infected, treatment-experienced patients. Efficacy and safety results from DUET have been reported recently.

Methods: In the DUET trials, AIDS-defining illnesses were identified using the relevant criteria that appear as Category C illnesses in the 1993 revised classification system for HIV infection issued by the USA Centers for Disease Control (CDC). Deaths from any cause were counted. Data presented are part of the primary analysis. All patients were treated for at least 24 weeks or discontinued.

Results: 1,203 patients were analysed: 599 vs 604 in the TMC125 versus placebo groups. Baseline characteristics were comparable between arms. Overall results were 6.8% vs 3.7% for placebo plus BR vs TMC125 plus BR, respectively.

Table: Clinical endpoints (AIDS-defining illnesses or death)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TMC125, n (%)</th>
<th>Placebo, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>22 (3.2)**</td>
<td>21 (3.1)***</td>
</tr>
<tr>
<td>CDC A</td>
<td>3 (0.4)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>CDC B</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>CDC C</td>
<td>20 (2.9)</td>
<td>22 (3.6)</td>
</tr>
<tr>
<td>Any AIDS-defining illness</td>
<td>22 (3.2)**</td>
<td>21 (3.1)***</td>
</tr>
<tr>
<td>Death</td>
<td>8 (1.3)</td>
<td>15 (2.5)</td>
</tr>
<tr>
<td>ENF</td>
<td>4 (0.6)</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>ENF using/reusing de novo</td>
<td>5 (0.7)</td>
<td>6 (1.0)</td>
</tr>
</tbody>
</table>

There was a statistically significant reduction in these events for patients receiving TMC125 over placebo in the subgroup that did not use ENF in the BR (p = 0.0051).

Conclusions: At Week 24, TMC125 plus BR provided a reduction in AIDS-defining illnesses and/or deaths versus placebo plus BR (statistically significant for patients not using ENF de novo). DUET trials are planned to continue until 96 weeks.

DUET study design and major inclusion criteria

- **1,203** patients were randomized: 605 and 604 in the TMC125 and placebo groups, respectively
- Background regimen (BR; darunavir/ritonavir, NRTIs) and optional enfuvirtide (ENF)

Assessment of clinical outcomes (AIDS-defining illnesses and deaths)

- At the time of this analysis, patients were monitored for 24 weeks or had discontinued
- Analysis was by ITT population and patients with at least one day of treatment and at least one AIDS-defining illness (AIDS or death) event counted as an event in the ITT population
- Patients could receive rescue therapy

Conclusions: DUET 1 and 2 – some patients received raltegravir - in the clinic and tyrosine therapy

DUET study design and major inclusion criteria

- **1,203** patients were randomized: 605 and 604 in the TMC125 and placebo groups, respectively
- Background regimen (BR; darunavir/ritonavir, NRTIs) and optional enfuvirtide (ENF)

Baseline characteristics from pooled DUET-1 and DUET-2

- Baseline characteristics were comparable between arms
- Overall results were 6.8% vs 3.7% for placebo plus BR vs TMC125 plus BR, respectively

DUET study design and major inclusion criteria

- **1,203** patients were randomized: 605 and 604 in the TMC125 and placebo groups, respectively
- Background regimen (BR; darunavir/ritonavir, NRTIs) and optional enfuvirtide (ENF)

Proportion of patients with any new AIDS-defining illness or death

- **59%** vs **41%** for placebo plus BR vs TMC125 plus BR (p < 0.0001)

Conclusions

- In the pooled DUET-1 and -2 analysis, three out of five patients receiving TMC125 achieved <50 copies/mL undetectable viral load
- **59%** with TMC125 plus BR vs **41%** with placebo plus BR achieved <50 copies/mL
- **Most AEs** were mild-to-moderate and infrequently led to discontinuation
- There was a consistent trend for fewer clinical endpoints (any new AIDS-defining illnesses and/or deaths versus placebo plus BR (statistically significant for patients not using ENF de novo). DUET trials are planned to continue until 96 weeks.

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DUET 1:
- Argentina: L Arias, J Hidalgo, F Pulgar, L Goicochea
- Brazil: M Machado, C Evora, C Cravioto, C Mello, D Kazer, N Cooper, K Reis, A Losso, J Martinez, I Baggio, M Portes, F Caruso
- Italy: A Antinori, G Carosi, G Di Perri, R Esposito, A Lazzarin, F Mazzotta, G Pagano, E Raise, A Azzarita
- USA: J Suleiman, A Timerman

DUET 2:
- Argentina: J Del Rio, G Gatta, R Lozano, G Schoetzky, G Cavani
- Brazil: L Arantes, C Oliveira, C Siqueira, C Reis, A Losso
- Italy: A Antinori, G Carosi, G Di Perri, R Esposito, A Lazzarin, F Mazzotta, G Pagano, E Raise, A Azzarita
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