SAT0421

GUSELKUMAB DEMONSTRATED AN INDEPENDENT TREATMENT EFFECT ON FATIGUE AFTER ADJUSTMENT FOR CLINICAL RESPONSE (ACR20) IN PATIENTS WITH PSORIATIC ARTHRITIS: RESULTS FROM PHASE-3 TRIALS DISCOVER 1 & 2

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Background: DISCOVER 1 and 2 are phase-3 trials of gusekumab (GUS, a monoclonal antibody that specifically binds the p19-subunit of IL-23) in patients with psoriatic arthritis (PsA). In both trials, treatment with GUS led to significantly more improvement than placebo (PBO) in the primary endpoint (ACR20) as well as in other measures of arthritis and psoriasis at week (W) 24.1,2

Objectives: To evaluate the effect of GUS on fatigue in DISC 1 & 2 using the patient reported outcome (PRO) FACIT-Fatigue, which has demonstrated content validity and strong psychometric properties in clinical trials.3

Methods: DISC 1 & 2 enrolled patients with active PsA, despite nonbiologic DMARDS and/or NSAIDS, who were mostly biologic naïve except for ~30% of patients in DISC 1 who had received 1-2 TNFi. Patients were randomized (1:1:1) to GUS 100 mg q4W, or to matching PBO. Concomitant treatment with select nonbiologic DMARDS, oral corticosteroids, and NSAIDS was allowed. The FACIT-Fatigue is a 13-item PRO instrument assessing fatigue and its impact on daily activities and function over the past seven days, with a total score ranging from 0 to 52, higher score denoting less fatigue. A change of ≥4 points is identified as clinically meaningful.4 Change from baseline in FACIT-Fatigue was analyzed using MMRM (Figure). Independence of treatment effect on FACIT-Fatigue from effect on ACR20 was assessed using Mediation Analysis4 (Table) to estimate the natural direct effect (NDE), and natural indirect effect (NIE) mediated by ACR20 response.

Results: At baseline in DISC 1 & 2, the mean FACIT-fatigue scores (SD) were 30.4 (10.4) and 29.7 (9.7), respectively, indicating moderate to severe fatigue. In both DISCOVER 1 & 2 trials, treatment with GUS led to improvements in FACIT-Fatigue scores compared with PBO as early as W8 (Figure). 54%-63% of GUS patients compared with 35%-46% of PBO patients achieved clinically meaningful improvement (≥4 points) in FACIT-Fatigue (P≤0.003). Mediation analysis revealed that the independent treatment effects on fatigue after adjustment for ACR20 response (Natural Direct Effect [NDE], Table) were 12-36% in the q4W GUS dosing group and 69% -70% in the qW GUS group.

Conclusion: In 2 phase-3 trials, treatment with GUS of patients with active PsA led to significant improvements compared to PBO in fatigue, including substantial effects on FACIT-Fatigue that were independent of the effects on ACR 20, especially for the q4W dosing group.

References:

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Table. Mediation Analysis of the Effect of ACR 20 Response on Change from Baseline in FACIT-Fatigue Score at Week 24

<table>
<thead>
<tr>
<th>Effect</th>
<th>GUS 100 mg q4W vs. PBO Estimate (95% CI)</th>
<th>GUS 100 mg qW vs. PBO Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISCOVER 1</td>
<td>NDE 0.36 (1.7, 2.4) 2.60 (0.6, 4.5)*</td>
<td>NIE 2.75 (14.4, 43) 120 (0.3, 2.9)*</td>
</tr>
<tr>
<td>Total Effect</td>
<td>3.12 (10, 5.2)* 3.78 (19, 5.4)*</td>
<td>Proportion Independent 11% 68.5%</td>
</tr>
<tr>
<td>Proportion Mediated</td>
<td>88.3% 31.5%</td>
<td>Proportion Mediated</td>
</tr>
<tr>
<td>DISCOVER 2</td>
<td>NDE 1.44 (0.1, 3.0) 2.49 (10, 4.1)*</td>
<td>NIE 2.53 (1.6, 3.6)* 109 (0.4, 1.9)*</td>
</tr>
<tr>
<td>Total Effect</td>
<td>3.07 (2.4, 5.5)* 3.58 (2.1, 5.0)*</td>
<td>Proportion Independent 36.3% 69.7%</td>
</tr>
<tr>
<td>Proportion Mediated</td>
<td>63.7% 30.3%</td>
<td>Proportion Mediated</td>
</tr>
</tbody>
</table>

*P vs placebo=0.02
NDE=Natural Direct Effect (effect on FACIT-F beyond effect on ACR20), NIE=Natural Indirect Effect (effect on FACIT-F mediated by ACR20)

Mediation analysis used linear and logistics regression models with Bootstrapping method

SAT0422

FIRST-LINE CSDMARD MONOTHERAPY RETENTION IN PSORIATIC ARTHRITIS: METHOTREXATE OUTPERFORMS SULFASALAZINE

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Background: Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) are the first-line treatment for psoriatic arthritis (PsA), but there is conflicting data regarding their efficacy and scarce reports describing the duration of use (drug retention) of csDMARD in this population. Their position in treatment recommendations is a matter of growing debate due the availability of alternative treatment options with higher levels of evidence.


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