Effect of tezepelumab on exacerbations in patients with severe, uncontrolled asthma, according to baseline body mass index: results from the phase 2b PATHWAY study

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Introduction

• Tezepelumab is a human monoclonal antibody that specifically binds to thymic stromal lymphopoietin (TSLP), blocking it from interacting with its receptor complex.
• TSLP is an epithelial-derived cytokine that plays a key role in persistence and/or exacerbation of asthma.1
• In the phase 2b PATHWAY study (NCT02204132), tezepelumab significantly reduced exacerbations by up to 71% irrespective of baseline disease characteristics, and improved long-term asthma control and health-related quality of life compared with placebo in patients with severe, uncontrolled asthma.2
• An obesity-related phenotype in asthma has been described in multiple studies.3,4
• Patients with asthma and a high body mass index (BMI; > 30 kg/m²) are more likely to experience recurrent asthma symptoms and are more likely to have severe, persistent asthma than those with a low BMI (≤ 25 kg/m²).5
• Among patients with asthma, obesity has been associated with an altered inflammatory profile and increased levels of tumor necrosis factor, interleukin-6 and leptins, decreased blood eosinophil counts and levels of fractional exhaled nitric oxide (FeNO), and a reduced response to biologic and anti-interleukin-5 therapy.6

• This post hoc analysis evaluated the efficacy of tezepelumab according to baseline BMI in the PATHWAY study population.

Methods

Study design

• PATHWAY was a phase 2b, multicenter, randomized, double-blind, placebo-controlled study (Figure 1).7

• Patients were non-smokers, 18–75 years old, with asthma that was not well controlled despite treatment with inhaled glucocorticoids (ICS) plus a long-acting β2-agonist (LABA), with an exacerbation rate of ≥ 0.7 per person-year, and a forced expiratory volume in 1 second (FEV1) recovery of > 15% after treatment with a short-acting β2-agonist (Figure 1).

• Patients had at least two asthma exacerbations that led to systemic corticosteroid treatment or at least one exacerbation requiring hospitalization, in the 12 months before study entry.
• Patients were randomized 1:1:1:1 to receive subcutaneous tezepelumab (70 mg every 4 weeks, 210 mg every 4 weeks, 280 mg every 4 weeks [225 mg on week 1]) or placebo 225 mg every 4 weeks.

• In the pooled tezepelumab dose groups, AAER over 52 weeks was reduced by up to 71% irrespective of baseline disease characteristics, and improved long-term asthma control and health-related quality of life compared with placebo in patients with severe, uncontrolled asthma.2

Assessments and statistical analyses

• Patients were grouped according to their BMI at baseline: < 25, 25–< 30 or ≥ 30 kg/m².

• Overall, 550 patients were randomized to tezepelumab (70 mg Q4W, n = 225; 210 mg Q4W, n = 138; 280 mg Q4W, n = 135; placebo Q2W, n = 142) (Figure 1).

• Among patients with asthma, obesity has been associated with an altered inflammatory profile and increased levels of tumor necrosis factor, interleukin-6 and leptins, decreased blood eosinophil counts and levels of fractional exhaled nitric oxide (FeNO), and a reduced response to biologic and anti-interleukin-5 therapy.6

• In the tezepelumab 210 mg dose group, AAER over 52 weeks was reduced compared with placebo in patients with a BMI of < 25, 25–< 30 and ≥ 30 kg/m², respectively.3

• Median concentrations of tezepelumab were generally similar between BMI subgroups (means of 0.70–0.76 exacerbations per person-year).

• A total of 175, 185 and 190 patients had a BMI of < 25, 25–< 30 and ≥ 30 kg/m², respectively, compared with BMI ≥ 30 kg/m².

• In addition, the mean and median serum concentrations of tezepelumab at steady state were calculated for each BMI subgroup.

• Data are presented for tezepelumab serum concentrations at steady state in patients grouped by baseline BMI (Figure 4).

Results

Baseline demographics and clinical characteristics

• Overall, 550 patients were randomized to tezepelumab (70 mg Q4W, n = 225; 210 mg Q4W, n = 138; 280 mg Q4W, n = 135; placebo Q2W, n = 142) (Figure 1).

• A total of 175, 185 and 190 patients had a BMI of < 25, 25–< 30 and ≥ 30 kg/m², respectively.

• Lower BMI was associated with younger age, higher baseline blood eosinophil counts and levels of FeNO and higher sOROS than higher BMI (Table 1).

• Among placebo recipients, AAER over 52 weeks was similar for the three BMI subgroups (means of 0.70–0.76 exacerbations per person-year).

• In the pooled tezepelumab dose groups, AAER over 53 weeks was reduced by 85% (95% CI: 49–96%), 84% (95% CI: 49–95%) and 86% (95% CI: 33–98%) in patients with a BMI of < 25, 25–< 30 and ≥ 30 kg/m², respectively, compared with placebo (Figure 2).

• In the pooled placebo dose groups, AAER over 53 weeks was reduced by 76% (95% CI: 57–86%), 70% (95% CI: 43–85%) and 78% (95% CI: 65–92%) in patients with a BMI of < 25, 25–< 30 and ≥ 30 kg/m², respectively, compared with placebo (Figure 3).

Tezepelumab serum concentration at steady state

• Median concentrations of tezepelumab were generally similar between BMI subgroups, with slightly lower concentrations observed in patients with a BMI = 30 kg/m² (Figure 4).

Conclusions

• Lower BMI was associated with younger age, higher baseline blood eosinophil counts and higher levels of FeNO than higher BMI.

• Treatment with tezepelumab reduced exacerbations compared with placebo in patients with severe, uncontrolled asthma, irrespective of baseline BMI.

• Tezepelumab serum concentrations at steady state were mildly correlated with BMI; however, this did not result in a meaningful impact on the efficacy of tezepelumab in reducing exacerbations.

• This analysis provides further evidence that tezepelumab can meaningfully reduce exacerbations in a broad population of patients with severe, uncontrolled asthma.

References


Table 1. Baseline demographics and clinical characteristics of the PATHWAY population grouped by baseline BMI

<table>
<thead>
<tr>
<th>BMI category (kg/m²)</th>
<th>Age, years</th>
<th>Pre-BD FEV1, % predicted</th>
<th>Pre-BD FEV1, 100% predicted</th>
<th>Pre-BD FVC, % predicted</th>
<th>Pre-BD FVC, 100% predicted</th>
<th>Pre-BD FEV1/ FVC ratio</th>
<th>Median baseline blood eosinophil count (cells/µL)</th>
<th>Median baseline FeNO level (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>37 (17)</td>
<td>59.3 (12.0)</td>
<td>74.7 (20.4)</td>
<td>0.70 (0.27)</td>
<td>54.0 (20.0)</td>
<td>0.31 (0.12)</td>
<td>257 (212, 312)</td>
<td>3 (1, 8)</td>
</tr>
<tr>
<td>25–&lt; 30</td>
<td>37 (17)</td>
<td>59.9 (11.3)</td>
<td>75.5 (20.5)</td>
<td>0.71 (0.26)</td>
<td>55.0 (21.0)</td>
<td>0.31 (0.13)</td>
<td>267 (210, 313)</td>
<td>3 (1, 8)</td>
</tr>
<tr>
<td>≥ 30</td>
<td>37 (17)</td>
<td>60.6 (12.7)</td>
<td>76.1 (20.6)</td>
<td>0.72 (0.25)</td>
<td>53.0 (21.0)</td>
<td>0.30 (0.12)</td>
<td>274 (218, 321)</td>
<td>3 (1, 8)</td>
</tr>
</tbody>
</table>

Note: Data are mean (SD) unless otherwise specified. BD, bronchodilator; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; OROS, oral respiratory outcome score; Q4W, every 4 weeks; sOROS, standardized OROS; SD, standard deviation.