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

Christopher S Ambrose,[1] Gene Colice,[2] Kinga Sałapa,[3] Jane R Parnes,[4] and Jonathan Corren[5]

[1]BioPharmaceuticals Medical, AstraZeneca, Gaithersburg, MD, USA; [2]Late Respiratory, Inflammation & Autoimmunity (RIA), BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA; [3]Biometrics, Late Respiratory, Inflammation & Autoimmunity (RIA), AstraZeneca, Warsaw, Poland; [4]Amgen, Thousand Oaks, CA, USA; [5]David Geffen School of Medicine, University of California at Los Angeles (UCLA), Los Angeles, CA, USA

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## Introduction

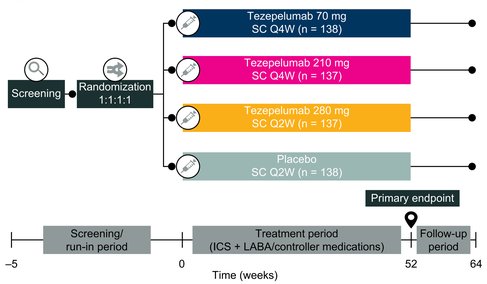
- Tezepelumab is a human monoclonal antibody that specifically binds to thymic stromal lymphopoietin (TSLP), blocking it from interacting with its receptor complex.[1,2]
- TSLP is an epithelial-derived cytokine that plays a key role in the initiation and persistence of airway inflammation in asthma.[3]
- In the phase 2b PATHWAY study (NCT02054130), tezepelumab significantly reduced exacerbations by up to 71% irrespective of baseline disease characteristics, and improved lung function, 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.[4–6]
  - Patients with asthma and a high body mass index (BMI; ≥ 30 kg/m$^2$) are more likely to experience recurrent asthma symptoms and are more likely to have severe, persistent asthma than those with a low BMI (< 30 kg/m$^2$).[6]
  - 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 corticosteroid therapy.[7]
- 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**).[2]
- Patients were non-smokers, 18–75 years old, with asthma that was not well controlled despite treatment with medium-dose (250–500 µg/day fluticasone dry powder inhaler [DPI] or equivalent) or high-dose (> 500 µg/day fluticasone DPI or equivalent) inhaled corticosteroids (ICS) plus a long-acting β-agonist.

**Figure 1. Study design**




ICS, inhaled corticosteroids; LABA, long-acting β-agonist; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneously.

- 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 [Q4W], 210 mg Q4W, 280 mg every 2 weeks [Q2W]) or placebo Q2W for 52 weeks.

### Assessments and statistical analyses

- Patients were grouped according to their BMI at baseline: < 25, 25–< 30 or ≥ 30 kg/m$^2$.
- The annualized asthma exacerbation rate (AAER) was determined for patients who received placebo or tezepelumab 70, 210 or 280 mg in each BMI subgroup.
- Rate ratios and 95% confidence intervals (CIs) for tezepelumab dose groups versus placebo were estimated within each BMI subgroup using a negative binomial model, with treatment, baseline peripheral blood eosinophil count (≥ 250 cells/µL vs < 250 cells/µL) and baseline ICS dose (medium vs high) included as covariates.
- In addition, the mean and median serum concentrations of tezepelumab at steady state were calculated for each BMI subgroup.
- Data are presented for tezepelumab 210 mg Q4W (the dosage used in ongoing phase 3 studies) and pooled from all three tezepelumab dose groups.

## Results

### Baseline demographics and clinical characteristics

- Overall, 550 patients were randomized to tezepelumab (70 mg Q4W, n = 138; 210 mg Q4W, n = 137; 280 mg Q2W, n = 137) or placebo Q2W (n = 138).
- A total of 175, 185 and 190 patients had a BMI of < 25, 25–< 30 and ≥ 30 kg/m$^2$, respectively.
- Lower BMI was associated with younger age, higher baseline blood eosinophil counts and higher levels of FeNO than higher BMI (**Table 1**; **Figure 2**).

### AAER

- 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 tezepelumab 210 mg dose group, AAER over 52 weeks was reduced by 83% (95% CI: 49–94), 62% (95% CI: 4–85) and 68% (95% CI: 13–89), in patients with a BMI of < 25, 25–< 30 and ≥ 30 kg/m$^2$, respectively, compared with placebo (**Figure 3**).
- In the pooled tezepelumab dose groups, AAER over 52 weeks was reduced by 79% (95% CI: 57–89), 70% (95% CI: 41–85) and 50% (95% CI: 6–73) in patients with a BMI of < 25, 25–< 30 and ≥ 30 kg/m$^2$, respectively, compared with placebo (**Figure 3**).

### Tezepelumab serum concentration at steady state

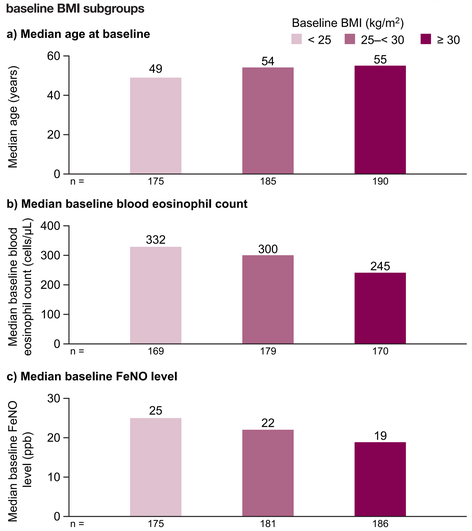
- Median concentrations of tezepelumab were generally similar between BMI subgroups, with slightly lower concentrations observed in patients with a BMI ≥ 30 kg/m$^2$ (**Figure 4**).

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

| | Placebo (n = 138) | Tezepelumab 210 mg Q4W (n = 137) | Pooled tezepelumab (n = 412) |
|---|---|---|---|
| **BMI < 25 kg/m$^2$** | | | |
| n | 44 | 39 | 131 |
| Age, years<br>Mean (SD)<br>Median (min, max) | <br>50.5 (11.8)<br>50.0 (24.0, 74.0) | <br>50.3 (13.8)<br>53.0 (25.0, 75.0) | <br>48.5 (13.6)<br>48.0 (20.0, 75.0) |
| BMI, kg/m$^2$<br>Mean (SD)<br>Median (min, max) | <br>22.5 (1.9)<br>22.7 (18.0, 25.0) | <br>22.7 (1.6)<br>22.8 (19.8, 25.0) | <br>22.6 (1.7)<br>22.9 (18.3, 25.0) |
| Pre-BD $FEV_1$, % predicted | 61.4 (16.3) | 56.3 (13.3) | 57.9 (13.0) |
| Median blood eosinophil count, cells/µL | 351.0[a] | 328.0[b] | 331.0[c] |
| Median FeNO, ppb | 24.6 | 24.0 | 25.0 |
| ACQ-6 score† | 2.6 (0.8) | 2.5 (0.8) | 2.6 (0.8) |
| Asthma exacerbations in the past 12 months, n (%)<br>1 or 2<br>≥ 3 | <br>35 (79.5)<br>9 (20.5) | <br>30 (76.9)<br>9 (23.1) | <br>110 (84.0)<br>21 (16.0) |
| **BMI 25–< 30 kg/m$^2$** | | | |
| n | 47 | 45 | 138 |
| Age, years<br>Mean (SD)<br>Median (min, max) | <br>51.4 (12.6)<br>54.0 (20.0, 68.0) | <br>54.1 (12.1)<br>55.0 (21.0, 73.0) | <br>52.3 (11.7)<br>53.0 (21.0, 74.0) |
| BMI, kg/m$^2$<br>Mean (SD)<br>Median (min, max) | <br>27.8 (1.4)<br>27.7 (25.1, 30.0) | <br>27.4 (1.3)<br>27.5 (25.1, 29.5) | <br>27.5 (1.4)<br>27.6 (25.0, 30.0) |
| Pre-BD $FEV_1$, % predicted | 59.3 (12.3) | 59.2 (12.9) | 60.6 (12.7) |
| Median blood eosinophil count, cells/µL | 300.0[d] | 384.0 | 309.5[e] |
| Median FeNO, ppb | 23.3[f] | 22.5 | 21.0[g] |
| ACQ-6 score† | 2.7 (0.7) | 2.7 (0.9) | 2.7 (0.9) |
| Asthma exacerbations in the past 12 months, n (%)<br>1 or 2<br>≥ 3 | <br>39 (83.0)<br>8 (17.0) | <br>34 (75.6)<br>11 (24.4) | <br>107 (77.5)<br>31 (22.5) |
| **BMI ≥ 30 kg/m$^2$** | | | |
| n | 47 | 53 | 143 |
| Age, years<br>Mean (SD)<br>Median (min, max) | <br>54.9 (10.4)<br>57.0 (31.0, 72.0) | <br>53.2 (12.3)<br>56.0 (21.0, 74.0) | <br>52.8 (11.7)<br>55.0 (21.0, 74.0) |
| BMI, kg/m$^2$<br>Mean (SD)<br>Median (min, max) | <br>34.7 (3.5)<br>34.5 (30.1, 44.4) | <br>33.7 (2.6)<br>32.9 (30.4, 39.5) | <br>33.8 (2.6)<br>33.5 (30.0, 39.8) |
| Pre-BD $FEV_1$, % predicted | 59.3 (12.0) | 60.9 (11.3) | 59.6 (12.2) |
| Median blood eosinophil count, cells/µL | 244.5[h] | 220.0[i] | 245.0[j] |
| Median FeNO, ppb | 21.5 | 16.0[l] | 18.0[k] |
| ACQ-6 score† | 2.8 (0.6) | 2.8 (0.7) | 2.8 (0.7) |
| Asthma exacerbations in the past 12 months, n (%)<br>1 or 2<br>≥ 3 | <br>36 (76.6)<br>11 (23.4) | <br>41 (77.4)<br>12 (22.6) | <br>114 (79.7)<br>29 (20.3) |

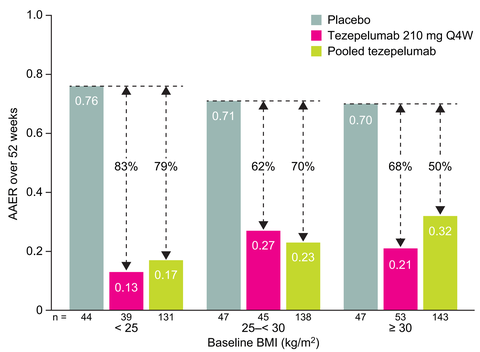
Data are mean (SD) unless otherwise specified.
[a]n = 42; [b]n = 38; [c]n = 127; [d]n = 45; [e]n = 134; [f]n = 46; [g]n = 135; [h]n = 44; [i]n = 126; [j]n = 51; [k]n = 139.
†< 0.75: well controlled; < 1.5: partially controlled; ≥ 1.5: uncontrolled.
ACQ, Asthma Control Questionnaire; BD, bronchodilator; BMI, body mass index; FeNO, fractional exhaled nitric oxide; $FEV_1$, forced expiratory volume in 1 second; ppb, parts per billion; Q4W, every 4 weeks; SD, standard deviation.

**Figure 2. Key demographics and clinical characteristics that differed among baseline BMI subgroups**



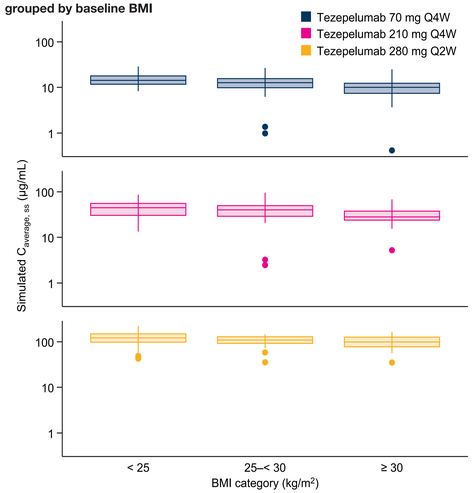

BMI, body mass index; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

**Figure 3. AAER over 52 weeks in patients grouped by baseline BMI**




AAER, annualized asthma exacerbation rate; BMI, body mass index; Q4W, every 4 weeks.

**Figure 4. Serum concentrations of tezepelumab at steady state in patients grouped by baseline BMI**




BMI, body mass index; $C_{average, ss}$, median concentration at steady state; Q2W, every 2 weeks; Q4W, every 4 weeks.

## 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.

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### Disclosures

CSA, GC and KS are employees of AstraZeneca. JRP is an employee of Amgen. JC received grants and personal fees from AstraZeneca during the conduct of the study. He has also received grants and personal fees from Genentech, Novartis, Regeneron and Sanofi outside of the submitted work.

The product mentioned is investigational and not approved in any country.

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