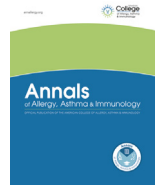




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Tezepelumab improves patient-reported outcomes in patients with severe, uncontrolled asthma in PATHWAY

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ABSTRACT

Background: Patients with severe, uncontrolled asthma experience frequent exacerbations and hospitalization, leading to poor health-related quality of life. In the phase 2b PATHWAY study (NCT02054130), tezepelumab reduced exacerbations by up to 71% and improved lung function, asthma control, and health-related quality of life vs placebo.

Objective: This analysis further assessed the impact of tezepelumab on patient-reported outcomes (PROs) in PATHWAY.

Methods: Adults with severe, uncontrolled asthma were randomized to subcutaneous tezepelumab (70 mg every 4 weeks, 210 mg every 4 weeks, or 280 mg every 2 weeks) or placebo for 52 weeks. PROs were assessed using the asthma control questionnaire–6 (ACQ-6) and the asthma quality of life questionnaire (standardized) for patients aged 12 years or older (AQLQ(S)+12). The proportions of responders (defined by improvements of ≥ 0.5 in ACQ-6 or AQLQ(S)+12 scores) and patients whose asthma was well-controlled, partially-controlled, or uncontrolled in the tezepelumab and placebo groups were identified. The Asthma Daily Diary questionnaire was used to assess changes in overall symptom severity.

Results: Overall, 550 patients were randomized. Up to 82% and 77% of tezepelumab-treated patients were ACQ-6 and AQLQ(S)+12 responders, respectively, compared with 70% and 64% of placebo-treated patients, respectively. The proportions of patients with well-controlled or partially-controlled asthma were higher in the tezepelumab-treated group than in the placebo group. In addition, tezepelumab improved the overall symptom severity.

Conclusion: Tezepelumab treatment improved PROs vs placebo, as indicated by the higher proportion of ACQ-6 and AQLQ(S)+12 responders and improvements in symptom severity in the tezepelumab dose groups. These data further support the benefits of tezepelumab in patients with severe, uncontrolled asthma.

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and may own shares in AstraZeneca. Dr Parnes is an employee of Amgen and owns shares in Amgen. Dr van der Merwe was an employee of AstraZeneca at the time of the study and is a present employee of DBV Technologies.

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Introduction

Approximately 10% of patients with asthma in the USA have severe asthma.¹ These patients experience recurrent exacerbations^{2–4} and poorly controlled symptoms despite the standard-of-care treatment,^{1,5–7} which contributes to poor health-related quality of life (HRQoL).^{5,7} New biologic therapies that have been developed for the treatment of severe asthma have limited efficacy in some patients.^{8–10} Thus, for these patients, an unmet need remains for effective therapies to reduce asthma symptoms, prevent exacerbations, and improve HRQoL.¹¹

Tezepelumab is a human monoclonal antibody (immunoglobulin G2λ) that binds specifically to thymic stromal lymphopoietin (TSLP), blocking it from interacting with its heterodimeric receptor.^{12,13} TSLP is an epithelial-derived cytokine and is a key regulator of many downstream inflammatory pathways involved in response to airborne particles such as viruses and allergens.^{14–16} Expression of TSLP is increased in the airways of patients with asthma and correlates with disease severity.^{17–19} In the PATHWAY phase 2b trial (ClinicalTrials.gov identifier: NCT02054130), tezepelumab significantly reduced asthma exacerbations over 52 weeks by up to 71% compared with placebo in patients with severe, uncontrolled asthma. Reductions in exacerbations were seen in patients irrespective of baseline biomarker levels, including blood eosinophil counts and fractional exhaled nitric oxide levels.^{13,20,21} Importantly, tezepelumab also improved clinical measures of lung function, asthma control, and HRQoL.¹³ In a previous analysis of PATHWAY, patients treated with tezepelumab had greater improvements from baseline in the Asthma Control Questionnaire-6 (ACQ-6) and Asthma Quality of Life Questionnaire (standardized) for patients aged 12 years or older (AQLQ[S]+12) scores than those treated with placebo.¹³

In a recent survey of patients with severe asthma, individuals who considered their asthma controlled often still experienced frequent symptoms that affected their daily lives.²² Increasingly, guidance from regulatory bodies recognizes the importance of subjective measures of disease and recommends the inclusion of patient-reported outcomes (PROs) in clinical trials.^{23,24} As such, PROs, such as assessments of HRQoL and asthma symptoms, are becoming increasingly important to both physicians and patients for informing treatment choices and to health authorities and payers for assessing the treatment benefit during drug development. In addition, responder analyses, which are recommended by the US Food and Drug Administration for use in the interpretation of the effect of a given drug on PROs, are important in determining the clinical relevance of trial outcomes.²³ In this post hoc analysis of data from the PATHWAY study, we aimed to further evaluate the effects of tezepelumab on PROs by determining the patient response to treatment-based measures of asthma control, HRQoL, and daily asthma-related health status.

Methods

Study Design and Participants

The PATHWAY study was a phase 2b, randomized, multicenter, double-blind, placebo-controlled trial. The full design and inclusion and exclusion criteria of this study have been described previously.¹³ Patients included in the study were 18–75 years old, current nonsmokers (for at least 6 months and with a lifetime history of less than 10 pack-years), and had asthma that was uncontrolled despite treatment with medium- or high-dose inhaled corticosteroids (ICS) (250–500 μg or >500 μg per day of fluticasone dry powder inhaler or equivalent, respectively) for at least 6 months before enrollment. Included patients also had a history of at least 2 asthma exacerbations that led to systemic corticosteroid treatment

or at least 1 severe exacerbation that resulted in hospitalization in the 12 months before study entry. In addition, included patients had an ACQ-6²⁵ score of at least 1.5 on at least 2 occasions during screening (scores range from 0 to 6, with a lower score indicating better disease control). Patients with any clinically important pulmonary diseases other than asthma were excluded.

Patients were randomized (1:1:1:1) to receive subcutaneous doses of tezepelumab 70 mg every 4 weeks (Q4W), 210 mg Q4W, or 280 mg every 2 weeks (Q2W), or placebo Q2W for 52 weeks. Participants were stratified by study site (non-Japanese or Japanese), and then by blood eosinophil count (≥ 250 cells/ μ L or < 250 cells/ μ L) and ICS dose level (medium or high). Final active doses were administered to patients at week 48 for tezepelumab 70 mg Q4W and 210 mg Q4W groups (placebo was received at week 50 to maintain blinding), at week 50 for the tezepelumab 280 mg Q2W group, and at week 50 for the placebo group. Patients continued to receive their prescribed background controller medications at a stable dose for the duration of the study.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. Approvals from independent ethics committees were obtained, and all patients provided written informed consent in accordance with local requirements.

Outcomes

Asthma control was assessed using ACQ-6 and was measured every 2 weeks throughout the treatment period. The ACQ-6 score was calculated as the unweighted mean of the responses to the 6 questions provided. Reductions in the ACQ-6 score of greater than or equal to 0.5 from baseline were considered clinically meaningful²⁶ and were used to identify responders to treatment. The proportions of patients whose asthma was well-controlled (ACQ-6 score of ≤ 0.75), partially controlled (ACQ-6 score of > 0.75 – < 1.5), or uncontrolled (ACQ-6 score of ≥ 1.5) were assessed at week 50. The time to first well-controlled or partially-controlled asthma through to week 50 was calculated.

HRQoL was assessed using the AQLQ(S)+12.²⁷ The AQLQ(S)+12 was completed every 4 weeks throughout the treatment period. Increases from baseline in the overall AQLQ(S)+12 score of greater than or equal to 0.5 were considered clinically meaningful²⁸ and were used to identify responders to treatment.

The ACQ-6 and AQLQ(S)+12 scores were recorded using an electronic patient-reported outcomes (ePRO) device, as described previously.¹³ Owing to a programming error within the ePRO device, a low proportion of patients were able to complete the questionnaires at week 52. Therefore, the focus of statistical inference is given to AQLQ(S)+12 and ACQ-6 scores at time points before week 52 (weeks 48 and 50, respectively).

Daily asthma-related health status was assessed using the Asthma Daily Diary questionnaire, which was completed by patients using the ePRO device each evening before going to sleep and each morning upon awakening. The questionnaire consisted of 3 items (frequency of daytime asthma symptoms, the severity of daytime asthma symptoms, and severity of night time asthma symptoms). Scores for these items ranged from 0 (no symptoms) to 4 (worst possible symptoms). The Asthma Daily Diary score was calculated as a 14-day summary of the responses for the 3 items during this period, with a lower score indicating less severe symptoms. The minimum clinically important difference in the Asthma Daily Diary score has not yet been determined.

Statistical Analyses

Generalized estimating equations were used to quantify responders to treatment. Odds ratios (OR) were estimated using a

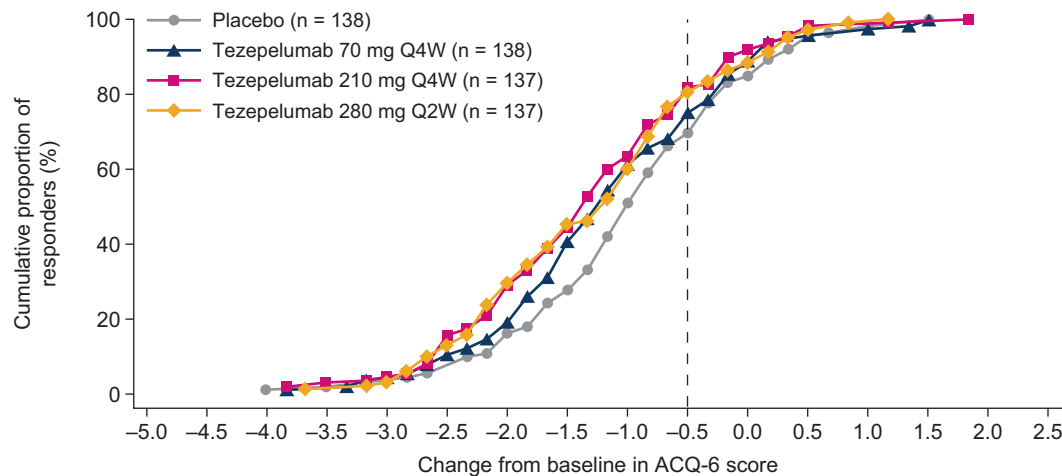


Figure 1. Cumulative proportion of ACQ-6 responders at week 50. Response was defined as a reduction from baseline in the ACQ-6 score of greater than or equal to 0.5 (marked by the reference line). ACQ-6, Asthma Control Questionnaire 6; Q2W, every 2 weeks; Q4W, every 4 weeks.

generalized estimating equations model for repeated-measures binary data with treatment group, visit, treatment-by-visit interaction, baseline blood eosinophil count (≥ 250 cells/ μL or < 250 cells/ μL), baseline ICS dose level (medium or high), and baseline score for the relevant questionnaire (ACQ-6 or AQLQ(S)+12) as fixed effects. The AQLQ(S)+12 responder analysis was quantified using overall scores only. Descriptive statistics (n, %) were used to report the proportions of responders or patients whose asthma was well-controlled, partially controlled, or uncontrolled. In addition, a plot showing the cumulative proportion of responders at week 50, week 48, and week 52 was used to characterize the distribution of changes from baseline in ACQ-6, AQLQ(S)+12, and Asthma Daily Diary scores, respectively.

A Cox proportional-hazards model was fitted to summarize time to first well-controlled or partially-controlled asthma for more than 50 weeks (as hazard ratio with 95% confidence interval [CI]). Treatment group, baseline blood eosinophil count (≥ 250 cells/ μL or

< 250 cells/ μL), and baseline ICS dose level (medium or high) were included as covariates in the model. The analysis compared each tezepelumab treatment group with the placebo group separately. A Kaplan–Meier plot was produced to visualize the time (in days) to first partially- or well-controlled asthma for more than 50 weeks.

All analyses were conducted without control of type I error; as such, *P* values are not presented.

Results

A total of 550 patients underwent randomization: 138 were assigned to tezepelumab 70 mg Q4W, 137 to tezepelumab 210 mg Q4W, 137 to tezepelumab 280 mg Q2W, and 138 to placebo Q2W.¹³ Patient demographics and clinical characteristics at baseline have been reported previously, and were similar among the 4 treatment groups.¹³ Baseline mean (standard deviation [SD]) ACQ-6 scores were 2.66 (0.69) and 2.69 (0.77) for placebo and pooled

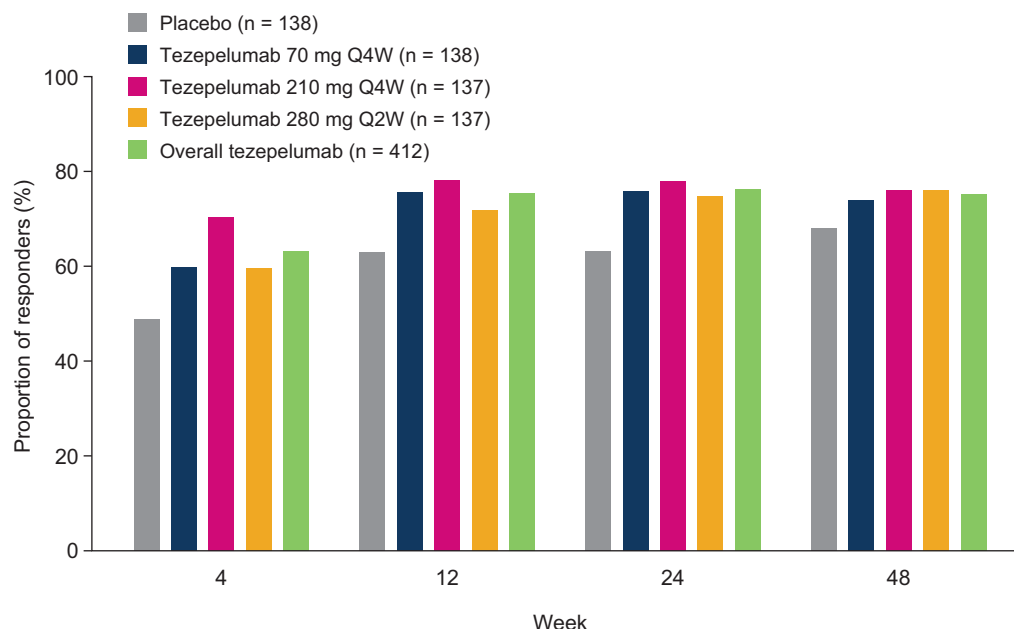


Figure 2. Proportion of ACQ-6 responders at key visits. Response was defined as a reduction from baseline in the ACQ-6 score of greater than or equal to 0.5. ACQ-6, Asthma Control Questionnaire 6; Q2W, every 2 weeks; Q4W, every 4 weeks.

Table 1
ACQ-6 Responders at Week 50

Subgroup	Placebo (n = 138)	Tezepelumab 70 mg Q4W (n = 138)	Tezepelumab 210 mg Q4W (n = 137)	Tezepelumab 280 mg Q2W (n = 137)	Overall tezepelumab (n = 412)
Overall Patients in analysis, n	112	116	110	102	328
Responders, ^a n (%)	78 (69.6)	87 (75.0)	90 (81.8)	82 (80.4)	259 (79.0)
Odds ratio (95% CI)		1.40 (0.79–2.51)	1.94 (1.08–3.47)	1.86 (1.03–3.36)	1.71 (1.08–2.69)

Abbreviations: ACQ-6, Asthma Control Questionnaire 6; CI, confidence interval; Q2W, every 2 weeks; Q4W, every 4 weeks.

^aResponder is defined as a change from baseline in ACQ-6 score of greater than or equal to –0.5. ACQ-6 score was calculated as the unweighted mean of the responses to the 6 questions. If any responses were missing, the ACQ-6 score was not calculated.

tezepelumab groups, respectively.¹³ Baseline mean (SD) AQLQ(S)+12 overall scores were 4.09 (0.87) and 4.15 (0.92) for placebo and pooled tezepelumab groups, respectively.¹³ Baseline mean (SD) Asthma Daily Diary scores were 1.70 (0.59), 1.67 (0.62), 1.74 (0.57) 1.67 (0.60) and 1.69 (0.60) for placebo and tezepelumab 70 mg, 210 mg, 280 mg and pooled groups, respectively.

Asthma Control Questionnaire-6

The proportion of ACQ-6 responders (reduction of ≥ 0.5 in ACQ-6 total score) at week 50 (Fig 1) and at key visits (weeks 4, 12, 24, and 48) was higher in all tezepelumab groups than in the placebo group (Fig 2); 75.0%, 81.8%, and 80.4% of patients who received tezepelumab 70 mg, 210 mg, and 280 mg, respectively, were responders at week 50, compared with 69.6% of patients who received placebo. Patients treated with tezepelumab 210 mg Q4W or 280 mg Q2W were more likely to be ACQ-6 responders than those treated with placebo: the ORs (95% CI) were 1.94 (1.08–3.47) and 1.86 (1.03–3.36), respectively (Table 1).

At week 50, the combined proportions of patients with well-controlled or partially controlled asthma (mean ACQ-6 score of ≤ 0.75 or >0.75 – <1.5 , respectively) were numerically higher in all tezepelumab treatment groups than in the placebo group (Fig 3). Treatment with tezepelumab reduced the median time taken to achieve the first record of well-controlled or partially-controlled asthma compared with placebo (70 days [tezepelumab 210 mg Q4W] vs 120 days [placebo]) (Fig 4).

Asthma Quality of Life Questionnaire (Standardized) for Patients Aged 12 Years or Older

The proportion of AQLQ(S)+12 responders (increase in overall AQLQ(S)+12 score of ≥ 0.5) was consistently higher across all tezepelumab dose groups at week 48 (Fig 5) and at key visits (weeks 4, 12, 24, and 48) than in the placebo group (Fig 6). At week 48, the proportion of AQLQ(S)+12 responders was 71.8%, 76.3%, and 76.8% in the tezepelumab 70 mg, 210 mg, and 280 mg dose groups, respectively, compared with 63.8% in the placebo group. Patients treated with tezepelumab 210 mg Q4W or 280 mg Q2W were more likely to be AQLQ(S)+12 responders than those who received a placebo. The ORs (95% CI) were 1.96 (1.08–3.57) and 2.02 (1.11–3.67), respectively.

Asthma Daily Diary

At week 52, the cumulative proportion of Asthma Daily Diary responders (defined for the purpose of this analysis as patients with an improvement of 0.5–1 points in Asthma Daily Diary score) was generally higher in all tezepelumab dose groups than in the placebo group (Fig 7). The greatest differences in the proportion of Asthma Daily Diary responders between tezepelumab and placebo groups were observed among patients with an improvement from baseline in Asthma Daily Diary score of 0.5 to 1 points (Fig 7). When Asthma Daily Diary responders were defined as patients with at least 1-point improvement from baseline in the Asthma Daily Diary score at week 52, 28.6%, 36.2%, and 33.0% of patients in the tezepelumab

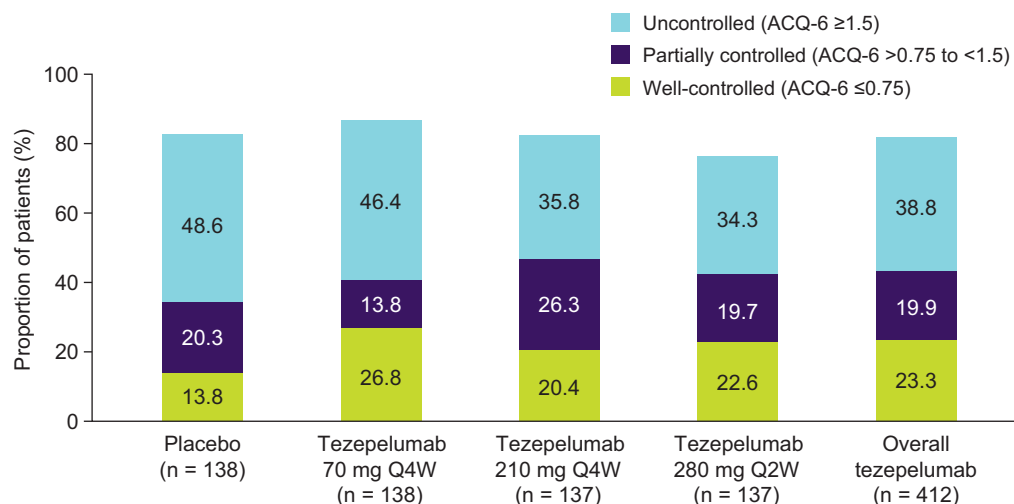


Figure 3. Proportion of patients with well-controlled, partially-controlled, or uncontrolled asthma at week 50. If any responses to ACQ-6 questions were missing, the ACQ-6 score was not calculated. ACQ-6, Asthma Control Questionnaire 6; Q2W, every 2 weeks; Q4W, every 4 weeks.

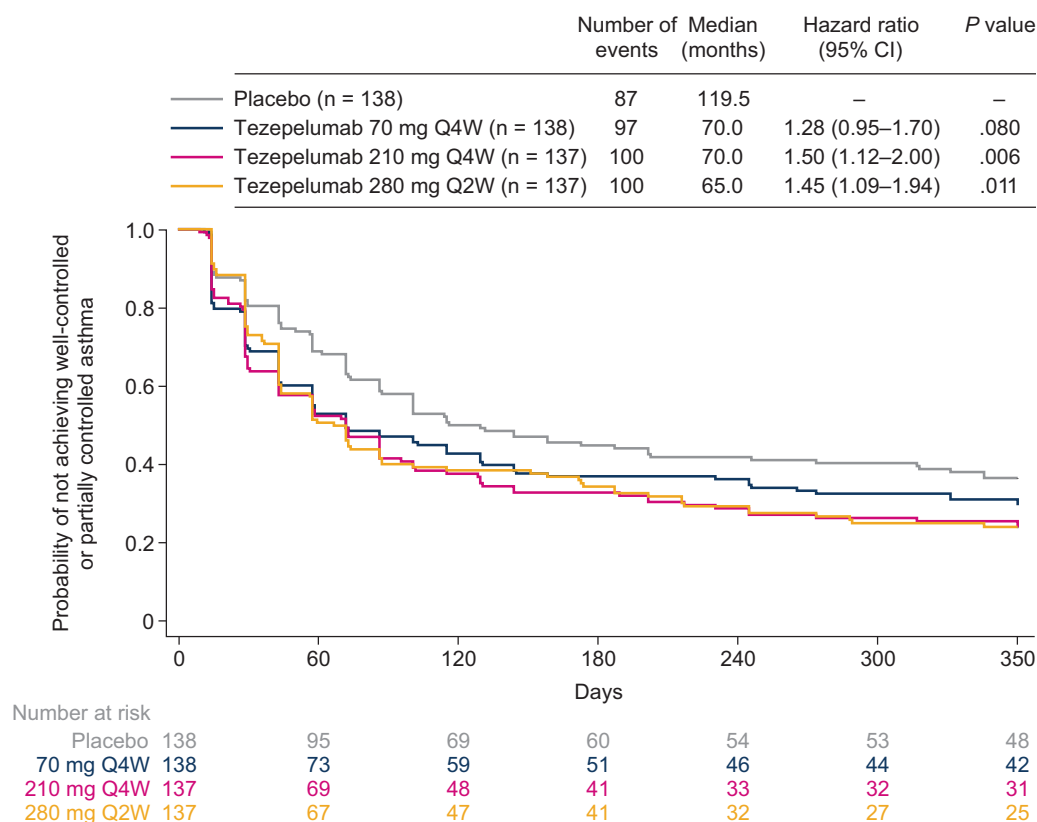


Figure 4. Kaplan–Meier estimator plot of time to first well-controlled or partially-controlled asthma (defined using ACQ-6 score). Well-controlled: ACQ-6 less than or equal to 0.75; partially-controlled: ACQ-6 greater than 0.75 to less than 1.5. ACQ-6, Asthma Control Questionnaire 6; Q2W, every 2 weeks; Q4W, every 4 weeks.

70 mg, 210 mg, and 280 mg dose groups were responders, respectively, compared with 23.7% of patients in the placebo group. When Asthma Daily Diary responders were defined as patients with an improvement of at least 0.5 points from baseline in Asthma Daily Diary score, 52.9%, 61.0%, and 60.2% of patients were responders in the tezepelumab 70 mg, 210 mg, and 280 mg groups, respectively, compared with 44.9% of patients in the placebo group.

Discussion

Despite standard-of-care treatment, a proportion of patients with severe asthma have uncontrolled disease.^{4,29} In a previous

analysis of PATHWAY phase 2b study data, tezepelumab improved PROs compared with placebo in patients with severe, uncontrolled asthma, as demonstrated by improvements from baseline to end of treatment in ACQ-6 and AQLQ(S)+12 scores. In this post hoc responder analysis, the proportion of responders, assessed using the ACQ-6 and AQLQ(S)+12, was higher in patients treated with tezepelumab than in those treated with placebo. In addition, treatment with tezepelumab reduced the median time to first well-controlled or partially-controlled asthma by approximately 40% compared with the placebo. Furthermore, a greater proportion of patients in the tezepelumab groups had improvements from baseline in the Asthma Daily

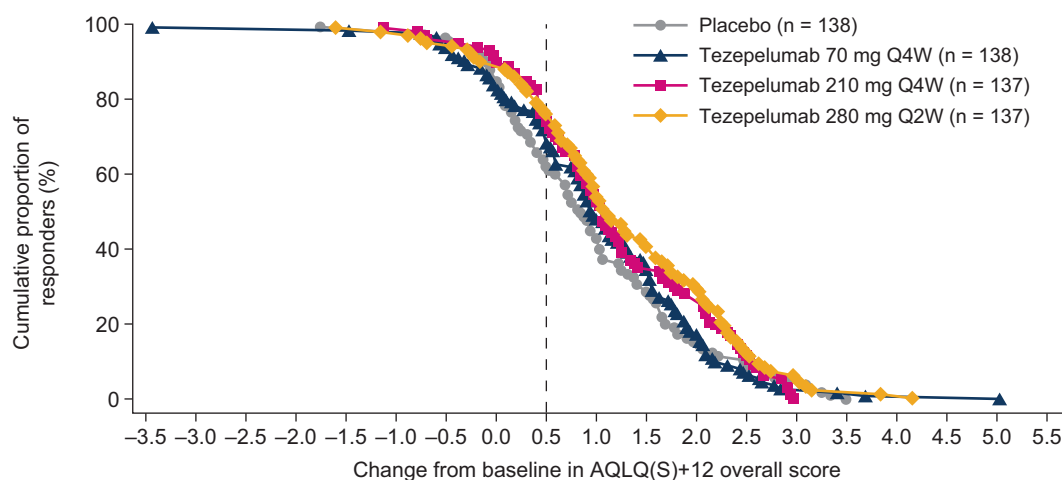


Figure 5. Cumulative proportion of AQLQ(S)+12 responders at week 48. The minimal clinically important difference is 0.5 (marked by the reference line). Response was defined as an increase from baseline in AQLQ(S)+12 score of greater than or equal to 0.5. AQLQ(S)+12, Asthma Quality of Life Questionnaire (standardized) for patients aged 12 years or older; Q2W, every 2 weeks; Q4W, every 4 weeks.

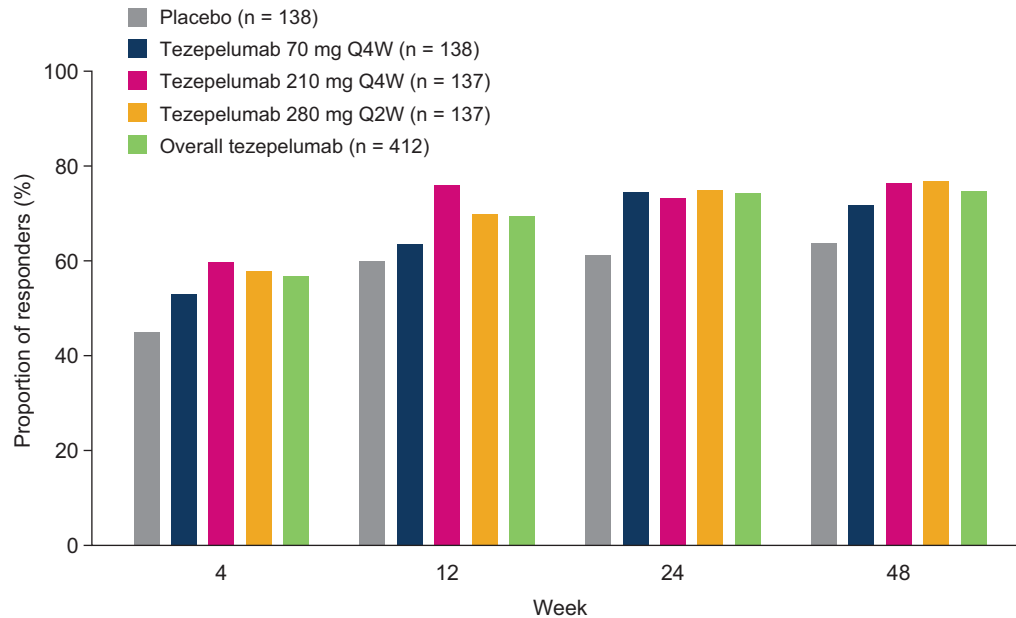


Figure 6. The proportion of AQLQ(S)+12 responders (defined as an increase from baseline of ≥ 0.5) at key visits. AQLQ(S)+12, Asthma Quality of Life Questionnaire (standardized) for patients aged 12 years or older; Q2W, every 2 weeks; Q4W, every 4 weeks.

Diary score compared with the placebo group. The most notable differences were observed when responders were defined as a score improvement of at least 0.5 or 1 point.

Although the descriptive characterization of symptom improvement was captured by the Asthma Daily Diary, it must be noted that the questionnaire has not yet been validated, and a minimum clinically important difference in the score has not yet been determined. Further studies are required to evaluate this and other PRO measures to ensure that they are fit for purpose to measure patient experiences in the clinical research setting and to yield meaningful outcomes for patients and health care providers.³⁰

PROs in clinical trials are often analyzed by calculating mean changes from baseline to end of treatment in a given measure or score. However, it can be challenging to determine whether these data are reflective of treatment benefit in clinical practice. The use of clinically meaningful cut-offs in the interpretation of PROs data allows for quantification of the proportion of patients who

benefited from (or responded to) a given treatment and is also important in understanding the clinical relevance of trial outcomes. Hence, the use of responder analyses in the interpretation of clinical trial data is recommended by regulatory bodies.²³

The overall proportion of responders in the placebo group was high but comparable with observations from studies of other biologic treatments for asthma, in which the proportions of placebo group patients achieving clinically meaningful improvements in ACQ-6 and AQLQ(S)+12 scores were 61%–78% and 70%–77%, respectively.^{31–34} It can be hypothesized that the high proportion of placebo group responders in these studies may be a result of increased adherence to standard-of-care treatments while participating in the studies. Additionally, several studies have demonstrated that the perceived benefits of clinical trial enrollment from the patient's perspective can induce a positive response to placebo treatment.^{35,36}

An ongoing phase 3 study (NAVIGATOR, [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03347279) identifier: NCT03347279) will further investigate the effect of

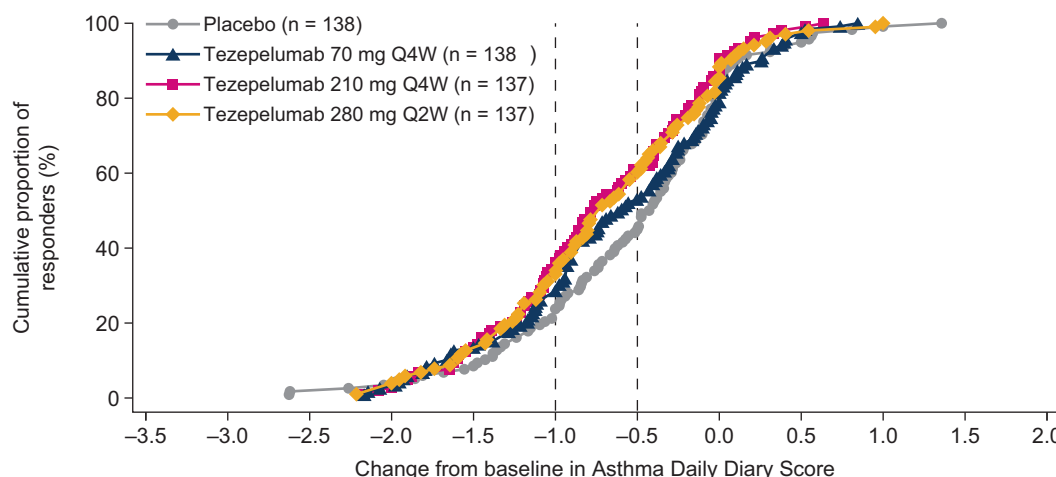


Figure 7. Cumulative proportion of Asthma Daily Diary responders at week 52. The dotted black lines indicate cut-offs in which the highest difference in responder proportion is observed. Q2W, every 2 weeks; Q4W, every 4 weeks.

tezepelumab treatment using PROs, including daily asthma symptom scores, health status, and HRQoL, in a larger study population than that of PATHWAY.

In this post hoc analysis of data from the PATHWAY phase 2b study, treatment with tezepelumab resulted in clinically meaningful improvements in asthma control, HRQoL, and daily asthma symptoms in patients with severe, uncontrolled asthma. These data provide additional evidence that blocking TSLP with tezepelumab is an effective strategy for the treatment of severe, uncontrolled asthma and further support the benefits of tezepelumab in this patient population.

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