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ORIGINAL RESEARCH

Efficacy of Tezepelumab in Patients with Severe, Uncontrolled Asthma with and without Nasal Polyposis: A *Post Hoc* Analysis of the Phase 2b PATHWAY Study

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Background: Tezepelumab is a human monoclonal antibody that blocks thymic stromal lymphopoietin, an epithelial cytokine implicated in asthma pathogenesis, from binding to its heterodimeric receptor. In the phase 2b PATHWAY study, tezepelumab significantly reduced annualized asthma exacerbation rates (AAERs) versus placebo, irrespective of baseline disease characteristics, and improved lung function and symptom control, in adults with severe, uncontrolled asthma. This *post hoc* analysis assessed the efficacy of tezepelumab in adults with severe, uncontrolled asthma with and without nasal polyposis (NP).

Methods: In this *post hoc* analysis of the PATHWAY study (NCT02054130), participants (N=550) were randomized 1:1:1:1 to receive subcutaneous tezepelumab 70 mg every 4 weeks (Q4W), 210 mg Q4W or 280 mg every 2 weeks (Q2W), or placebo Q2W, for 52 weeks. The AAER over 52 weeks and the change from baseline to week 52 in blood eosinophil count, fractional exhaled nitric oxide (FeNO) levels and serum levels of interleukin (IL)-5 and IL-13 with tezepelumab 210 mg (the phase 3 dose) and placebo were analyzed in patients grouped by self-reported presence (NP+) or absence (NP−) of NP at screening.

Results: At baseline, NP+ patients had higher blood eosinophil counts, higher FeNO levels and higher serum IL-5 and IL-13 levels than NP− patients. Tezepelumab 210 mg reduced the AAER versus placebo to a similar extent in both NP+ and NP− patients (NP+, 75% [95% confidence interval (CI): 15, 93], n=23; NP−, 73% [95% CI: 47, 86], n=112). Patients treated with tezepelumab 210 mg demonstrated greater reductions in blood eosinophil count and levels of FeNO, IL-5 and IL-13 than placebo-treated patients, irrespective of NP status.

Discussion: Tezepelumab reduced exacerbations and reduced type 2 inflammatory biomarkers in patients with and those without NP, supporting its efficacy in a broad population of patients with severe asthma.

Keywords: asthma, biomarkers, nasal polyps, sinusitis, tezepelumab, thymic stromal lymphopoietin

Introduction

Nasal polyposis (NP), the presence of benign growths of inflamed tissue in the nasal cavity, is found in a subset of patients with chronic rhinosinusitis.[1] Many of the histological and inflammatory features present in the upper airway in chronic rhinosinusitis with nasal polyposis (CRSwNP), such as eosinophilic inflammation and tissue remodeling, are similar to those present in the lower airway in asthma.[2,3]

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CRSwNP and asthma are common comorbidities of one another. The prevalence of CRSwNP in patients with asthma is approximately 7%,[4] rising as high as 35–45% in those with severe asthma,[5,6] while approximately 20–60% of patients with CRSwNP have asthma.[7] Furthermore, asthma and NP may coexist in patients with aspirin-exacerbated respiratory disease.[8] Individuals who have both asthma and CRSwNP tend to have a severe form of both diseases.[9,10] Patients with asthma and NP have more severe lower airway obstruction, higher levels of lower airway inflammation and poorer asthma control than those without NP.[3] Consequently, these patients have a high disease burden, which has a marked impact on their health-related quality of life.[3]

Severe asthma and severe CRSwNP are typically associated with type 2 (T2) inflammation, characterized by elevated levels of biomarkers including but not limited to blood eosinophils and serum interleukin (IL)-5.[11,12] Consistent with a shared pathophysiology between asthma and CRSwNP, biologic therapies targeting T2 inflammation, which are approved for the treatment of severe asthma (eg benralizumab, mepolizumab, omalizumab, dupilumab), have demonstrated equivalent or greater clinical efficacy in patients with asthma and comorbid NP than in those without NP.[13–17] However, currently available biologics are incompletely efficacious, as they reduce asthma exacerbation rates in study populations (including subgroups with NP) by approximately 50%.[18–20]

Thymic stromal lymphopoietin (TSLP) is an epithelial-derived cytokine that is produced in response to airborne stimuli, such as allergens, viruses and diesel exhaust, and plays a key role in the initiation and persistence of airway inflammation by activating multiple downstream inflammatory pathways.[21–25] TSLP expression is elevated in the airways of patients with asthma compared with healthy individuals,[23,26,27] and in nasal polyp tissue from patients with CRSwNP compared with healthy sinus tissue or that from patients with CRS without NP.[28,29] The presence of TSLP correlates with the number of eosinophils in nasal polyp tissue,[28] and the activity of TSLP in polyp tissue is believed to be sufficient to trigger an inflammatory response.[29] In patients with asthma, the level of TSLP expression in airway tissue has been shown to correlate with airway obstruction and disease severity.[23,26]

Tezepelumab is a human monoclonal antibody (immunoglobulin [Ig] G2λ) that binds specifically to TSLP, preventing its interaction with its heterodimeric receptor.[30,31] In the phase 2b PATHWAY study (ClinicalTrials.gov identifier: NCT02054130) in adults with severe, uncontrolled asthma, tezepelumab significantly reduced annualized asthma exacerbation rates (AAERs) by up to 71% versus placebo, irrespective of baseline blood eosinophil count, fractional exhaled nitric oxide (FeNO) levels or allergic status.[31,32] Reductions in exacerbations versus placebo were also observed across all seasons.[33] Here, we report a *post hoc* analysis of PATHWAY evaluating the effect of tezepelumab in patients with severe, uncontrolled asthma with and without self-reported NP.

Methods

PATHWAY was a phase 2b, multicenter, randomized, double-blind, placebo-controlled study. The full design and inclusion and exclusion criteria have been described previously.[31] Eligible patients were current non-smokers (a smoking history of <10 pack years who must have stopped smoking for ≥6 months), 18–75 years old, with severe, uncontrolled asthma 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_2 agonist. Patients were required to have a history of at least two asthma exacerbations that led to systemic corticosteroid treatment, or at least one severe exacerbation that resulted in hospitalization, in the 12 months before study entry. Patients were also required to have an Asthma Control Questionnaire-6 score greater than 1.5 (indicative of uncontrolled asthma) on two separate occasions during screening. Patients with any clinically important pulmonary disease other than asthma were excluded.

Before randomization, patients were stratified according to study site (Japanese or non-Japanese) and subsequently by blood eosinophil count (≥250 cells/μL or <250 cells/μL) and ICS dose level (medium or high). Patients were randomized to receive subcutaneous tezepelumab 70 mg every 4 weeks (Q4W), 210 mg Q4W or 280 mg every 2 weeks (Q2W), or placebo Q2W, for 52 weeks. Patients who were randomized to a Q4W dosing regimen received placebo on alternate weeks to maintain blinding. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. Approvals from Copernicus Group central Institutional Review Board (Durham, NC, USA) and local independent ethics committees were obtained, and all

patients provided written informed consent in accordance with local requirements.

This *post hoc* analysis evaluated the effect of tezepelumab in patients with and those without self-reported NP in the PATHWAY study. The primary efficacy endpoint in PATHWAY was the AAER, defined as the total number of asthma exacerbations divided by the total person-year follow-up time. For this analysis, treatment differences between tezepelumab 210 mg (the dose being used in ongoing phase 3 trials) and placebo were analyzed in patients grouped according to history of NP: NP+, that is, participants with any self-reported medical history of NP at screening, and NP−. AAER with 95% confidence intervals (CIs) for tezepelumab 210 mg and placebo, and rate ratios with 95% CIs for the difference between treatments, were estimated within NP subgroups using a negative binomial regression model, with treatment group, baseline blood eosinophil count (≥250 cells/μL or <250 cells/μL) and baseline ICS dose level (medium or high) included as covariates.

Patients with severe asthma, particularly those with comorbid CRSwNP, are likely to have disease characterized by predominantly T2 inflammation. Therefore, the following T2 biomarkers were assessed at baseline and post-baseline timepoints up to week 52: blood eosinophil counts, by standard hematology analyzer and manual differentials; FeNO levels, by breath test; and serum levels of cytokines, IL-5 and IL-13, quantified using a high-sensitivity sandwiched immunoassay (Simoa, Quanterix, Lexington, MA, USA). Changes from baseline in these parameters were determined for tezepelumab 210 mg Q4W and placebo within NP subgroups using a mixed model for repeated measures analysis with the following covariates: treatment group; baseline blood eosinophil count (≥250 cells/μL or <250 cells/μL); baseline ICS dose level (medium or high); baseline biomarker level; visit number; NP status (NP+ or NP–); and treatment-by-visit-number-by-NP-status interaction (as well as lower-order interaction terms including these factors). Least-squares (LS) means with standard error, and LS mean differences between tezepelumab 210 mg Q4W and placebo with 95% CIs, were generated for each parameter over time.

All analyses were conducted without control of type 1 error; as such, *p* values are not presented.

Results

Baseline Characteristics

Overall, 550 patients were randomized to receive tezepelumab (70 mg Q4W, 210 mg Q4W or 280 mg Q2W) or placebo Q2W (n=138). In total, 18.7% of patients had previously smoked and the median duration of smoking was 10 years. NP+ patients comprised 15.2% of the study population (NP+, n=82; NP−, n=458; no NP status, n=10) (Figure S1). Similar baseline demographics were seen across patients with and those without NP (Table 1). However, differences in baseline levels of T2 biomarkers were observed between the two groups. Blood eosinophil counts, FeNO levels and serum IL-5 and IL-13 levels at baseline were higher in NP+ versus NP− patients, with a greater proportion of NP+ patients than NP− patients having blood eosinophil counts of ≥300 cells/μL (Table 1). At baseline, a higher proportion of NP+ patients than NP− patients were taking high-dose ICS and maintenance oral corticosteroid (OCS) and had a history of three or more exacerbations in the previous year (Table 1).

Exacerbation Rates

Among patients who received placebo, the AAER over 52 weeks was higher in NP+ patients than in NP− patients (NP+, 1.08 [95% CI: 0.65, 1.68]; NP−, 0.68 [95% CI: 0.54, 0.85]) (Figure 1). The AAER was reduced by tezepelumab 210 mg treatment versus placebo to a similar extent in both NP+ and NP− patients (NP+, 75% [95% CI: 15, 93], n=23; NP−, 73% [95% CI: 47, 86], n=112) (Figure 1). In both NP+ and NP− patients, a higher proportion of patients in the placebo group experienced one, two or at least three exacerbations than in the tezepelumab 210 mg group (Table 2).

Biomarker Changes

Blood eosinophil counts and levels of FeNO and serum IL-5 and IL-13 decreased in patients who received tezepelumab 210 mg versus placebo, irrespective of NP status (Figure 2). Differences between tezepelumab and placebo were seen as early as week 4 and were sustained until week 52 (Figure 2).

Discussion

This *post hoc* analysis of the PATHWAY study population showed that patients with severe asthma and NP had higher levels of T2 inflammatory biomarkers including blood eosinophils, FeNO and serum IL-5 and IL-13, and more severe disease, than those without NP. In addition, this analysis demonstrated that tezepelumab reduced the AAER to a similar extent in patients with and those without NP and reduced levels of T2 inflammatory biomarkers in both NP subgroups.

Table 1 Baseline Demographics and Clinical Characteristics of Patients with and Those Without NP

	NP+			NP−		
	Placebo (n=18)	**Tezepelumab 210 mg Q4W (n=23)**	**Overall[a] (n=82)**	**Placebo (n=117)**	**Tezepelumab 210 mg Q4W (n=112)**	**Overall[a] (n=458)**
Age (years), mean±SD	55.9±9.2	51.3±12.7	52.2±11.2	51.9±11.8	53.1±12.6	51.5±12.4
Women, n (%)	10 (55.6)	15 (65.2)	49 (59.8)	82 (70.1)	70 (62.5)	304 (66.4)
Central blood eosinophil count						
Mean±SD (cells/μL)	472.8±350.2	470.4±262.0	537.7±367.8	367.5±327.0	346.1±365.9	342.3±345.3
Median (cells/μL)	320	440	435	260	260	250
High (≥300 cells/μL), n (%)	11 (61.1)	17 (73.9)	61 (74.4)	59 (50.4)	51 (45.5)	205 (44.8)
ICS dose, n (%)						
Medium[b]	6 (33.3)	10 (43.5)	32 (39.0)	65 (55.6)	60 (53.4)	243 (53.1)
High[c]	12 (66.7)	13 (56.6)	50 (61.0)	52 (44.4)	52 (46.4)	215 (46.9)
Maintenance OCS use, n (%)	5 (27.8)	3 (13.0)	17 (20.7)	9 (7.7)	6 (5.4)	34 (7.4)
Number of exacerbations in previous 12 months, n (%)						
1 or 2	11 (61.1)	17 (73.9)	59 (72.0)	96 (82.1)	86 (76.8)	372 (81.2)
≥3	7 (38.9)	6 (26.1)	23 (28.0)	21 (17.9)	26 (23.2)	86 (18.8)
Pre-BD FEV_1 (L), mean±SD	2.00±0.60	1.95±0.73	1.97±0.67	1.80±0.59	1.81±0.55	1.83±0.59
ACQ-6 score, mean±SD	2.51±0.91	2.85±0.72	2.65±0.79	2.67±0.65	2.69±0.78	2.70±0.74
FeNO (ppb), mean±SD	39.91±32.81	48.02±39.03	48.14±49.70	37.29±40.84	28.20±26.68	32.15±35.94
FeNO high (≥median[d]), n (%)	10 (55.6)	17 (73.9)	56 (69.1)	59 (50.9)	50 (45.5)	214 (47.3)
Serum IL-5[e]						
N	18	22	59	113	104	324
Mean±SD (ng/L)	1.19±1.04	1.84±1.84	1.87±1.64	1.13±1.88	1.88±8.03	1.26±4.72
Median (ng/L)	0.92	1.08	1.20	0.57	0.60	0.53
Serum IL-13						
n	14	13	40	86	77	253
Mean±SD (ng/L)	0.06±0.05	0.14±0.19	0.12±0.13	0.06±0.08	0.05±0.06	0.06±0.11
Median (ng/L)	0.04	0.06	0.08	0.04	0.03	0.03

Notes: [a]Overall includes placebo and tezepelumab 70 mg, 210 mg and 280 mg dose groups. [b]250–500 μg/day fluticasone dry powder inhaler or equivalent. [c]>500 μg/day fluticasone dry powder inhaler or equivalent. [d]Median FeNO level, 22.0 ppb. [e]IL-5 was not measured in the 70 mg dose group. Baseline was defined as day 1 (pre-administration of study drug); in the case of missing data, the last available value prior to day 1 was used.

Abbreviations: ACQ-6, Asthma Control Questionnaire (6-item); BD, bronchodilator; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; IL, interleukin; NP, nasal polyposis; OCS, oral corticosteroids; Q4W, every 4 weeks; SD, standard deviation.

We observed that approximately 15% of patients in PATHWAY had NP, a lower proportion than has been reported in some other severe asthma studies (35–45%).[5,6] This may be because NP was self-reported in PATHWAY, whereas the presence of NP was confirmed endoscopically in the other studies. At baseline, PATHWAY participants with NP appeared to have more severe asthma than those without NP, as shown by higher proportions of the former group using high-dose ICS, using maintenance OCS and having a history of at least three exacerbations in the previous year. However, we note that the small number of NP+ patients in this analysis (n=82) limits our ability to draw firm conclusions around disease severity in the two groups. Patients with NP also had higher levels of T2 inflammatory cytokines and biomarkers at baseline than those without NP. Furthermore, across the course of the study, placebo-treated patients with NP had a higher

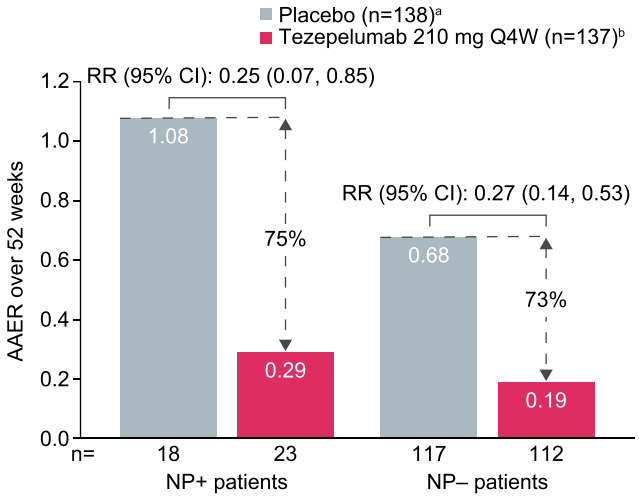

Figure 1 AAER over 52 weeks in patients with and those without NP. [a]Three patients in the placebo group had no NP status. [b]Two patients in the tezepelumab 210 mg dose group had no NP status. Percentage reductions relative to the placebo group were calculated from RRs.

Abbreviations: AAER, annualized asthma exacerbation rate; CI, confidence interval; NP, nasal polyposis; Q4W, every 4 weeks; RR, rate ratio.

AAER than those without NP. These findings are consistent with reports from the literature.[3,9,12] For example, Bilodeau et al. showed that, among patients with asthma, those with comorbid CRSwNP had more poorly controlled asthma, increased airway obstruction and more marked lower airway inflammation than those without CRSwNP.[3]

In our analysis, the AAER was reduced by tezepelumab 210 mg treatment versus placebo to a similar extent in both NP+ and NP− patients with severe asthma (75% and 73%, respectively); the magnitude of the reduction in AAER was similar to that seen with the same dose in the overall PATHWAY population.[31] This is in contrast with findings with anti-IL-5 treatment. A *post hoc* analysis of two phase 3 benralizumab trials found a greater reduction in exacerbations with active treatment in patients with both severe, uncontrolled, eosinophilic asthma (blood eosinophil count ≥300 cells/μL) and comorbid NP versus those without NP (50% vs 32%, respectively).[34] In another study of anti-IL-5 treatment, reslizumab was found to reduce exacerbations versus placebo to a greater extent in patients with uncontrolled, eosinophilic asthma and comorbid NP than in those without NP (83% vs 44%, respectively).[35] A meta-analysis of two phase 3 studies of mepolizumab in patients with severe, eosinophilic asthma also found that the annual rate of clinically significant exacerbations was reduced versus placebo by 59% in patients with comorbid NP and by 48% in those without comorbid NP.[36] It is noted that the study design and study populations varied between the PATHWAY trial and trials of other biologics, which limits the strength of indirect comparisons of these treatments.

Because T2 inflammation is expected to be elevated in both asthma and CRSwNP, we examined T2 cytokines and biomarker levels in the context of CRSwNP comorbidity. As observed in the overall PATHWAY population,[32,37] serum IL-5 and IL-13 levels, in addition to their respective downstream biomarkers, blood eosinophil counts and FeNO levels, were reduced by tezepelumab treatment versus placebo in this analysis. Interestingly, there were no notable differences in the speed or magnitude of the biomarker reductions between the NP subgroups. The positive effects of tezepelumab on T2 cytokines and biomarkers suggest that blocking TSLP has an impact on multiple key downstream inflammatory mediators and that tezepelumab may have efficacy in patients with CRSwNP. Biomarker data from patients with CRSwNP treated with dupilumab demonstrated a decrease in local and circulating T2-related molecules in response to treatment, including tissue IL-13[38] and nasal IL-5 levels[39] as well as circulating levels of total IgE and thymus and activation regulated chemokine.[38] A transient but non-significant increase in blood eosinophilia was also reported with dupilumab.[38]

Table 2 Proportions of Patients Who Experienced 0, 1, 2 or ≥3 Exacerbations Over 52 Weeks

	NP+		NP–	
	Placebo (n=18)	Tezepelumab 210 mg Q4W (n=23)	Placebo (n=117)	Tezepelumab 210 mg Q4W (n=112)
Number of exacerbations, n (%)				
0	9 (50.0)	19 (82.6)	84 (71.8)	95 (84.8)
1	3 (16.7)	3 (13.0)	14 (12.0)	14 (12.5)
2	3 (16.7)	0 (0.0)	7 (6.0)	3 (2.7)
≥3	3 (16.7)	1 (4.3)	12 (10.3)	0 (0.0)

Abbreviations: NP, nasal polyposis; Q4W, every 4 weeks.

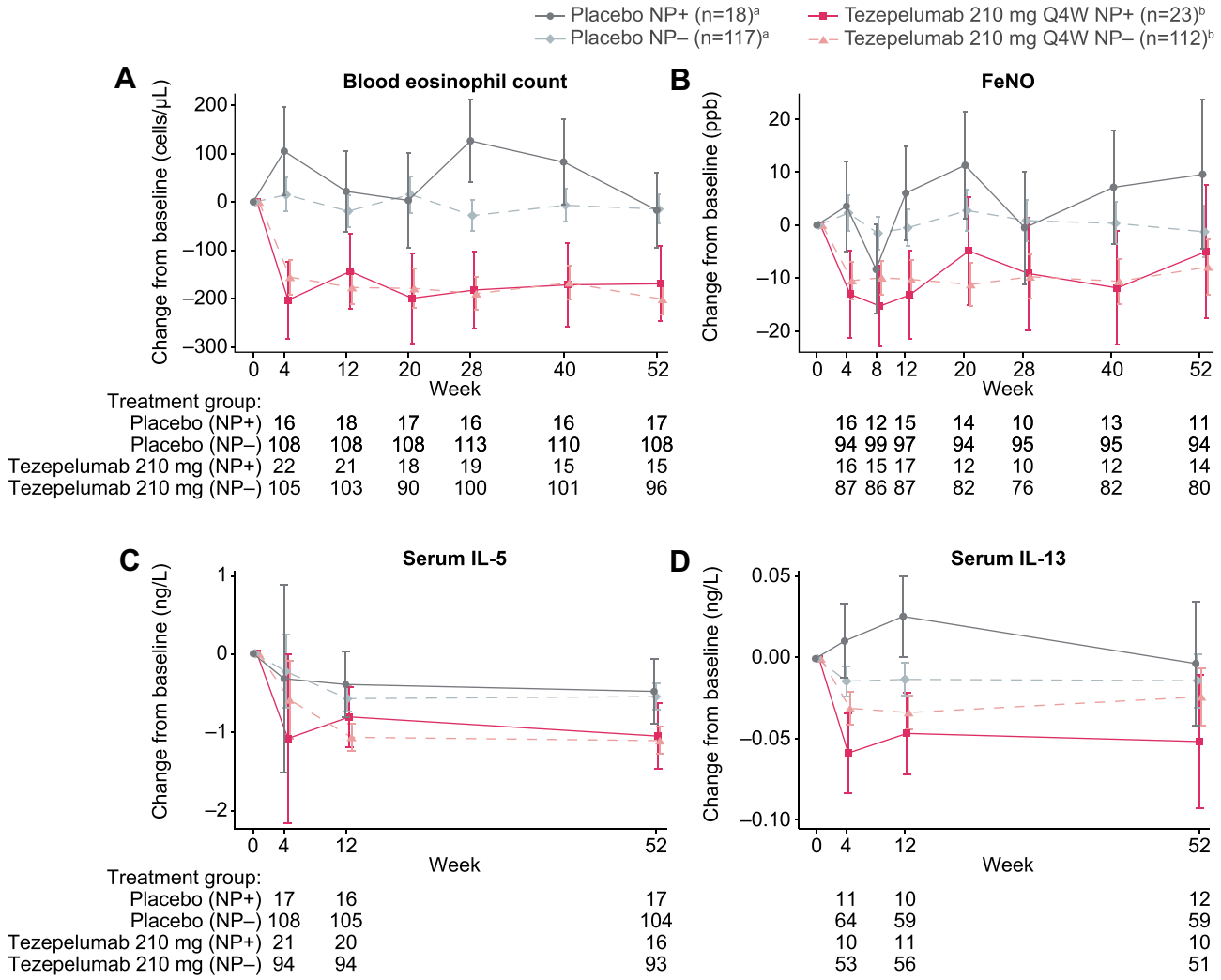

Figure 2 Change from baseline in (**A**) blood eosinophil count, (**B**) FeNO, (**C**) serum IL-5 and (**D**) serum IL-13, over 52 weeks by NP status. [a]Three patients in the placebo group had no NP status. [b]Two patients in the tezepelumab 210 mg dose group had no NP status. Data are least-squares means with 95% CI. Numbers underneath the graph represent the number of patients at each time point.

Abbreviations: CI, confidence interval; FeNO, fractional exhaled nitric oxide; IL, interleukin; NP, nasal polyposis; Q4W, every 4 weeks.

Our analysis has some limitations. First, NP status was self-reported by the participants rather than being confirmed clinically. This may have resulted in the inclusion of patients with NP in the non-NP group, which could have affected the study results. Inclusion of patients with a clinically confirmed diagnosis of NP only would have allowed for more accurate assessment of the efficacy of tezepelumab in this patient population. Second, there were only a small number of NP + patients, leading to greater uncertainty in estimates of treatment effect in this subgroup. In particular, regarding the AAER, not all participants may have experienced an exacerbation during the study period. There was also a large volume of missing data for serum IL-13. The efficacy of tezepelumab in patients with NP will be assessed further in the phase 3 NAVIGATOR study (ClinicalTrials.gov identifier: NCT03347279), which includes a considerably larger patient population than PATHWAY. Finally, no NP-specific outcome measures were assessed in PATHWAY, although T2 biomarker levels are relevant to this condition. Outcomes assessed in the phase 3 NAVIGATOR study will include the Sino-Nasal Outcomes Test, which is an NP-specific measure of health-related quality of life and will provide additional, relevant data on the effect of tezepelumab in patients with severe asthma and NP.[40]

Conclusions

In this *post hoc* analysis, we observed that patients with NP had more severe asthma and higher levels of T2 inflammatory biomarkers than those without NP. Tezepelumab reduced exacerbations and reduced T2

inflammatory cytokines and biomarkers in patients with and those without NP, supporting its efficacy in a broad population of patients with severe asthma.

Abbreviations

AAER, annualized asthma exacerbation rate; CI, confidence interval; CRS, chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyposis; DPI, dry powder inhaler; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; Ig, immunoglobulin; IL, interleukin; LS, least-squares; NP, nasal polyposis; OCS, oral corticosteroid; Q2W, every 2 weeks; Q4W, every 4 weeks; T2, type 2; TSLP, thymic stromal lymphopoietin.

Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Ethics Approval and Informed Consent

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Conference for Harmonisation 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.

Consent for Publication

Not applicable.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

CE, KS, ÅH and GC are employees of AstraZeneca and may have stock options in AstraZeneca. JC received grants from AstraZeneca during the conduct of the study, and has received grants and personal fees from Genentech, personal fees from Teva Pharmaceuticals, grants from Sanofi and personal fees from Vectura Group outside of the submitted work. JRP is an employee of Amgen Inc., and holds stock and stock options in Amgen Inc. JRP has patents US20180296669A1 and WO201819479A1, Treatment of Asthma with Anti-TSLP Antibody, pending. The authors report no other conflicts of interest in this work.

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