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BRIEF REPORT

Effect of Tezepelumab on Sino-Nasal Outcome Test (SNOT)-22 Domain and Symptom-Specific Scores in Patients with Severe, Uncontrolled Asthma and a History of Chronic Rhinosinusitis with Nasal Polyps

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ABSTRACT

Introduction: Tezepelumab blocks the activity of thymic stromal lymphopoietin, an epithelial cytokine implicated in the pathogenesis of asthma and chronic rhinosinusitis with nasal polyps (CRSwNP). In a previous analysis, tezepelumab improved asthma and rhinosinusitis symptoms compared with placebo in patients with severe, uncontrolled asthma and a history of CRSwNP in the 2 years before randomization in the NAVIGATOR study. This post hoc analysis of patients with a CRSwNP diagnosis at any time before randomization in NAVIGATOR enabled domain and symptom-specific analyses of Sino-Nasal Outcome Test (SNOT)-22 outcomes.

Methods: Patients (aged 12–80 years) with severe, uncontrolled asthma were randomized to tezepelumab 210 mg or placebo subcutaneously every 4 weeks for 52 weeks. SNOT-22

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total, domain, and item scores were assessed in patients with a history of CRSwNP. Annualized asthma exacerbation rate (primary efficacy outcome), pre-bronchodilator forced expiratory volume in 1 s, and Asthma Control Questionnaire-6, Asthma Quality of Life Questionnaire (standardized) for patients 12 years and older, and Asthma Symptom Diary scores were also assessed in patients with and without a history of CRSwNP.

***Results*:** Of 1059 patients with severe asthma, 165 (15.6%) had a history of CRSwNP. Tezepelumab treatment resulted in sustained improvements versus placebo in SNOT-22 total score throughout the 52-week study period [least-squares mean difference (95% confidence interval) −11.08 (−17.80, −4.35)]. Tezepelumab improved all five SNOT-22 domain scores (sleep, nasal, function, ear/facial, and emotion) and the five SNOT-22 item scores of most clinical interest (decreased sense of smell/taste, nasal blockage, reduced productivity, waking up tired, and cough). Tezepelumab improved asthma-related clinical outcomes in patients with and without a history of CRSwNP.

***Conclusion*:** In patients with severe, uncontrolled asthma and a history of CRSwNP, tezepelumab improved rhinosinusitis symptoms across multiple domains, as well as asthma exacerbations, lung function, asthma control, and health-related quality of life.

***ClinicalTrials.gov Identifier*:** NCT03347279 (https://classic.clinicaltrials.gov/ct2/show/NCT03347279).

Keywords: Asthma; Biologic; Chronic rhinosinusitis; Nasal polyps; Sino-Nasal Outcome Test-22; Tezepelumab; Thymic stromal lymphopoietin

Key Summary Points

Why carry out this study?

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common respiratory comorbidity of severe asthma and has a significant impact on the health-related quality of life (HRQoL) of patients with both these diseases.

Tezepelumab, a human monoclonal antibody, has been found to improve both asthma and rhinosinusitis symptoms and HRQoL compared with placebo in patients with severe, uncontrolled asthma and a history of CRSwNP in the 2 years before randomization in the NAVIGATOR study.

This post hoc analysis extends these findings by evaluating the efficacy of tezepelumab in patients with a CRSwNP diagnosis reported at any time before randomization in the NAVIGATOR study. This larger study population aligns with those evaluated for other biologics and allowed a deeper analysis of domain and symptom-specific Sino-Nasal Outcome Test (SNOT)-22 outcomes.

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What was learned from the study?
Consistent with previous findings, the findings of this post hoc analysis demonstrated that tezepelumab improved rhinosinusitis symptoms compared with placebo in patients with severe, uncontrolled asthma and a history of CRSwNP.
Patients receiving tezepelumab showed sustained improvements in SNOT-22 total score and all five SNOT-22 domain scores throughout the 52-week study period compared with placebo. Tezepelumab also improved all five of the individual SNOT-22 symptom-specific item scores previously reported to be of most clinical importance.
Tezepelumab treatment also resulted in improvements in asthma exacerbations, lung function, asthma control, and asthma-related quality of life in patients with severe, uncontrolled asthma and a history of CRSwNP.

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease of the upper airway that is associated with significant morbidity, loss of smell, impaired quality of sleep, nasal congestion, and facial pressure [1]. The health-related quality of life (HRQoL) of patients with CRSwNP has been reported to be similar to that in patients with Parkinson's disease and congestive heart failure [2].

CRSwNP is a common respiratory comorbidity of severe asthma [3]. Individuals with both of these diseases tend to have more severe sinonasal symptoms, more extensive lower airway inflammation, impaired lung function, lower asthma symptom control, and a reduced HRQoL compared with those with asthma or CRSwNP alone [1]. Tezepelumab is a fully human monoclonal antibody (immunoglobulin [Ig]G2λ) that blocks the activity of thymic stromal lymphopoietin (TSLP), an epithelial cytokine that has been implicated in pathophysiological processes underlying asthma and CRSwNP [4–6]. In the NAVIGATOR study (NCT03347279), tezepelumab treatment significantly reduced the annualized asthma exacerbation rate (AAER) and improved lung function, asthma control, asthma symptoms, and HRQoL compared with placebo in patients with severe, uncontrolled asthma ($n=1059$) [7].

In a predefined exploratory analysis, tezepelumab improved rhinosinusitis symptoms in patients with severe, uncontrolled asthma and a history of CRSwNP in the 2 years before randomization in NAVIGATOR ($n=118$), as assessed using the Sino-Nasal Outcome Test (SNOT)-22 [8]. Patients with a history of CRSwNP remain at risk of disease recurrence, even after functional endoscopic sinus surgery, with recurrence rates ranging from 35% to 40% at 6 to 18 months to 66% at 10 years [9, 10]. Accordingly, the current post hoc analysis evaluated the efficacy of tezepelumab in the larger population of patients with a history of CRSwNP at any time before randomization in the NAVIGATOR study ($n=165$). This study population is closely aligned with those evaluated in studies of other biologics in patients with severe asthma and comorbid CRSwNP, including dupilumab, benralizumab, and mepolizumab [11–14]. The absolute and percentage changes from baseline in SNOT-22 total score are reported, which helps comparison with the data published for other biologics. In addition, the larger cohort of patients with a history of CRSwNP enabled a deeper analysis of the SNOT-22 clinical outcomes. Specifically, we report SNOT-22 outcomes by domain as well as changes in the five individual SNOT-22 symptom-specific item scores previously reported to be of most clinical interest [15].

METHODS

Study Design and Outcomes

NAVIGATOR was a phase 3, multicenter, randomized, double-blind, placebo-controlled study. Patients (aged 12–80 years) with severe, uncontrolled asthma were randomized (1:1) to receive tezepelumab 210 mg or placebo subcutaneously every 4 weeks for 52 weeks. Full study design

and eligibility criteria have been described previously [7].

This post hoc analysis evaluated the efficacy of tezepelumab in patients with and without a history of CRSwNP at any time before randomization in the NAVIGATOR study, regardless of severity or age at diagnosis. CRSwNP status was based on the reported presence or absence in a patient's respiratory disease history in their medical record of "nasal polyps" along with a "diagnosis of rhinitis" or "diagnosis of chronic sinusitis". No additional diagnostic testing or objective measurement of a patient's CRSwNP status was completed at baseline.

SNOT-22 scores were assessed in patients with a history of CRSwNP. The SNOT-22 items are categorized into the following five validated domains: ear/facial (four items), emotion (three items), function (three items), nasal (eight items), and sleep (four items) [16]. Changes from baseline in SNOT-22 total scores [range 0 (no problem) to 110 (problem as bad as it can be); minimal clinically important difference (MCID) 8.9] [17] and domain scores (range 0–5) were assessed at week 28 and week 52. In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), patients with moderate to severe, uncontrolled asthma and a history of comorbid chronic rhinosinusitis or CRSwNP rated "decreased sense of smell/taste" followed by "nasal blockage", "cough", "reduced productivity", and "waking up tired" as the five most clinically important SNOT-22 items affecting their health [15]. These five SNOT-22 item scores (range 0–5) were assessed in the current study at baseline, week 28, and week 52. The following asthma-related clinical outcomes were assessed in patients with and without a history of CRSwNP: AAER over 52 weeks and changes from baseline in pre-bronchodilator forced expiratory volume in 1 s (FEV_1; MCID 0.1 L) [18] and Asthma Control Questionnaire-6 [ACQ-6; range 0 (no impairment) to 6 (maximum impairment); MCID 0.5] [19], Asthma Quality of Life Questionnaire (standardized) for patients 12 years and older [AQLQ[S] + 12; range 1 (maximum impairment) to 7 (no impairment); MCID 0.5] [20], and Asthma Symptom Diary [ASD; range 0 (no symptoms) to 4 (worst possible symptoms); MCID 0.5] [21] scores. MCID values are provided for reference because they are relevant to the interpretation of changes from baseline.

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 were obtained from the Copernicus Central Institutional Review Board (Cary, NC, USA) and local independent ethics committees. All patients or their guardians provided written informed consent in accordance with local requirements.

Statistical Analyses

The statistical analyses for asthma-related clinical outcomes and SNOT-22 total and domain scores were as described previously [8]. All analyses are descriptive, with no type 1 error control; as such, *p* values are not presented. Estimates of the least-squares (LS) mean change from baseline to week 52 in SNOT-22 item scores were compared between treatment groups using a repeated measures model, with treatment group, region, age group, baseline SNOT-22 score, visit, and treatment-by-visit interaction as covariates. SAS 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analyses.

RESULTS

Baseline Demographics and Clinical Characteristics

In the NAVIGATOR study, 1061 patients were randomized, of whom 1059 received study treatment (tezepelumab, $n = 528$; placebo, $n = 531$); 165 (15.6%) had a history of CRSwNP (tezepelumab, $n = 90$; placebo, $n = 75$) and 894 (84.4%) did not (tezepelumab, $n = 438$; placebo, $n = 456$). Within each subgroup, baseline demographics and clinical characteristics were balanced between patients receiving tezepelumab and those receiving placebo (Table 1).

Compared with those without CRSwNP, patients with a history of CRSwNP were more likely to be male, were older at the time of asthma diagnosis, and were less likely to have

Table 1 Baseline demographics and clinical characteristics of patients with and without a history of CRSwNP in the NAVIGATOR study

Demographic/characteristic	History of CRSwNP			No history of CRSwNP		
	Placebo (*n* = 75)	Tezepelumab 210 mg Q4W (*n* = 90)	Overall (*n* = 165)	Placebo (*n* = 456)	Tezepelumab 210 mg Q4W (*n* = 438)	Overall (*n* = 894)
Age, years, mean (SD)	52.0 (12.4)	52.6 (12.4)	52.3 (12.3)	48.5 (16.4)	49.4 (16.9)	48.9 (16.6)
Age group, *n* (%)						
Adolescent (≥ 12 to < 18 years)	2 (2.7)	1 (1.1)	3 (1.8)	39 (8.6)	40 (9.1)	79 (8.8)
Adult (≥ 18 to < 65 years)	66 (88.0)	76 (84.4)	142 (86.1)	350 (76.8)	315 (71.9)	665 (74.4)
Adult (≥ 65 years)	7 (9.3)	13 (14.4)	20 (12.1)	67 (14.7)	83 (18.9)	150 (16.8)
Male, *n* (%)	36 (48.0)	38 (42.2)	74 (44.8)	158 (34.6)	155 (35.4)	313 (35.0)
BMI, kg/m^2, mean (SD)	27.23 (4.84)	28.67 (6.44)	28.02 (5.79)	28.48 (7.17)	28.69 (7.22)	28.58 (7.19)
Age at asthma diagnosis, years, mean (SD)	30.9 (15.5)	33.0 (17.5)	32.1 (16.6)	25.6 (19.4)	26.3 (20.0)	25.9 (19.7)
Time since asthma diagnosis, years, mean (SD)	20.9 (12.0)	19.4 (15.4)	20.1 (13.9)	22.7 (16.3)	22.9 (16.7)	22.8 (16.5)
ICS dose level,[a] *n* (%)						
Medium	16 (21.3)	21 (23.3)	37 (22.4)	116 (25.4)	110 (25.1)	226 (25.3)
High	59 (78.7)	69 (76.7)	128 (77.6)	339 (74.3)	328 (74.9)	667 (74.6)
Maintenance OCS use, *n* (%)	10 (13.3)	12 (13.3)	22 (13.3)	41 (9.0)	37 (8.4)	78 (8.7)
Pre-bronchodilator FEV_1, L, mean (SD)	1.84 (0.71)	1.91 (0.72)	1.88 (0.71)	1.85 (0.71)	1.81 (0.72)	1.83 (0.71)
Number of exacerbations in the past 12 months, *n* (%)						
≤ 2	38 (50.7)	46 (51.1)	84 (50.9)	287 (62.9)	264 (60.3)	551 (61.6)
> 2	37 (49.3)	44 (48.9)	81 (49.1)	169 (37.1)	174 (39.7)	343 (38.4)
FeNO level, ppb, median (min, max)	45.0 (5.0, 265.0)	41.0 (5.0, 213.0)	42.0 (5.0, 265.0)	28.0 (5.0, 231.0)	29.0 (5.0, 235.0)	28.0 (5.0, 235.0)
Blood eosinophil count, cells/μL, median (min, max)	400.0 (0, 8170.0)	340.0 (20, 3650.0)	360.0 (0, 8170.0)	240.0 (0.0, 4640.0)	240.0 (0.0, 1390.0)	240.0 (0.0, 4640.0)

Table 1 continued

Demographic/characteristic	History of CRSwNP			No history of CRSwNP		
	Placebo (*n* = 75)	Tezepelumab 210 mg Q4W (*n* = 90)	Overall (*n* = 165)	Placebo (*n* = 456)	Tezepelumab 210 mg Q4W (*n* = 438)	Overall (*n* = 894)
Serum total IgE, IU/mL, median (min, max)	146.0 (8.5, 7406.3)	174.4 (1.5, 4357.4)	160.6 (1.5, 7406.3)	207.8 (1.5, 9740.9)	198.9 (1.5, 12,823.2)	204.8 (1.5, 12,823.2)
FEIA positive for any perennial aeroallergen,[b] *n* (%)	32 (42.7)	43 (47.8)	75 (45.5)	309 (67.8)	296 (67.6)	605 (67.7)
ACQ-6 score, mean (SD)[c]	2.83 (0.86)	2.86 (0.82)	2.85 (0.84)	2.79 (0.81)	2.81 (0.81)	2.80 (0.81)
AQLQ(S) + 12 score, mean (SD)[d]	3.84 (1.01)	3.90 (0.99)	3.87 (1.00)	3.92 (1.00)	3.86 (1.03)	3.89 (1.02)
ASD score, mean (SD)[e]	1.44 (0.71)	1.41 (0.68)	1.42 (0.69)	1.39 (0.69)	1.39 (0.70)	1.39 (0.69)

[a]Medium-dose ICS: fluticasone propionate 500 μg/day or equivalent; high-dose ICS: fluticasone propionate > 500 μg/day or equivalent. One patient from the placebo group with no history of CRSwNP received fluticasone propionate < 500 μg/day or equivalent

[b]Positive status was defined as at least one positive (≥ 0.35 kilo units of allergen-specific IgE per liter) result on a FEIA test (ImmunoCAP, Thermo Fisher Scientific) for serum specific IgE against one or more of the following perennial aeroallergens: animal (cat dander, dog dander, cockroach), house dust mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), and mold mix

[c]ACQ-6 scores range from 0 (no impairment) to 6 (maximum impairment)

[d]AQLQ(S) + 12 scores range from 1 (maximum impairment) to 7 (no impairment)

[e]ASD scores range from 0 (no symptoms) to 4 (worst possible symptoms)

ACQ-6 Asthma Control Questionnaire-6, *AQLQ(S) + 12* Asthma Quality of Life Questionnaire (standardized) for patients 12 years and older, *ASD* Asthma Symptom Diary, *BMI* body mass index, *CRSwNP* chronic rhinosinusitis with nasal polyps, *FEIA* fluorescence enzyme immunoassay, *FeNO* fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 s, *ICS* inhaled corticosteroid, *IgE* immunoglobulin E, *OCS* oral corticosteroid, *Q4W* every 4 weeks, *SD* standard deviation

perennial aeroallergen sensitivity. A greater proportion of patients with a history of CRSwNP had experienced three or more asthma exacerbations in the 12 months before randomization than those without CRSwNP. Patients with a history of CRSwNP had higher fractional exhaled nitric oxide levels, higher blood eosinophil counts, and lower total IgE levels at baseline than those without. Approximately half of the patients with a history of CRSwNP had previously undergone nasal polyp surgery [tezepelumab, $n=44$ (48.9%); placebo, $n=39$ (52.0%)].

SNOT-22 Outcomes

Baseline SNOT-22 total scores were similar between treatment arms (Fig. 1a). Tezepelumab treatment resulted in an improvement from baseline in SNOT-22 total score compared with placebo at week 28 (LS mean difference −12.00 [95% confidence interval (CI) −18.78, −5.22] and at week 52 [−11.08 (95% CI −17.80, −4.35)]. The percentage change from baseline in SNOT-22 total score was greater with tezepelumab than with placebo at week 28 [LS mean difference −26% (95% CI −49, −3)] and at week 52 [−28% (95% CI −47, −9)] (Fig. 1b).

The SNOT-22 nasal domain was the most impaired at baseline, followed by the sleep, function, emotion, and ear/facial domains (Fig. 1c–g). Compared with placebo, tezepelumab improved all SNOT-22 domain scores from baseline to week 28 and week 52. At week 52, the greatest improvements were seen in the sleep domain followed by the nasal and function domains. Tezepelumab reduced all five of the symptoms of most clinical interest. The greatest improvement was seen for decreased sense of smell/taste, followed by nasal blockage, reduced productivity, waking up tired, and cough (Fig. 2).

Asthma-Related Clinical Outcomes

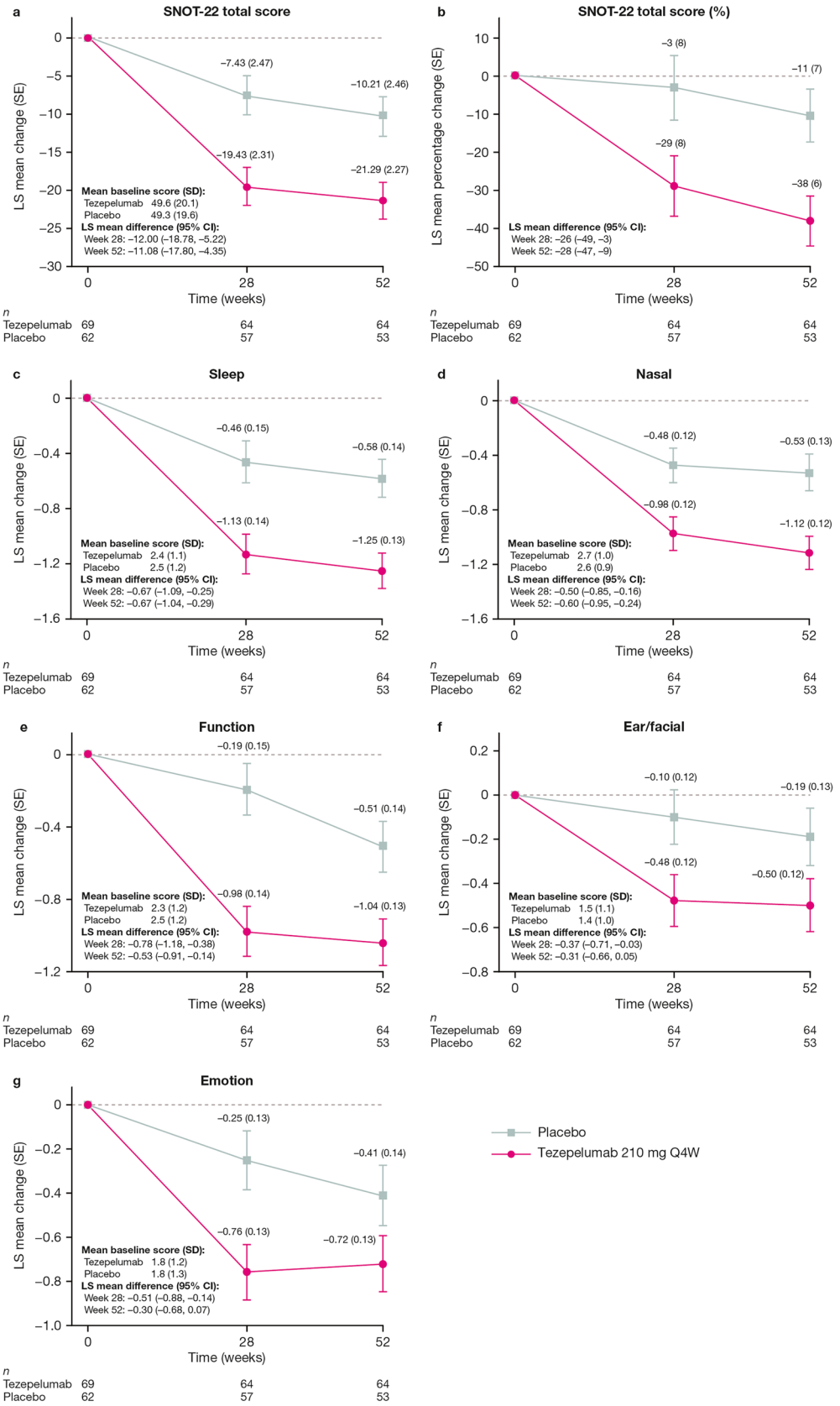
Tezepelumab reduced the AAER over 52 weeks compared with placebo by 69% (95% CI 50, 81) in patients with a history of CRSwNP and by 53% (95% CI 42, 62) in those without CRSwNP. Baseline pre-bronchodilator FEV_1 was similar in patients with and without a history of CRSwNP (Table 1). Tezepelumab treatment resulted in an improvement in pre-bronchodilator FEV_1 compared with placebo in patients regardless of their CRSwNP history. The LS mean difference (95% CI) for the change in pre-bronchodilator FEV_1 from baseline to week 52 was 0.20 (0.07, 0.32) L in patients with a history of CRSwNP and 0.12 (0.07, 0.17) L in patients without.

Baseline ACQ-6, AQLQ(S)+12, and ASD scores were similar in patients with and without a history of CRSwNP (Table 1). Tezepelumab treatment resulted in an improvement in ACQ-6 score compared with placebo. The LS mean difference (95% CI) for the change in ACQ-6 score from baseline to week 52 was −0.63 (−0.95, −0.31) in patients with a history of CRSwNP and −0.27 (−0.41, −0.13) in those without. At week 52, the improvement in AQLQ(S)+12 score with tezepelumab compared with placebo was greater in patients with a history of CRSwNP [LS mean difference (95% CI) 0.77 (0.43, 1.12)] than in those without [LS mean difference (95% CI) 0.25 (0.10, 0.40)]. Tezepelumab improved ASD scores compared with placebo in patients with and without a history of CRSwNP; the LS mean differences (95% CI) for the change from baseline to week 52 were −0.32 (−0.51, −0.13) and −0.08 (−0.16, 0.01), respectively.

DISCUSSION

This post hoc analysis demonstrated that tezepelumab improved rhinosinusitis and asthma-related clinical outcomes compared with placebo in patients with severe, uncontrolled asthma and a history of CRSwNP at any time before randomization in the phase 3 NAVIGATOR study.

The findings are consistent with and extend the results of the previous analysis completed in patients with a history of CRSwNP in the 2 years before randomization in the NAVIGATOR study [8]. Patients who received tezepelumab showed sustained improvements in SNOT-22 total score compared with placebo, from the first post-baseline time point assessed


a
SNOT-22 total score
LS mean change (SE)
0
−5
−10
−15
−20
−25
−30
−7.43 (2.47)
−10.21 (2.46)
−19.43 (2.31)
−21.29 (2.27)
Mean baseline score (SD):
Tezepelumab 49.6 (20.1)
Placebo 49.3 (19.6)
LS mean difference (95% CI):
Week 28: −12.00 (−18.78, −5.22)
Week 52: −11.08 (−17.80, −4.35)
0
28
52
Time (weeks)
n
Tezepelumab 69 64 64
Placebo 62 57 53
b
SNOT-22 total score (%)
LS mean percentage change (SE)
10
0
−10
−20
−30
−40
−50
−3 (8)
−11 (7)
−29 (8)
−38 (6)
LS mean difference (95% CI):
Week 28: −26 (−49, −3)
Week 52: −28 (−47, −9)
0
28
52
Time (weeks)
n
Tezepelumab 69 64 64
Placebo 62 57 53
c
Sleep
LS mean change (SE)
0
−0.4
−0.8
−1.2
−1.6
−0.46 (0.15)
−0.58 (0.14)
−1.13 (0.14)
−1.25 (0.13)
Mean baseline score (SD):
Tezepelumab 2.4 (1.1)
Placebo 2.5 (1.2)
LS mean difference (95% CI):
Week 28: −0.67 (−1.09, −0.25)
Week 52: −0.67 (−1.04, −0.29)
0
28
52
Time (weeks)
n
Tezepelumab 69 64 64
Placebo 62 57 53
d
Nasal
LS mean change (SE)
0
−0.4
−0.8
−1.2
−1.6
−0.48 (0.12)
−0.53 (0.13)
−0.98 (0.12)
−1.12 (0.12)
Mean baseline score (SD):
Tezepelumab 2.7 (1.0)
Placebo 2.6 (0.9)
LS mean difference (95% CI):
Week 28: −0.50 (−0.85, −0.16)
Week 52: −0.60 (−0.95, −0.24)
0
28
52
Time (weeks)
n
Tezepelumab 69 64 64
Placebo 62 57 53
e
Function
LS mean change (SE)
0
−0.4
−0.8
−1.2
−0.19 (0.15)
−0.51 (0.14)
−0.98 (0.14)
−1.04 (0.13)
Mean baseline score (SD):
Tezepelumab 2.3 (1.2)
Placebo 2.5 (1.2)
LS mean difference (95% CI):
Week 28: −0.78 (−1.18, −0.38)
Week 52: −0.53 (−0.91, −0.14)
0
28
52
Time (weeks)
n
Tezepelumab 69 64 64
Placebo 62 57 53
f
Ear/facial
LS mean change (SE)
0.2
0
−0.2
−0.4
−0.6
−0.8
−0.10 (0.12)
−0.19 (0.13)
−0.48 (0.12)
−0.50 (0.12)
Mean baseline score (SD):
Tezepelumab 1.5 (1.1)
Placebo 1.4 (1.0)
LS mean difference (95% CI):
Week 28: −0.37 (−0.71, −0.03)
Week 52: −0.31 (−0.66, 0.05)
0
28
52
Time (weeks)
n
Tezepelumab 69 64 64
Placebo 62 57 53
g
Emotion
LS mean change (SE)
0
−0.2
−0.4
−0.6
−0.8
−1.0
−0.25 (0.13)
−0.41 (0.14)
−0.76 (0.13)
−0.72 (0.13)
Mean baseline score (SD):
Tezepelumab 1.8 (1.2)
Placebo 1.8 (1.3)
LS mean difference (95% CI):
Week 28: −0.51 (−0.88, −0.14)
Week 52: −0.30 (−0.68, 0.07)
0
28
52
Time (weeks)
n
Tezepelumab 69 64 64
Placebo 62 57 53
Placebo
Tezepelumab 210 mg Q4W

◂**Fig. 1** **a–g** Changes from baseline in SNOT-22 total and domain scores in patients with a history of CRSwNP in the NAVIGATOR study. *n* is the number of patients with a change from baseline value at each time point. The dotted line represents no treatment difference. *CI* confidence interval, *CRSwNP* chronic rhinosinusitis with nasal polyps, *LS* least-squares, *Q4W* every 4 weeks, *SD* standard deviation, *SE* standard error, *SNOT-22* Sino-Nasal Outcome Test-22

(week 28) and throughout the 52-week study treatment period. The magnitude of this improvement in SNOT-22 total score was similar to that seen in patients with a history of CRSwNP in the 2 years before randomization in NAVIGATOR [8]. The findings were also comparable to those reported for other type 2-targeted biologics such as dupilumab (anti-interleukin-4 receptor α) in LIBERTY ASTHMA QUEST [15], benralizumab (anti-interleukin-5 receptor) in ANDHI (NCT03170271) [12], and mepolizumab (anti-interleukin-5) in MUSCA (NCT02281318) [13]. The greatest insights from this analysis arise from the evaluation of the SNOT-22 domain and symptom-specific item scores, which was enabled by the larger sample size of the cohort with a history of CRSwNP at any time before randomization in NAVIGATOR. Tezepelumab reduced all five SNOT-22 domain scores compared with placebo at week 28 and week 52, with the greatest improvements occurring in the sleep, nasal, and function domains. Furthermore, patients treated with tezepelumab demonstrated improvements compared with placebo in all five of the SNOT-22 items previously reported to be of most clinical interest (decreased sense of smell/taste, nasal blockage, reduced productivity, waking up tired, and cough) [15]. For each of these symptoms, the magnitude of the treatment effect was similar to that reported for dupilumab in the LIBERTY ASTHMA QUEST study [15].

CRSwNP has been significantly associated with adult-onset asthma (after 18 years of age) or late-onset asthma (after 40 years of age) [22]. In NAVIGATOR, patients with CRSwNP were older than those without CRSwNP at the time of asthma diagnosis. Patients with asthma and comorbid CRSwNP tend to have more severe asthma symptoms than those without [1]. In agreement, a greater proportion of the patients with a history of CRSwNP had experienced at least three asthma exacerbations in the 12 months before entering the NAVIGATOR study than those without CRSwNP. Consistent with previous findings [8], tezepelumab treatment reduced the AAER over 52 weeks compared with placebo and improved pre-bronchodilator FEV_1. The study findings also demonstrate that, compared with placebo, tezepelumab treatment resulted in an improvement from baseline in AQLQ(S) + 12 score in patients with a history of CRSwNP that was clinically meaningful and numerically higher than that observed in patients without CRSwNP. Compared with placebo, tezepelumab treatment also resulted in an improvement in ACQ-6 score that exceeded the MCID in patients with CRSwNP, while the improvement in ASD score did not exceed the MCID in either subgroup.

Limitations of this study include the post hoc nature of the analysis, which was not powered to evaluate the efficacy of tezepelumab in patients with CRSwNP. Furthermore, the CRSwNP status of patients was determined from medical records; endoscopy was not performed at baseline and no objective assessment of nasal polyp size was carried out. Finally, SNOT-22 assessments were completed at week 28 and week 52 only. Future studies will investigate the time course of the improvements in rhinosinusitis symptoms with greater resolution.

Safety findings have been previously reported for the overall study population [7]. There were no meaningful differences in the frequencies and types of adverse events reported for the tezepelumab and placebo groups. The most common adverse events were nasopharyngitis, upper respiratory tract infection, headache, and asthma.

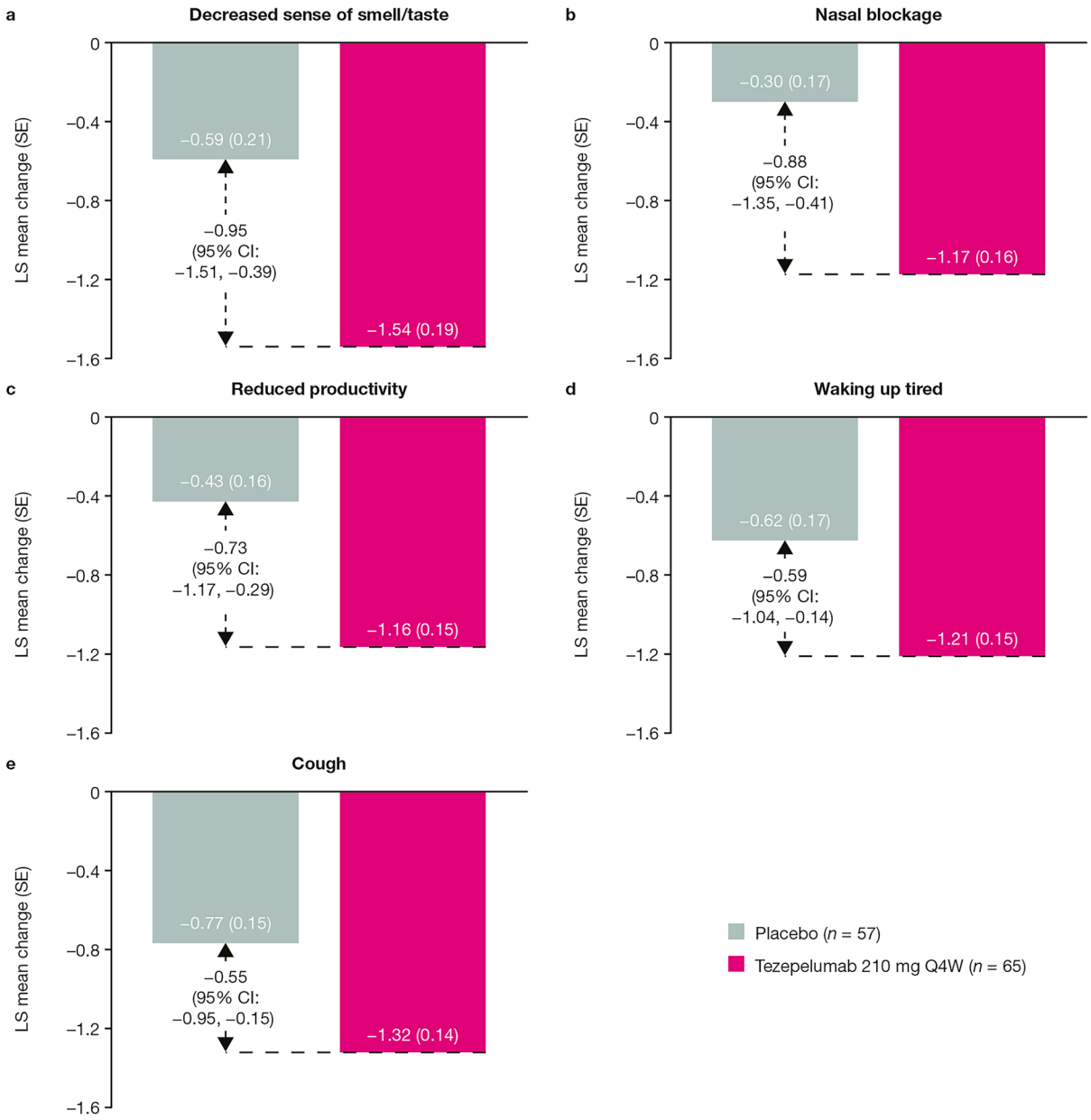


Fig. 2 **a–e** Changes from baseline to week 52 in the five SNOT-22 item scores of most clinical interest in patients with a history of CRSwNP in the NAVIGATOR study. *n* is the number of patients contributing to the analysis, i.e., the number of patients with a baseline value and no missing independent variables included in the model. *CI* confidence interval, *CRSwNP* chronic rhinosinusitis with nasal polyps, *LS* least-squares, *Q4W* every 4 weeks, *SE* standard error, *SNOT-22* Sino-Nasal Outcome Test-22

CONCLUSIONS

These results further demonstrate the efficacy of tezepelumab in improving rhinosinusitis symptoms, lung function, asthma control, and HRQoL in patients with severe, uncontrolled asthma and a history of CRSwNP.

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Data Availability. This study is registered at ClinicalTrials.gov with the identifier NCT03347279 (registration date November 20, 2017). 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. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available, outlining further details: https://vivli.org/ourmember/astrazeneca/.

Declarations

Conflict of Interest. Joshua S. Jacobs has received fees for sponsored research, consultancy and speaking from AstraZeneca, Genentech, GSK, Regeneron Pharmaceuticals, and Teva Pharmaceuticals; Joseph K. Han has received consultancy fees from AstraZeneca, Genentech, Gossamer Bio, Novartis, Regeneron Pharmaceuticals, and Sanofi; Jason K. Lee has received research support from AstraZeneca, Genentech, GSK, Medexus, Novartis, Regeneron Pharmaceuticals, Roche, Sanofi, and Takeda; has received fees for speakers bureau from Aralez Bio, AstraZeneca, GSK, Medexus, Merck, Mylan, Novartis, and Sanofi; and receives consultancy fees from and is an advisory committee member of AstraZeneca, GSK, Medexus, Novartis, Regeneron Pharmaceuticals, and Sanofi; Tanya M. Laidlaw has served on scientific advisory boards for Eli Lilly, GSK, Regeneron Pharmaceuticals, and Sanofi; Nicole L. Martin, Christopher S. Ambrose, Neil Martin, and Joseph D. Spahn are employees of AstraZeneca and may own stock or stock options in AstraZeneca; Scott Caveney is an employee of

Amgen and owns stock in Amgen; Flavia C. L. Hoyte has received honoraria from AstraZeneca, Genentech, Sanofi and Teva Pharmaceuticals; has participated in research with Genentech and Sanofi, for which her institution has been remunerated; and her family owns stock in Amgen.

Ethical Approval. 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 were obtained from the Copernicus Central Institutional Review Board (Cary, NC, USA), and local independent ethics committees. All patients or their guardians provided written informed consent in accordance with local requirements.

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