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BRIEF REPORT

Tezepelumab can Restore Normal Lung Function in Patients with Severe, Uncontrolled Asthma: Pooled Results from the PATHWAY and NAVIGATOR Studies

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ABSTRACT

Introduction: This post hoc analysis assessed the ability of tezepelumab treatment to restore normal lung function in patients with severe, uncontrolled asthma with abnormal lung function at baseline pooled from the PATHWAY and NAVIGATOR studies.

Methods: PATHWAY and NAVIGATOR were multicentre, randomized, double-blind, placebo-controlled studies. Patients (12–80 years old) included in this analysis received tezepelumab 210 mg subcutaneously every 4 weeks or matched placebo for 52 weeks. Patients had a percent predicted pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1) of < 80% (< 90% for adolescents in NAVIGATOR) at screening. The change from baseline to week 52 in pre-BD FEV_1 was assessed by baseline percent predicted pre-BD FEV_1 subgroup [abnormal (< 80%) and normal (≥ 80%)]. The proportion of

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patients with abnormal lung function at baseline who achieved normal lung function at week 52 was assessed overall and by biomarker level and disease duration subgroups.

***Results*:** Of the 665 and 669 patients who received tezepelumab or placebo, respectively, 564 and 569 had abnormal lung function at baseline. Tezepelumab improved the pre-BD FEV_1 from baseline to week 52 versus placebo by 0.14 L [95% confidence interval (CI) 0.09–0.19] and 0.13 L (95% CI 0.01–0.24) in patients with abnormal and normal lung function at baseline, respectively. A higher proportion of tezepelumab than placebo recipients with abnormal lung function at baseline achieved normal lung function at week 52 (17.2% vs. 9.9%, respectively). Among tezepelumab recipients, those with higher levels of type 2 inflammatory biomarkers and a shorter duration of disease at baseline were more likely to achieve normal lung function at week 52.

***Conclusion*:** In patients with severe, uncontrolled asthma, a greater proportion of tezepelumab than placebo recipients with abnormal lung function at baseline achieved normal lung function at week 52.

***Trial Registration*:** PATHWAY: NCT02054130; NAVIGATOR: NCT03347279.

Keywords: Biologic; Lung function; Prebronchodilator percent predicted normal; Randomized placebo-controlled trial; Severe asthma; Tezepelumab

Key Summary Points

Why carry out this study?

Tezepelumab is a human monoclonal antibody that blocks the activity of thymic stromal lymphopoietin (TSLP), an epithelial cytokine implicated in asthma pathogenesis and type 2 inflammation.

Previous findings from phase 2 and phase 3 trials of tezepelumab in patients with severe, uncontrolled asthma demonstrated improved lung function and clearance of airway mucus plugs with tezepelumab treatment compared with placebo.

This post hoc analysis assessed the ability of tezepelumab treatment to restore normal lung function in patients with severe, uncontrolled asthma with abnormal lung function at baseline pooled from the PATHWAY and NAVIGATOR studies.

What was learned from the study?

Treatment with tezepelumab over 52 weeks was associated with improved lung function and normalization of lung function in patients with abnormal lung function at baseline.

These results support the efficacy of tezepelumab in improving and normalizing lung function in patients with severe, uncontrolled asthma.

These findings also support previous evidence of the benefits of providing anti-inflammatory treatments like tezepelumab to patients earlier in the course of their disease.

INTRODUCTION

Severe asthma is characterized by airway inflammation and remodelling [1, 2]. Over time, these changes can result in irreversible airway obstruction and progressive decline of lung function [2, 3]. Additionally, the presence of mucus plugs contributes to airway obstruction and

consequently reduced lung function in asthma [4, 5]. There is evidence that airway obstruction and increased levels of type 2 inflammatory biomarkers, including blood eosinophils and fractional exhaled nitric oxide (FeNO), are associated with reduced lung function in severe asthma [6], which is linked to a longer duration of disease [7]. Tezepelumab is a human monoclonal antibody that blocks the activity of thymic stromal lymphopoietin (TSLP), an epithelial cytokine implicated in the pathogenesis of asthma and type 2 inflammation [8–10]. In the phase 2b PATHWAY and phase 3 NAVIGATOR studies (ClinicalTrials.gov identifiers: NCT02054130 and NCT03347279, respectively), treatment with tezepelumab significantly reduced asthma exacerbations and improved lung function [including percent predicted pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1)], asthma control and health-related quality of life compared with placebo in patients with severe, uncontrolled asthma [9–11]. Additionally, tezepelumab reduced asthma exacerbations and improved lung function compared with placebo in patients with severe, uncontrolled asthma with and without persistent airflow obstruction [12]. In the phase 2 CASCADE study (ClinicalTrials.gov identifier: NCT03688074), tezepelumab recipients with moderate-to-severe asthma had reduced mucus plug scores and increased airway lumen size and showed improvement in lung function compared with placebo recipients [4]; these findings suggest a suppressive effect of tezepelumab on airway remodelling and lung function decline. This post hoc analysis assessed the ability of tezepelumab treatment to restore normal lung function in patients with severe, uncontrolled asthma with abnormal lung function at baseline pooled from the PATHWAY and NAVIGATOR studies.

METHODS

Study Design and Patient Population

PATHWAY and NAVIGATOR were multicentre, randomized, double-blind, placebo-controlled, parallel-group trials with similar designs in patients aged 18–75 years and 12–80 years, respectively. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The original studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonisation good clinical practice guidelines, and applicable regulatory requirements, and consent was obtained from all study participants. Full details of the study designs and patient eligibility criteria have been described previously [9–11]. This pooled analysis included patients from PATHWAY and NAVIGATOR with severe, uncontrolled asthma who received tezepelumab 210 mg subcutaneously every 4 weeks for 52 weeks or matched placebo. In both trials, patients must have had a percent predicted pre-BD FEV_1 of less than 80% (< 90% for adolescents in NAVIGATOR) at screening (week −4). Additionally, patients in both trials were required to have a post-BD FEV_1 reversibility of at least 12% and at least 200 mL during screening or during the 12 months before screening.

Endpoints

For this analysis, patient lung function was categorized as abnormal or normal [baseline (week 0, rather than screening) percent predicted pre-BD FEV_1 < 80% or ≥ 80%, respectively]. The following endpoints were assessed in the tezepelumab and placebo groups overall: the change in pre-BD FEV_1 from baseline to week 52 by baseline lung function (abnormal or normal); the proportion of patients with abnormal lung function at baseline who achieved normal lung function at week 52; and the proportion of patients who had normal lung function at baseline and maintained normal lung function at week 52. The following additional subgroups were analysed for patients who had abnormal lung function at baseline and achieved normal lung function at week 52: baseline FeNO level (< 25 ppb or ≥ 25 ppb), baseline blood eosinophil count (BEC; < 300 cells/μL or ≥ 300 cells/μL) and duration of asthma (< 20 years or ≥ 20 years).

Statistical Analyses

The mean changes from baseline to week 52 in pre-BD FEV_1 in the abnormal and normal lung function subgroups were reported as least-squares means and were estimated using a repeated measures model. Treatment group, study (PATHWAY or NAVIGATOR), baseline pre-BD FEV_1, visit, subgroup, treatment-by-visit, treatment-by-subgroup, visit-by-subgroup and treatment-by-visit-by-subgroup were included as covariates in the model. Baseline was defined as the last non-missing measurement recorded before randomization. The proportions of patients who shifted from abnormal lung function at baseline to normal lung function at week 52 or retained normal lung function at week 52 were calculated for patients with available percent predicted pre-BD FEV_1 data at baseline and week 52.

RESULTS

Overall, 1334 patients from PATHWAY and NAVIGATOR were included in this pooled analysis (tezepelumab, n = 665; placebo, n = 669). Of the patients with available baseline percent predicted pre-BD FEV_1 data, there were 564 and 569 with abnormal lung function (percent predicted pre-BD FEV_1 < 80%) at baseline in the tezepelumab and placebo groups, respectively (Table 1). There were 101 and 100 patients with normal lung function (percent predicted pre-BD FEV_1 ≥ 80%) at baseline in the tezepelumab and placebo groups, respectively (Table 1). Baseline demographics and clinical characteristics by lung function at baseline, as well as in the overall pooled population, are summarized in Table 1. Compared with those with normal lung function at baseline, patients with abnormal lung function at baseline had a higher mean age, higher median baseline BEC, lower median FeNO level and a longer time since asthma diagnosis, and a greater proportion were receiving maintenance oral corticosteroids. As expected, patients with abnormal lung function at baseline demonstrated a higher percent bronchodilator reversibility compared with those with normal lung function at baseline. Tezepelumab improved the pre-BD FEV_1 from baseline to week 52 compared with placebo by 0.14 L [95% confidence interval (CI) 0.09–0.19] and 0.13 L (95% CI 0.01–0.24) in patients with abnormal and normal lung function at baseline, respectively (Fig. 1). A total of 592 tezepelumab recipients and 584 placebo recipients had available baseline and week 52 percent predicted pre-BD FEV_1 data. Of these, 17.2% of tezepelumab recipients (n/N = 102/592) and 9.9% of placebo recipients (n/N = 58/584) shifted from abnormal lung function at baseline to normal lung function at week 52 (Fig. 2a). Baseline demographics and clinical characteristics of patients with abnormal lung function at baseline who did and did not achieve normal lung function at week 52 are summarized in Table S1. Overall, those with abnormal lung function at baseline who achieved normal lung function at week 52 had a lower mean age, higher median baseline inflammatory biomarker levels (BEC and FeNO), better lung function (pre-BD FEV_1 and percent predicted pre-BD FEV_1) and had a shorter time since asthma diagnosis than those with abnormal lung function at both baseline and week 52. Among the small number of patients with normal lung function at baseline, a similar proportion of tezepelumab and placebo recipients maintained normal lung function at week 52 (63.4% vs. 59.0%, respectively). Across the inflammatory biomarker (FeNO and BEC) subgroups assessed in patients with abnormal lung function at baseline, a higher proportion of tezepelumab recipients achieved normal lung function at week 52 than placebo recipients (Fig. 2b, c). The greatest shifts from abnormal lung function at baseline to normal lung function at week 52 in tezepelumab recipients were observed in patients with high type 2 inflammatory biomarkers at baseline (FeNO level, 20.4% vs. 13.7% for ≥ 25 ppb versus < 25 ppb, respectively; BECs, 24.0% vs. 12.3% for ≥ 300 cells/μL versus < 300 cells/μL, respectively). When patients were grouped by duration of disease, a higher proportion of tezepelumab than placebo

Table 1 Baseline demographics and clinical characteristics of patients grouped by lung function at baseline, and of the overall pooled population

Baseline demographic/characteristic	Abnormal lung function at baseline (percent predicted pre-BD FEV_1 < 80%)			Normal lung function at baseline (percent predicted pre-BD FEV_1 ≥ 80%)			Overall pooled population *N* = 1334
	Tezepelumab 210 mg Q4W *n* = 564	Placebo *n* = 569	Overall *n* = 1133	Tezepelumab 210 mg Q4W *n* = 101	Placebo *n* = 100	Overall *n* = 201	
Age, years, mean (SD)	52.1 (14.2)	50.9 (13.5)	51.5 (13.9)	41.4 (19.9)	42.7 (21.2)	42.0 (20.5)	50.1 (15.4)
Female, *n* (%)	359 (63.7)	367 (64.5)	726 (64.1)	63 (62.4)	64 (64.0)	127 (63.2)	853 (63.9)
Male, *n* (%)	205 (36.3)	202 (35.5)	407 (35.9)	38 (37.6)	36 (36.0)	74 (36.8)	481 (36.1)
Race, *n* (%)							
White	400 (70.9)	382 (67.1)	782 (69.0)	60 (59.4)	68 (68.0)	128 (63.7)	910 (68.2)
Black or African American	25 (4.4)	33 (5.8)	58 (5.1)	8 (7.9)	4 (4.0)	12 (6.0)	70 (5.2)
Asian	121 (21.5)	132 (23.2)	253 (22.3)	30 (29.7)	23 (23.0)	53 (26.4)	306 (22.9)
Other[a]	18 (3.2)	22 (3.9)	40 (3.5)	3 (3.0)	5 (5.0)	8 (4.0)	48 (3.6)
Ethnicity, *n* (%)							
Hispanic or Latino	60 (10.6)	62 (10.9)	122 (10.8)	24 (23.8)	20 (20.0)	44 (21.9)	166 (12.4)
BMI, kg/m^2, mean (SD)	28.9 (6.7)	28.7 (6.7)	28.8 (6.7)	27.1 (6.6)	26.4 (6.2)	26.8 (6.4)	28.5 (6.7)
ICS dose group, *n* (%)[b]							
Medium	161 (28.5)	174 (30.6)	335 (29.6)	40 (39.6)	31 (31.0)	71 (35.3)	406 (30.4)
High	403 (71.5)	394 (69.2)	797 (70.3)	61 (60.4)	69 (69.0)	130 (64.7)	927 (69.5)
Maintenance OCS use, *n* (%)	50 (8.9)	57 (10.0)	107 (9.4)	8 (7.9)	7 (7.0)	15 (7.5)	122 (9.1)
Number of exacerbations in the previous 12 months, mean (SD)	2.7 (1.5)	2.7 (1.4)	2.7 (1.4)	2.6 (1.0)	2.5 (1.0)	2.5 (1.0)	2.7 (1.4)
Pre-BD FEV_1, *L*, mean (SD)	1.7 (0.6)	1.7 (0.6)	1.7 (0.6)	2.7 (0.7)	2.7 (0.7)	2.7 (0.7)	1.8 (0.7)

Table 1 continued

Baseline demographic/ characteristic	Abnormal lung function at baseline (percent predicted pre-BD FEV_1 < 80%)			Normal lung function at baseline (percent predicted pre-BD FEV_1 ≥ 80%)			Overall pooled population *N* = 1334
	Tezepelumab 210 mg Q4W *n* = 564	Placebo *n* = 569	Overall *n* = 1133	Tezepelumab 210 mg Q4W *n* = 101	Placebo *n* = 100	Overall *n* = 201	
Percent predicted pre-BD FEV_1, mean (SD)	57.2 (13.6)	57.5 (13.5)	57.3 (13.5)	88.5 (7.2)	88.9 (9.6)	88.7 (8.4)	62.1 (17.1)
Percent FEV_1 reversibility, mean (SD)	18.0 (17.0)	18.2 (17.0)	18.1 (17.0)	6.2 (6.9)	7.5 (6.8)	6.9 (6.9)	16.4 (16.4)
Serum total IgE level, IU/mL, median (min, max)	166.1 (1.5, 12 823.2)	171.0 (1.5, 11 859.6)	170.6 (1.5, 12 823.2)	227.8 (1.5, 3041.2)	217.6 (1.5, 6136.5)	222.0 (1.5, 6136.5)	179.4 (1.5, 12 823.2)
BEC, cells/ μL, median (min, max)	265 (0, 3180)	260 (0, 8170)	260 (0, 8170)	230 (20, 3650)	250 (0, 960)	240 (0, 3650)	260 (0, 8170)
BEC subgroup, *n* (%)							
< 300 cells/ μL	314 (55.7)	323 (56.8)	637 (56.2)	65 (64.4)	59 (59.0)	124 (61.7)	761 (57.0)
≥ 300 cells/ μL	250 (44.3)	246 (43.2)	496 (43.8)	36 (35.6)	41 (41.0)	77 (38.3)	573 (43.0)
FeNO level, ppb, median (min, max)	26.5 (4.0, 213.0)	29.0 (3.5, 276.3)	28.0 (3.5, 276.3)	40.5 (5.0, 235.0)	24.0 (7.0, 231.0)	30.0 (5.0, 235.0)	28.0 (4.0, 276.0)
FeNO level subgroup, *n* (%)							
< 25 ppb	257 (45.6)	243 (42.7)	500 (44.1)	34 (33.7)	51 (51.0)	85 (42.3)	585 (43.9)
≥ 25 to < 50 ppb	165 (29.3)	154 (27.1)	319 (28.2)	26 (25.7)	27 (27.0)	53 (26.4)	372 (27.9)
≥ 50 ppb	135 (23.9)	168 (29.5)	303 (26.7)	40 (39.6)	21 (21.0)	61 (30.3)	364 (27.3)
Time since asthma diagnosis, years, median (min, max)	19 (1, 69)	18 (1, 65)	18 (1, 69)	11 (1, 51)	13 (1, 61)	12 (1, 61)	17 (1, 69)

Table 1 continued

Baseline demographic/characteristic	Abnormal lung function at baseline (percent predicted pre-BD FEV_1 < 80%)			Normal lung function at baseline (percent predicted pre-BD FEV_1 ≥ 80%)			Overall pooled population *N* = 1334
	Tezepelumab 210 mg Q4W *n* = 564	Placebo *n* = 569	Overall *n* = 1133	Tezepelumab 210 mg Q4W *n* = 101	Placebo *n* = 100	Overall *n* = 201	
FEIA positive for any perennial aeroallergen, *n* (%)[c]	339 (60.1)	341 (59.9)	680 (60.0)	71 (70.3)	64 (64.0)	135 (67.2)	815 (61.1)

BD bronchodilator, *BEC* blood eosinophil count, *BMI* body mass index, *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

[a]Other includes Native Hawaiian or Other Pacific Islander, and American Indian or Alaska Native categories

[b]Medium-dose ICS: fluticasone propionate 250–500 μg/day or equivalent; high-dose ICS: fluticasone propionate > 500 μg/day or equivalent; there was one patient in the placebo group in the overall pooled population (originally from NAVIGATOR) who received fluticasone propionate < 500 μg/day or equivalent

[c]Positive for at least one common perennial aeroallergen [animal (cat dander, dog dander), cockroach, dust mite (*Dermatophagoides farina* or *D. pteronyssinus*) or moulds]

recipients with abnormal lung function at baseline and asthma for less than 20 years achieved normal lung function at week 52 (22.1% vs. 8.9%, respectively; Fig. 2d). Similar proportions of tezepelumab and placebo recipients with abnormal lung function at baseline and asthma for at least 20 years achieved normal lung function at week 52 (10.9% and 11.2%, respectively; Fig. 2d).

DISCUSSION

Building on earlier evidence demonstrating that tezepelumab improves lung function (pre-BD FEV_1) compared with placebo in patients with severe, uncontrolled asthma, these data demonstrate that tezepelumab can restore normal lung function among those with abnormal lung function at baseline. The shift from abnormal to normal lung function with tezepelumab was more likely in patients with high type 2 inflammatory biomarkers at baseline and in those with a duration of asthma of less than 20 years. Additionally, the magnitude of improvement observed was higher among patients with higher post-BD FEV_1 reversibility at baseline, which suggests that inclusion criteria related to bronchodilator response enriched towards a more responsive trial population. In addition to bronchodilation effects, improvements in lung function in patients who received tezepelumab versus placebo have also been associated with clearance of mucus plugs [4]. These findings suggest that tezepelumab treatment may help to reverse underlying inflammation, reduce airflow obstruction, and normalize lung function in patients with severe disease. Furthermore, these results provide additional evidence of the benefits of providing anti-inflammatory treatments like tezepelumab to patients earlier in the course of their disease, before irreversible lung damage has occurred. However, to definitively answer this question, interventional trials with multi-year follow up to examine the effects of biologic treatments on longer-term disease progression would be required.

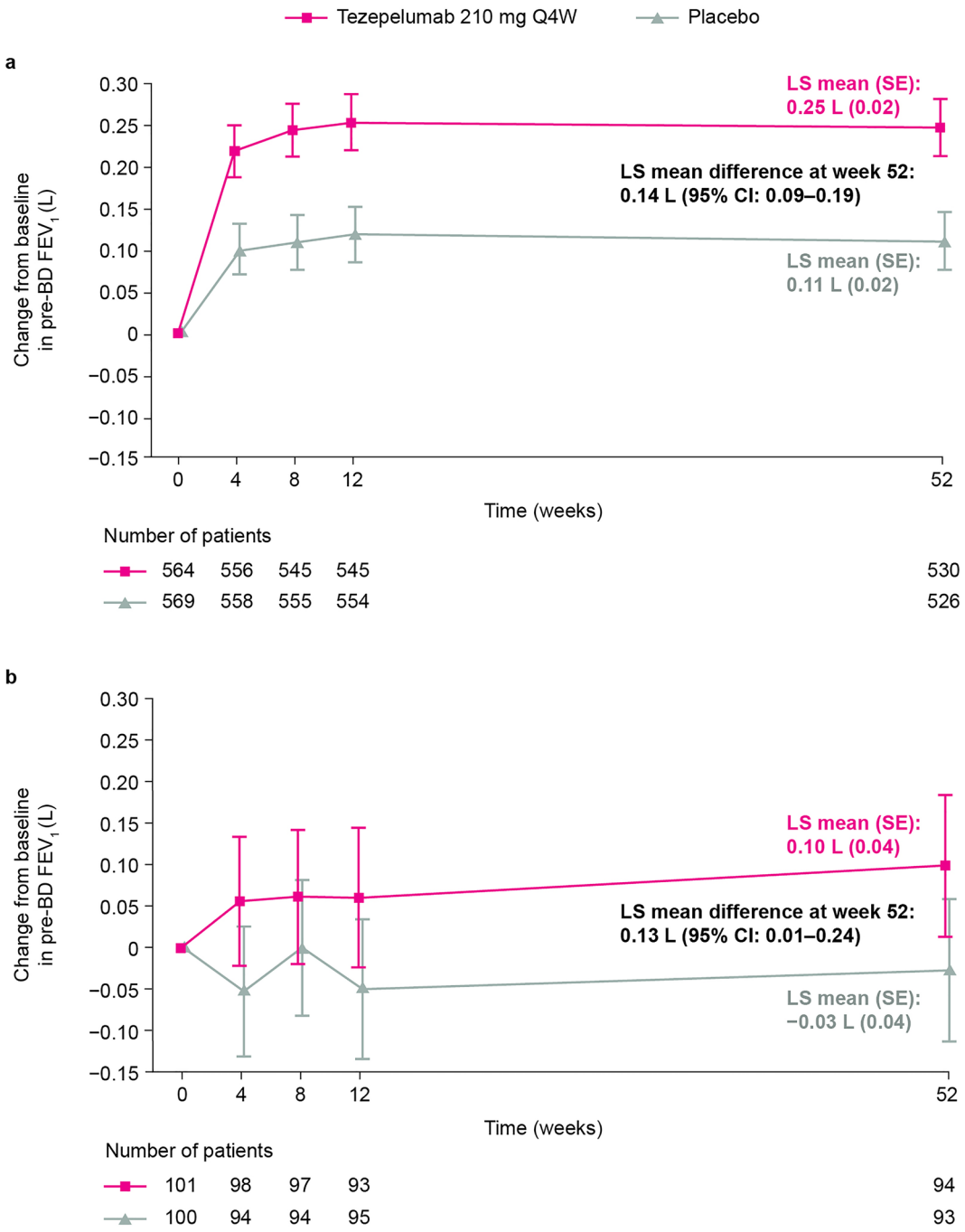

Fig. 1 The change from baseline to week 52 in pre-BD FEV_1 in patients with abnormal (**a**) and normal (**b**) lung function at baseline. Abnormal lung function: percent predicted pre-BD FEV_1 < 80%; normal lung function: percent predicted pre-BD FEV_1 ≥ 80%. Data are LS means (95% CI). *BD* bronchodilator, *CI* confidence interval, *FEV_1* forced expiratory volume in 1 s, *LS* least-squares, *Q4W* every 4 weeks, *SE* standard error

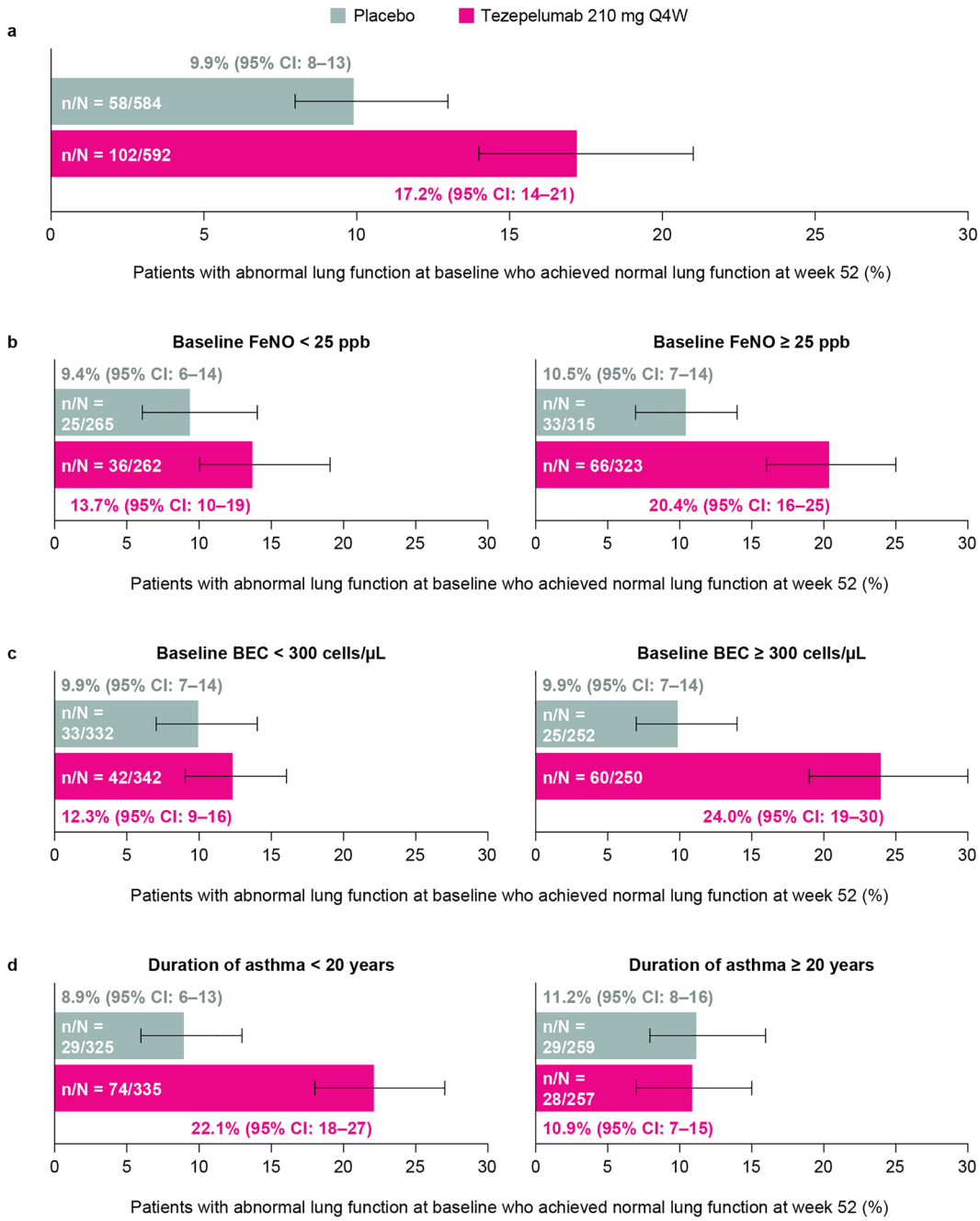

Fig. 2 The proportions of patients with abnormal lung function at baseline who achieved normal lung function at week 52 overall (**a**), by baseline FeNO levels (**b**), by baseline BECs (**c**) and by duration of disease (**d**). Abnormal lung function: percent predicted pre-BD FEV_1 < 80%; normal lung function: percent predicted pre-BD FEV_1 ≥ 80%. N is the number of patients with a non-missing baseline and non-missing week 52 result. *BD* bronchodilator, *BEC* blood eosinophil count, *CI* confidence interval, *FeNO* fractional exhaled nitric oxide, *FEV_1* forced expiratory volume in 1 s, *Q4W* every 4 weeks

CONCLUSIONS

Tezepelumab treatment was associated with improved lung function and normalization of lung function in patients with abnormal lung function at baseline. These results support the efficacy of tezepelumab in improving and normalizing lung function in patients with severe, uncontrolled asthma and highlight the benefits of earlier treatment with tezepelumab.

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Data Availability. All data generated or analysed during this study are included in this published article/as supplementary information files.

Declarations

Conflict of Interest. Ian D. Pavord has received speaker fees from Aerocrine AB, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Regeneron Pharmaceuticals, Sanofi and Teva Pharmaceuticals; has received payments for organization of educational events from AstraZeneca, GSK, Regeneron Pharmaceuticals, Sanofi and Teva Pharmaceuticals; has received consultancy fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Dey Pharma, Genentech, GSK, Knopp Biosciences, Merck, MSD, Napp Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, RespiVert, Sanofi, Schering-Plough and Teva Pharmaceuticals; has received international scientific meeting sponsorship from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Napp Pharmaceuticals, Regeneron Pharmaceuticals, Sanofi and Teva Pharmaceuticals; and has received a research grant from Chiesi. Christopher E. Brightling has received grants and consultancy fees from 4D Pharma, Areteia Therapeutics, AstraZeneca, Chiesi, Genentech, GSK, Global Access Diagnostics (formerly Mologic), Novartis, Regeneron Pharmaceuticals, Roche and Sanofi. Stephanie Korn has received fees for lectures and/or advisory board meetings from AstraZeneca, GSK, Novartis, Roche, Sanofi and Teva Pharmaceuticals. Nicole L. Martin, Sandhia S. Ponnarambil and Christopher S. Ambrose are employees of AstraZeneca and may own stock or stock options in AstraZeneca. Nestor A. Molfino and Jane R. Parnes are employees of Amgen and own stock in Amgen.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The original studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonisation good clinical practice guidelines, and applicable regulatory requirements and consent was obtained from all study participants.

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