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Andrew Menzies-Gow, Michael Wechsler, Christopher Brightling, Stephanie Korn, Jonathan Corren, et al.. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study. *The Lancet Respiratory Medicine*, 2023, 11 (5), pp.425-488. 10.1016/S2213-2600(22)00492-1 . hal-03960913

HAL Id: hal-03960913

<https://hal.science/hal-03960913v1>

Submitted on 20 Feb 2024

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Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study

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Abstract

Background:

Tezepelumab is a human monoclonal antibody that blocks thymic stromal lymphopoietin. The drug has been tested previously in the phase 3 NAVIGATOR ([NCT03347279](#)) and SOURCE ([NCT03406078](#)) studies, and was subsequently approved as a treatment for severe asthma. This extension study recruited from NAVIGATOR and SOURCE and aimed to evaluate the long-term safety and efficacy of tezepelumab in individuals with severe, uncontrolled asthma.

Methods:

DESTINATION was a phase 3, multicentre, randomised, double-blind, placebo-controlled, long-term extension study. The study was done across 182 sites (including hospitals, clinics, medical centres, clinical trial centres, and private practices) in 18 countries. Participants (aged 12-80 years) were required to have good treatment compliance in the parent study. Randomisation was stratified by the parent study and all participants were re-randomised. Those who were previously randomised to receive tezepelumab in either parent study continued treatment of subcutaneous tezepelumab (210 mg every 4 weeks); those who were previously randomised to receive placebo in either parent study were re-randomised 1:1 to receive either subcutaneous tezepelumab (210 mg every 4 weeks) or placebo (every 4 weeks) using a randomisation list prepared by a computerised system. Total treatment duration (including the parent studies) was 104 weeks for all groups. Participants, investigators, and site staff were masked to treatment assignment. The primary endpoints were exposure-adjusted incidence of adverse events and serious adverse events and the secondary endpoint was the annualised asthma exacerbation rate; these were assessed from week 0 of the parent studies to week 104 of DESTINATION in all participants who were randomised and who received at least one dose of tezepelumab or placebo in either of the parent studies. The trial is registered with ClinicalTrials.gov, [NCT03706079](#), and is closed to new participants.

Findings:

Participants were recruited between Jan 7, 2019, and Oct 15, 2020. For individuals who initially received tezepelumab (n=528) in NAVIGATOR, incidence of adverse events over 104 weeks was 49.62 (95% CI 45.16 to 54.39) per 100 patient-years, compared with 62.66 (56.93 to 68.81) for those receiving placebo (n=531; difference -13.04, 95% CI -17.83 to -8.18). For serious adverse events, incidence was 7.85 (6.14 to 9.89) per 100 patient-years for individuals who initially received tezepelumab and 12.45 (9.97 to 15.35) for those who received placebo (difference -4.59, -7.69 to -1.65). In SOURCE, incidence of adverse events was 47.15 (36.06 to 60.56) per 100 patient-years for those who initially received tezepelumab (n=74) and 69.97 (54.54 to 88.40) for those who received placebo (n=76; difference -22.82, -34.77 to -10.01). For serious adverse events, incidence was 13.14 (7.65 to 21.04) per 100 patient-years for those who initially received tezepelumab and 17.99 (10.66 to 28.44) for those who received placebo (difference -4.85, -14.88 to 4.53). Tezepelumab reduced the annualised asthma exacerbation rate over 104 weeks compared with placebo. In participants initially from NAVIGATOR, the annualised asthma exacerbation rate ratio over 104 weeks was 0.42 (95% CI 0.35 to 0.51); in those initially from SOURCE, the ratio over 104 weeks was 0.61 (0.38 to 0.96).

Interpretation:

Tezepelumab treatment was well tolerated for up to 2 years and resulted in sustained, clinically meaningful reductions in asthma exacerbations in individuals with severe, uncontrolled asthma. These findings are consistent with previous randomised, placebo-controlled studies and show the long-term safety and sustained efficacy of tezepelumab in individuals with severe, uncontrolled asthma.

Introduction

Biologics are recommended as add-on therapy in people with severe, uncontrolled asthma. Approval of these drugs is usually based on 1-year safety and efficacy studies, but these therapies are typically used for longer periods.¹ Long-term extension studies for biologics in severe asthma have been done.^{2–4} However, these do not have a placebo group to provide context for the safety and efficacy data.

Tezepelumab, a human monoclonal antibody (immunoglobulin [Ig] G2 λ), binds specifically to thymic stromal lymphopoietin (TSLP) and prevents the protein from interacting with its heterodimeric receptor.⁵ TSLP, an epithelial cytokine, has a central role in the initiation and persistence of airway inflammation in asthma.⁶ TSLP regulates multiple downstream inflammatory cascades and has effects on airway structural cells and airway hyper-responsiveness.⁶

Tezepelumab reduced the annualised asthma exacerbation rate, and improved lung function, asthma control, and health-related quality of life in people with severe, uncontrolled asthma in the phase 2b PATHWAY (NCT02054130)⁵ and phase 3 NAVIGATOR (NCT03347279) studies.⁷ In the corticosteroid-sparing, phase 3, SOURCE study (NCT03406078), although the primary endpoint of oral corticosteroid reduction was not met, tezepelumab reduced the annualised asthma exacerbation rate and improved lung function, asthma control, and health-related quality of life compared with placebo in people with oral corticosteroid-dependent asthma.⁸ On the basis of these studies, which had treatment durations of up to 1 year, tezepelumab was approved in December, 2021, by the US Food and Drug Administration as a treatment for severe asthma with no biomarker or phenotypic restrictions.⁹ The 2022 Global Initiative for Asthma (GINA) guidelines recommend anti-TSLP therapy for people with and without evidence of type 2 inflammation.¹

Here, we report results from DESTINATION (NCT03706079), a long-term, randomised, placebo-controlled extension study that enrolled people who completed treatment in the NAVIGATOR or SOURCE studies. The primary objective of DESTINATION was to evaluate the long-term safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma, compared with placebo, over 2 years of treatment (from week 0 of the parent studies to week 104 of DESTINATION). The secondary objective was to assess the long-term effect of tezepelumab on asthma exacerbations.

Methods

Study design

DESTINATION was a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group long-term extension study to evaluate the safety and efficacy of subcutaneous tezepelumab (210 mg) every 4 weeks in people who completed treatment in the 52-week NAVIGATOR study or the 48-week SOURCE study (appendix p 34). Full details of these studies have been published previously.¹⁰

The study was done in 18 countries (appendix p 3) across 182 sites comprised of hospitals, clinics, medical centres, clinical trial centres, university centres, and private practices.

The study protocol is included in the appendix (p 46). The study was done 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 independent ethics committees were obtained.

Participants

Participants were aged 12–80 years with severe, uncontrolled asthma and received medium-dose to high-dose inhaled corticosteroids, with at least one additional asthma controller medication with or without oral corticosteroids. Key inclusion criteria at randomisation were attendance at the end-of-treatment visit of the parent study, adequate treatment compliance during the parent study, and not meeting any of the discontinuation criteria from the parent study. Key exclusion criteria included the presence of any clinically important pulmonary disease other than asthma; pulmonary or systemic diseases other than asthma associated with elevated peripheral eosinophil counts; any clinically meaningful abnormal finding or important protocol deviations during the parent study; and any disorders that were not stable and could, in the opinion of the investigator, affect the safety of the participant (appendix p 6). All participants provided written informed consent in accordance with local requirements.

Randomisation and masking

DESTINATION randomisation was stratified by the parent study (appendix p 5 for stratification factors in NAVIGATOR and SOURCE). All participants were randomised to maintain masking and assigned new enrolment codes. Those who were previously randomised to receive tezepelumab in either parent study continued tezepelumab at the same dosing (210 mg subcutaneously every 4 weeks). Individuals who were previously randomised to receive placebo in either parent study were re-randomised 1:1 to receive either tezepelumab or placebo using a randomisation list prepared by a computerised system (Calyx Clinical Research Solutions). The resulting overall participant distribution in the long-term extension period was approximately 3:1 (tezepelumab to placebo). Participants, investigators, and site staff were masked to treatment assignment, which was assigned using an interactive voice and web response system. Treatment was administered to the participants by the investigators. Investigators were masked to treatment as tezepelumab and the placebo were identical in appearance.

Procedures

The screening and randomisation visit was the same day as the end-of-treatment visit in the parent studies (week 52 in NAVIGATOR and week 48 in SOURCE). In DESTINATION, participants received either tezepelumab 210 mg or placebo every 4 weeks subcutaneously for 52 weeks for those who previously completed NAVIGATOR and 56 weeks for those who previously completed SOURCE, resulting in a total of 104 weeks of treatment. Participants who were unable to attend an on-site initial visit for DESTINATION due to the COVID-19 pandemic were allowed to enter the study by the end of the safety follow-up period of the parent studies. Participants who completed the treatment period in DESTINATION entered one of two follow-up periods without treatment (appendix p 34). Participants recruited from NAVIGATOR could choose to enter either a 12-week follow-up period or a 36-week extended follow-up period. Data from the 36-week extended follow-up period are not included in the presented analyses. Individuals recruited from SOURCE were only eligible to enter the 12-week follow-up period due to the smaller sample size and logistical issues. Participants continued to receive their prescribed controller medications throughout the study. Step-down of oral corticosteroid or inhaled corticosteroids could be done at the discretion of the study physician using the protocol guidance for changes to background asthma medication, adapted from GINA.11

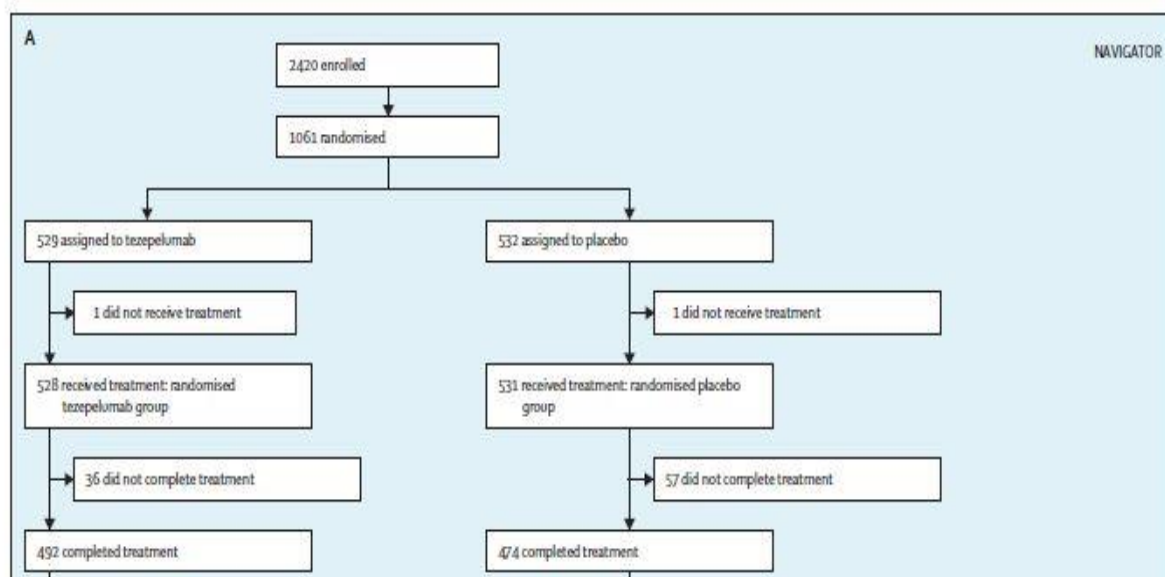
Outcomes

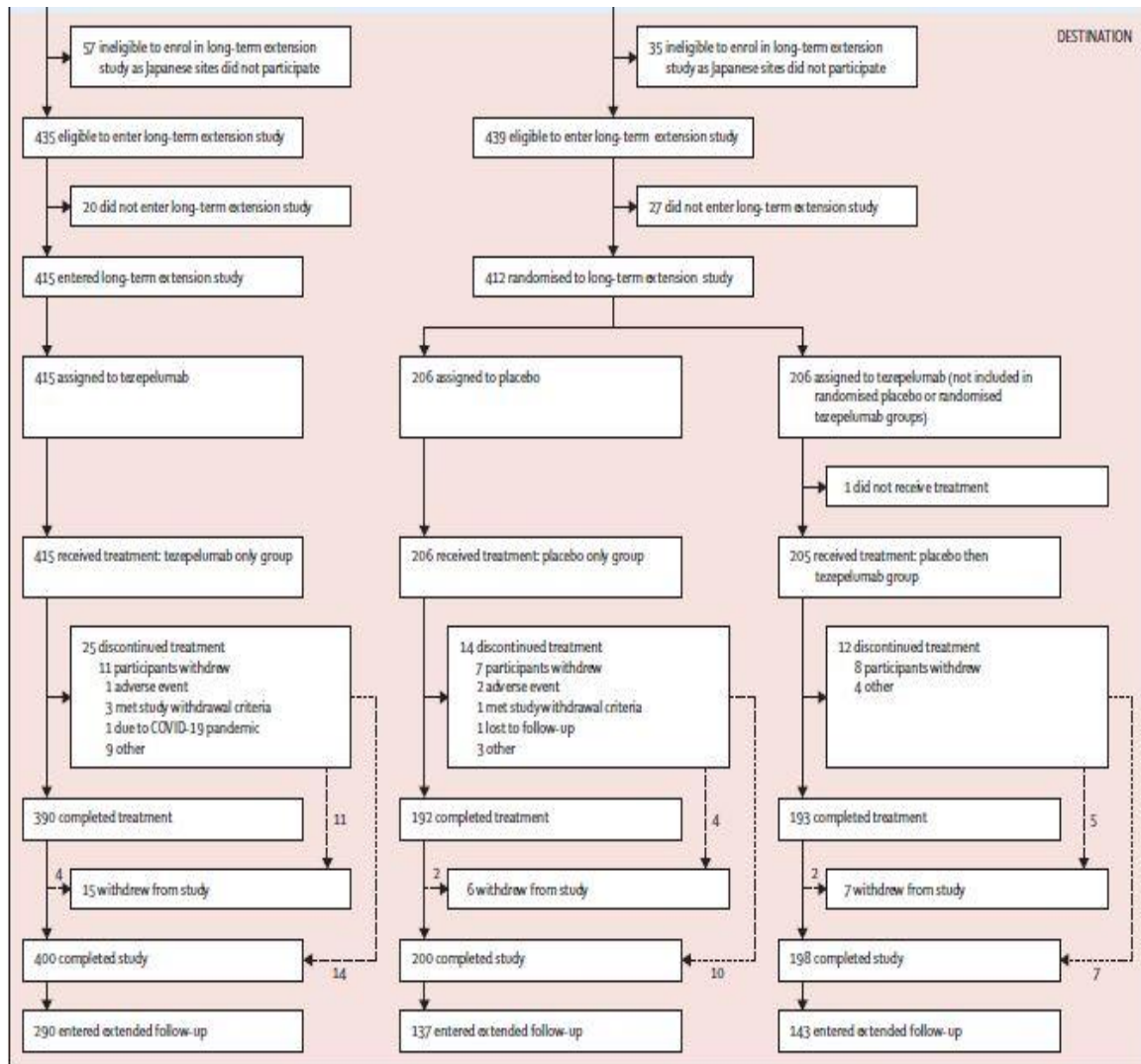
The primary endpoints were exposure-adjusted incidence of adverse events and serious adverse events over 104 weeks, including the treatment duration of the parent studies. The secondary endpoint was the annualised asthma exacerbation rate over 104 weeks. This rate was also assessed in subgroups of participants initially from NAVIGATOR (appendix p 5).

Exploratory outcomes related to asthma exacerbations were time-to-first exacerbation over 104 weeks and the annualised rate of exacerbations that were associated with hospitalisation (>24 hours in hospital) or an emergency department visit (<24 hours in an emergency department, and required systemic corticosteroids for ≥ 3 consecutive days) over 104 weeks. Other exploratory outcomes included change from baseline to week 104 in: pre-bronchodilator FEV1 (minimum clinically relevant difference=0.1 L); 12 six-item Asthma Control Questionnaire (ACQ-6; range, 0 [no impairment] to 6 [maximum impairment]; minimum clinically important difference=0.5 points); 11 St George's Respiratory Questionnaire score (SGRQ; range, 0 [no impairment] to 100 [maximum impairment]; minimum clinically important difference=4 points); 13 and type 2 biomarker levels (blood eosinophils, fractional exhaled nitric oxide [FeNO]; and serum total immunoglobulin E [IgE]). For all endpoints, baseline was defined as week 0 of the parent study.

Statistical analyses

No statistical hypotheses were formally tested during the study (ie, none of the analyses included type I error control). The primary safety and primary full analysis datasets comprised all participants who were randomised and who received at least one dose of tezepelumab or placebo in either of the parent studies, regardless of whether they were enrolled in DESTINATION. These primary treatment groups are referred to as randomised tezepelumab and randomised placebo and are defined in the appendix (appendix p 35). Safety analyses were also done in the all tezepelumab group, which comprised individuals randomised to tezepelumab in the parent study plus data from the long-term extension period from those who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION. Exposure was calculated from start of tezepelumab treatment; details of on-treatment and on-study analyses are included in the appendix (p 5).





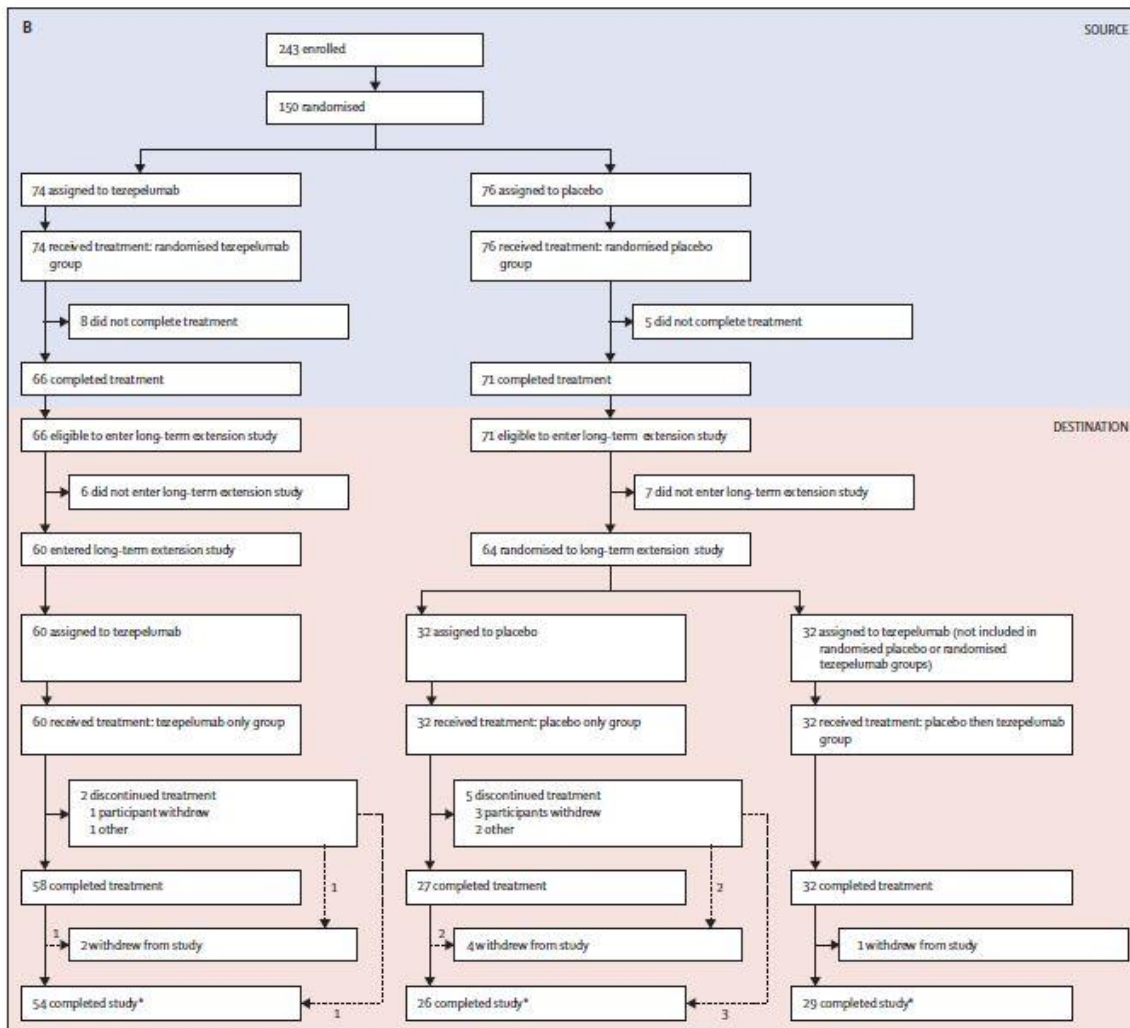


Figure 1: Study profile for participants initially from NAVIGATOR (A) and SOURCE (B)
 Treatment groups for the primary analysis set (ie, randomised tezepelumab and randomised placebo) and supportive long-term extension analysis set (ie, tezepelumab only, placebo only, and placebo then tezepelumab) are indicated. *Eight individuals were still in the safety follow-up at the time of database lock (four in the tezepelumab only group, two in the placebo only group, and two in the placebo then tezepelumab group).

The supportive long-term extension and supportive full analysis datasets only included participants who were enrolled in DESTINATION (appendix p 35). Participants were grouped as follows: those who received tezepelumab in the parent study and in DESTINATION (tezepelumab only group); those who received placebo in the parent study and switched to tezepelumab in DESTINATION (placebo then tezepelumab group); and those who received placebo in the parent study and in DESTINATION (placebo only group).

On-treatment adverse events and serious adverse events were summarised for the safety analysis set over the 104-week study period using exposure-adjusted incidence to account for variability in follow-up. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) system (version 24.1). Incidence per 100 patient-years were calculated as the number of participants reporting adverse events or serious adverse events divided by total exposure duration across all participants in the given treatment group, multiplied by 100. A post-hoc analysis of COVID-19-related adverse events was also done, adjusting only for exposure after the start of the pandemic. The secondary endpoint of annualised asthma exacerbation rate over 104 weeks in the tezepelumab and placebo groups was compared using a negative binomial model with the total number of asthma exacerbations experienced from baseline in the parent studies until week 104 in the long-term extension period as a response variable. Full statistical analyses for safety and efficacy related endpoints are described in the appendix (pp 4–5).

This study is registered with ClinicalTrials.gov, NCT03706079.

	NAVIGATOR randomised tezepelumab (n=528)	NAVIGATOR randomised placebo (n=531)	SOURCE randomised tezepelumab (n=74)	SOURCE randomised placebo (n=76)
Age, years	49.9 (16.3)	49.0 (15.9)	53.5 (12.1)	53.4 (11.9)
Sex				
Female	335 (63%)	337 (63%)	49 (66%)	45 (59%)
Male	193 (37%)	194 (37%)	25 (34%)	31 (41%)
BMI, kg per m ²	28.7 (7.1)	28.3 (6.9)	29.3 (6.7)	29.4 (7.4)
Race				
White	332 (63%)	327 (62%)	62 (84%)	64 (84%)
Black or African American	30 (6%)	31 (6%)	1 (1%)	0
Asian	146 (28%)	149 (28%)	11 (15%)	11 (15%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0	0	0
American Indian or Alaska Native	0	1 (<1%)	0	0
Other	19 (4%)	23 (4%)	0	1 (1%)
Ethnicity				
Hispanic or Latin American	83 (16%)	81 (15%)	10 (14%)	14 (18%)
Not Hispanic or Latin American	445 (84%)	450 (85%)	64 (86%)	62 (82%)
Inhaled corticosteroid dose group*				
Low	0	1 (<1%)	0	0
Medium	131 (25%)	132 (25%)	1 (1%)	0
High	397 (75%)	398 (75%)	73 (99%)	76 (100%)
Maintenance oral corticosteroid use	49 (9%)	51 (10%)	74 (100%)	76 (100%)
Pre-bronchodilator FEV ₁ , L	1.83 (0.72)	1.85 (0.71)	1.56 (0.50)	1.59 (0.64)
Pre-bronchodilator FEV ₁ , % predicted	62.8% (18.0)	62.7% (18.0)	54.3% (18.1)	53.3% (18.4)
Exacerbations in the past 12 months				
1	0	1 (<1%)	34 (46%)	30 (40%)
2	310 (59%)	324 (61%)	27 (37%)	25 (33%)
>2	218 (41%)	206 (39%)	13 (18%)	21 (28%)
FeNO concentration, ppb				
Mean	41.38 (36.30)	46.27 (44.73)	38.71 (40.82)	42.35 (37.44)
Median	31.0 (16.0-55.0)	30.0 (16.0-57.0)	26.0 (16.0-48.0)	28.0 (17.0-47.0)
FeNO group				
<25 ppb	213 (41%)	220 (42%)	32 (47%)	26 (38%)
≥25 to <50 ppb	158 (30%)	151 (29%)	20 (29%)	27 (39%)
≥50 ppb	151 (29%)	156 (30%)	16 (24%)	16 (23%)
Blood eosinophil count, cells per µL				
Mean	327 (293)	353 (488)	253 (203)	232 (154)
Median	250 (140-410)	250 (140-430)	215 (100-370)	200 (115-310)
Blood eosinophil count group				
<150 cells per µL	138 (26%)	138 (26%)	27 (37%)	24 (32%)
150 to <300 cells per µL	171 (32%)	171 (32%)	19 (26%)	28 (37%)
300 to <450 cells per µL	99 (19%)	95 (18%)	20 (27%)	16 (21%)
≥450 cells per µL	120 (23%)	127 (24%)	8 (11%)	8 (11%)

(Table 1 continues on next page)

	NAVIGATOR randomised tezepelumab (n=528)	NAVIGATOR randomised placebo (n=531)	SOURCE randomised tezepelumab (n=74)	SOURCE randomised placebo (n=76)
(Continued from previous page)				
Serum total IgE, IU per mL				
Mean	515.68 (959.75)	614.05 (1159.49)	298.71 (576.28)	300.89 (521.39)
Median	194.85 (56.15-545.10)	196.70 (51.90-597.00)	109.40 (32.30-278.90)	122.65 (39.35-304.75)
FEIA positive for any perennial aeroallergen	339 (64%)	341 (64%)	25 (34%)	34 (45%)
Data are mean (SD), n (%), or median (IQR) and are from the primary safety analysis dataset. The randomised tezepelumab group included all individuals randomised to tezepelumab in the parent study, and the randomised placebo group included all individuals randomised to placebo in the parent study excluding data from the long-term extension period for those re-randomised to receive tezepelumab. FeNO= fractional exhaled nitric oxide, ppb=parts per billion, IgE=immunoglobulin E, FEIA= fluorescence enzyme immunoassay. *Medium-dose inhaled corticosteroids: fluticasone propionate 500 µg per day or equivalent; high-dose inhaled corticosteroids: fluticasone propionate >500 µg per day or equivalent; one individual in the placebo group received fluticasone propionate <500 µg per day or equivalent.				
Table 1: Baseline demographics and clinical characteristics of participants				

Role of the funding source

The funders of the study, AstraZeneca and Amgen, contributed to the study design and data interpretation, and funded medical writing support for this manuscript. The study sponsor, AstraZeneca, did the study, coordinated the data management, and did the statistical analysis in collaboration with investigators at the academic centres, all of whom had access to the final study data.

Results

Participants were enrolled in NAVIGATOR from Nov 23, 2017, and in SOURCE from March 5, 2018. The first participant was enrolled in DESTINATION on Jan 7, 2019, and the last on Oct 15, 2020. The last end-of-treatment visit was Oct 26, 2021. The primary dataset included 1059 participants from NAVIGATOR (randomised tezepelumab n=528; randomised placebo n=531) and 150 participants from SOURCE (randomised tezepelumab n=74; randomised placebo n=76). Rollover rates into DESTINATION were high from both studies. In total, 951 participants (827 from NAVIGATOR and 124 from SOURCE) were randomised into DESTINATION. Participants from Japanese sites in NAVIGATOR (n=59 initiated on tezepelumab [57 completed treatment] and n=38 [35 completed treatment] taking placebo) did not participate in DESTINATION. Of those who completed treatment in the parent studies and enrolled in countries other than Japan, 95% (827/874) of NAVIGATOR participants and 91% (124/137) of SOURCE participants entered DESTINATION. Subsequently, 94% (775/827) of participants initially from NAVIGATOR and 94% (117/124) of participants initially from SOURCE who enrolled in DESTINATION completed treatment in the long-term extension period (figure 1).

Among participants from both parent studies, baseline demographics and clinical characteristics were well balanced between treatment groups (table 1). The participant demographics and clinical characteristics for the supportive long-term extension analysis dataset were similar to those of the primary analysis dataset (appendix p 8). Among those initially from NAVIGATOR, a smaller proportion of participants in the supportive long-term extension analysis dataset were receiving maintenance oral corticosteroids than in the primary analysis dataset.

	NAVIGATOR randomised tezepelumab (n=528)	NAVIGATOR randomised placebo (n=531)	SOURCE randomised tezepelumab (n=74)	SOURCE randomised placebo (n=76)
Total time at risk across all participants, years	917.0	699.0	129.4	100.0
Any adverse event				
n	455 (86%)	438 (83%)	61 (82%)	70 (92%)
Incidence per 100 patient-years (95% CI)	49.62 (45.16-54.39)	62.66 (56.93-68.81)	47.15 (36.06-60.56)	69.97 (54.54-88.40)
Any adverse event resulting in death				
n	7 (1%)	1 (<1%)	2 (3%)	0
Incidence per 100 patient-years (95% CI)	0.76 (0.31-1.57)	0.14 (0.00-0.80)	1.55 (0.19-5.58)	0.00 (0.00-2.99)
Any serious adverse event				
n	72 (14%)	87 (16%)	17 (23%)	18 (24%)
Incidence per 100 patient-years (95% CI)	7.85 (6.14-9.89)	12.45 (9.97-15.35)	13.14 (7.65-21.04)	17.99 (10.66-28.44)
Any adverse event leading to discontinuation of treatment				
n	15 (3%)	21 (4%)	2 (3%)	2 (3%)
Incidence per 100 patient-years (95% CI)	1.64 (0.92-2.70)	3.00 (1.86-4.59)	1.55 (0.19-5.58)	2.00 (0.24-7.22)
Most common adverse events*				
Nasopharyngitis	129 (24%)	123 (23%)	17 (23%)	22 (29%)
Upper respiratory tract infection	71 (14%)	88 (17%)	12 (16%)	8 (11%)
Headache	56 (11%)	53 (10%)	9 (12%)	10 (13%)
Asthma	27 (5%)	61 (12%)	8 (11%)	14 (18%)
Bacterial bronchitis	30 (6%)	18 (3%)	8 (11%)	7 (9%)
Data are n (%), unless otherwise specified, and are from the primary safety analysis dataset. The randomised tezepelumab group included all individuals randomised to tezepelumab in the parent study, and the randomised placebo group included all individuals randomised to placebo in the parent study excluding data from the long-term extension period for those re-randomised to receive tezepelumab. *Adverse events that occurred in ≥10% of patients in any treatment group, irrespective of causality.				

Table 2: Summary of on-treatment adverse events

Due to the randomisation scheme at the start of the long-term extension period, total exposure time (ie, time at risk) was greater in the randomised tezepelumab group than in the randomised placebo group, with more exposure time for the randomised tezepelumab group occurring during the COVID-19 pandemic (appendix p 37). The exposure-adjusted incidence of any adverse events, any serious adverse events, and any adverse event leading to treatment discontinuation in the on-treatment period were lower in the randomised tezepelumab group than in the randomised placebo group across both parent studies (tables 2 and 3). In the primary safety analysis set, the most common adverse events (occurring in $\geq 10\%$ of participants) across treatment groups from both parent studies were nasopharyngitis, upper respiratory tract infection, headache, and asthma (defined in the protocol as asthma-related signs or symptoms that were serious, not consistent with the participant's pre-existing history as judged by the investigator, or that led to discontinuation of study drug). Similar adverse events were observed in the supportive long-term extension analysis set (appendix pp 10–13).

The on-study pooled incidence of deaths were 0.80 per 100 patient-years in the all tezepelumab group and 0.58 per 100 patient-years in the randomised placebo group (difference 0.22; 95% CI -0.61 to 0.94), with 11 deaths in those receiving tezepelumab and five deaths in those receiving placebo (appendix pp 14–16). No patterns were identified in either the causes of the deaths or the relationship of the deaths to the study drug dosing. No deaths were considered to be causally related to tezepelumab by a masked independent adjudication committee (appendix pp 15–16). One death was considered causally related to tezepelumab by the investigator, but not by the adjudication committee, because of the individual's medical history. The individual had metastatic colon cancer diagnosed during the study but had a history of iron deficiency that was not fully evaluated with a colonoscopy before entry into the parent study.

During the on-treatment period, there were fewer serious adverse events categorised in the MedDRA respiratory, thoracic, and mediastinal disorder system organ class in the randomised tezepelumab group than in the randomised placebo group (incidence of 1.74 in the randomised tezepelumab group vs 6.29 in the randomised

placebo group per 100 patient-years among those initially from NAVIGATOR; difference -4.55 , 95% CI -6.73 to -2.68 ; and 2.32 in the randomised tezepelumab group vs 10.00 in the randomised placebo group per 100 patient-years among those initially from SOURCE; -7.68 , -15.39 to -1.75 ; appendix pp 17–19). This difference was largely due to fewer asthma exacerbations associated with hospitalisation or an emergency department visit in the randomised tezepelumab group than in the randomised placebo group.

The incidence of a serious adverse event categorised in the MedDRA cardiac disorder system organ class during the on-treatment period was higher in the randomised tezepelumab group than in the randomised placebo group (0.87 in the randomised tezepelumab group vs 0 in the randomised placebo group per 100 patient-years among those initially from NAVIGATOR; difference 0.87 , 95% CI 0.32 to 1.71 ; 3.09 in the randomised tezepelumab group vs 0 in the randomised placebo group per 100 patient-years among those initially from SOURCE; 3.09 , -0.67 to 7.69 ; appendix pp 17–20). Including on-treatment events in the placebo then tezepelumab group, and on-study events in both treatment arms, the pooled on-study incidence of serious adverse events categorised as cardiac disorders were 1.30 in the all tezepelumab group versus 0.23 in the randomised placebo group per 100 patient-years (appendix pp 20–24). No pattern in either the cause of the cardiac serious adverse events or the timing of the cardiac serious adverse events in relation to study drug administration was identified. All participants with a cardiac disorder serious adverse event had at least two risk factors at baseline and 44% (eight of 18) had a cardiac disorder that might have contributed to these events (appendix p 25). Neither investigators nor a masked independent adjudication committee attributed causality to tezepelumab for any cardiac serious adverse event (appendix pp 23–24). Cardiac disorder system organ class adverse events occurred at similar rates in the randomised tezepelumab and randomised placebo group during the on-study period (appendix pp 26–28). Analysis of major adverse cardiovascular events by a blinded, independent adjudication committee was prespecified in the study protocol and prospectively evaluated. The incidence of major adverse cardiovascular events was similar between groups, with few events observed: 0.65 for the all tezepelumab group and 0.46 for the randomised placebo group per 100 patient-years (difference 0.19 , 95% CI -0.58 to 0.85 ; appendix p 29). Despite no on-treatment serious adverse events within the cardiac disorder system organ class being reported among placebo recipients, there were four adjudicated major adverse cardiovascular events among placebo recipients: one cerebrovascular serious adverse event, one cardiovascular death that occurred during study follow-up, and two cardiovascular deaths that were originally reported to be of unknown cause.

The on-treatment incidence of serious adverse events in the infections and infestations system organ class was balanced between treatment groups (appendix pp 17–19). A post-hoc analysis of COVID-19-related adverse events was done, adjusting only for exposure after the start of the pandemic (appendix p 37). No increase in rates of COVID-19-related adverse events, serious adverse events, and fatal adverse events with tezepelumab compared with placebo was observed (appendix p 30); fatal COVID-19 adverse events occurred in two ($<1\%$) of 602 participants in the tezepelumab group and one ($<1\%$) of 607 participants in the placebo group.

There were similar rates of on-treatment pneumonia serious adverse events in the randomised tezepelumab group and the randomised placebo group (0.76 in the randomised tezepelumab group vs 1.29 in the randomised placebo group per 100 patient-years among those initially in NAVIGATOR, difference -0.52 , 95% CI -1.74 to 0.47 ; and 3.09 in the randomised tezepelumab group vs 2.00 in the randomised placebo group per 100 patient-years among those initially from SOURCE, 1.09 , -4.23 to 5.99).

	NAVIGATOR tezepelumab and placebo groups	SOURCE tezepelumab and placebo groups
Any adverse event	-13.04 (-17.83 to -8.18)	-22.82 (-34.77 to -10.01)
Any adverse event resulting in death	0.62 (-0.10 to 1.44)	1.55 (-2.19 to 5.47)
Any serious adverse event	-4.59 (-7.69 to -1.65)	-4.85 (-14.88 to 4.53)
Any adverse event leading to discontinuation of treatment	-1.37 (-3.05 to 0.08)	-0.45 (-5.62 to 3.74)

Data are difference (95% CI) in incidence per 100 patient-years for the randomised tezepelumab and randomised placebo groups, and are from the primary safety analysis dataset.

Table 3: Differences between tezepelumab and placebo groups for incidence of on-treatment adverse events

The on-treatment incidence of injection-site reactions was low and similar in the randomised tezepelumab and randomised placebo groups (2.40 in the randomised tezepelumab group vs 2.15 in the randomised placebo group per 100 patient-years among those initially in NAVIGATOR, difference 0.25, 95% CI -1.33 to 1.73; and 0.00 in the randomised tezepelumab group vs 1.00 in the randomised placebo group per 100 patient-years among those initially in SOURCE, -1.00, -5.46 to 1.91). On-treatment malignancies were balanced between treatment groups (appendix p 31). Among participants initially from NAVIGATOR, the on-treatment incidence of hypersensitivity serious adverse events was 0.33 in the randomised tezepelumab group and 0.29 in the randomised placebo groups per 100 patient-years (0.04, -0.74 to 0.71); there were no hypersensitivity serious adverse events among those from SOURCE. On-treatment hypersensitivity was reported by three individuals in the randomised tezepelumab group (ie, immune thrombocytopenia, drug hypersensitivity, and contact dermatitis) and two individuals in the randomised placebo group (ie, anaphylactic reaction and rash). No cases of anaphylaxis were observed in the randomised tezepelumab group.

Tezepelumab reduced the annualised asthma exacerbation rate over 104 weeks compared with placebo. In participants initially from NAVIGATOR, the annualised asthma exacerbation rate over 104 weeks in the randomised tezepelumab group was 0.82 (95% CI 0.71–0.95) compared with 1.93 (1.70–2.20) in the randomised placebo group (rate ratio 0.42, 95% CI 0.35–0.51; figure 2A). In participants initially from SOURCE, the annualised asthma exacerbation rate over 104 weeks in the randomised tezepelumab group was 1.07 (0.76–1.51) compared with 1.76 (1.27–2.45) in the randomised placebo group (rate ratio 0.61, 0.38–0.96; figure 2B). Findings were similar in participants initially from NAVIGATOR and SOURCE in the supportive long-term extension analysis set (figure 2C and 2D). Across participants from both parent studies, tezepelumab reduced the annualised rate of asthma exacerbations that were associated with hospitalisation or an emergency department visit over 104 weeks compared with placebo (figure 2E–H).

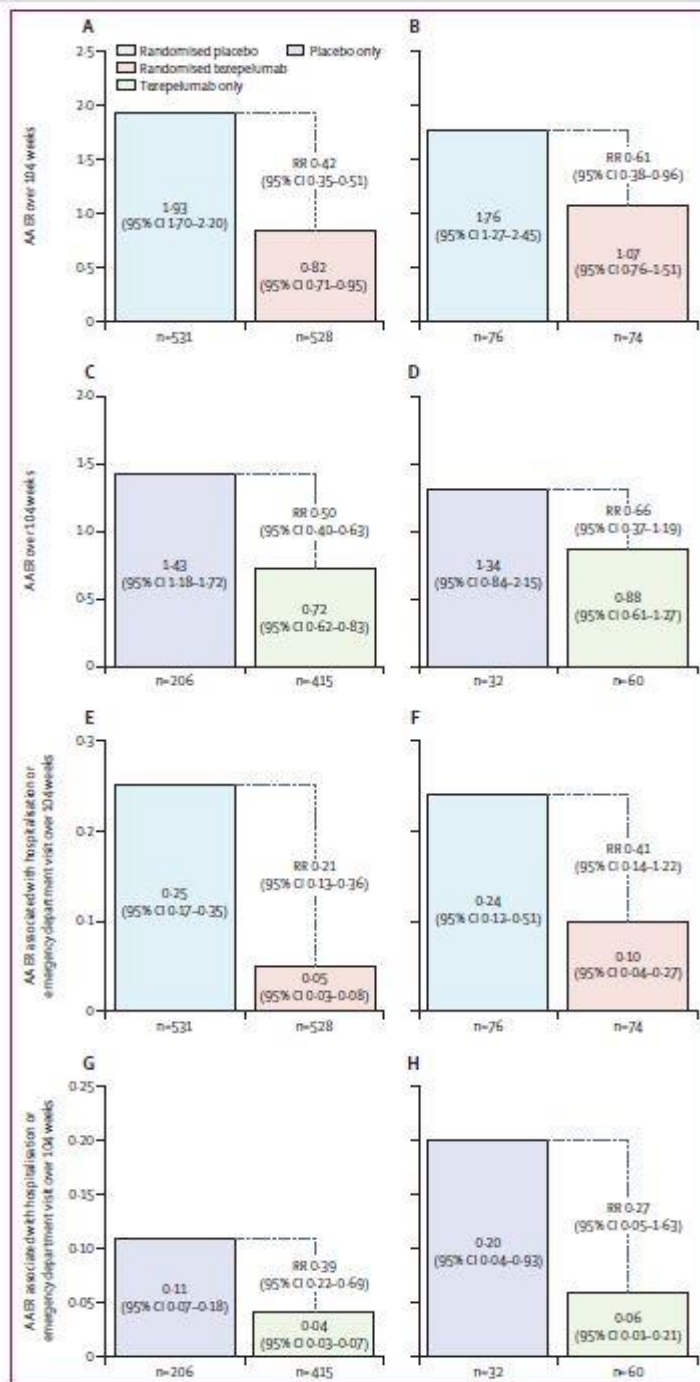


Figure 2: AAER and AAER associated with hospitalisation or emergency department visit over 104 weeks

Adjusted AAER from the primary full analysis dataset in participants initially from NAVIGATOR (A) and SOURCE (B); adjusted AAER from the supportive long-term extension analysis dataset in participants initially from NAVIGATOR (C) and SOURCE (D); adjusted AAER associated with hospitalisation or an emergency department visit from the primary full analysis dataset in participants initially from NAVIGATOR (E) and SOURCE (F); adjusted AAER associated with hospitalisation or an emergency department visit from the supportive long-term extension analysis dataset in participants initially from NAVIGATOR (G) and SOURCE (H). AAER=annualised asthma exacerbation rate. RR=rate ratio.

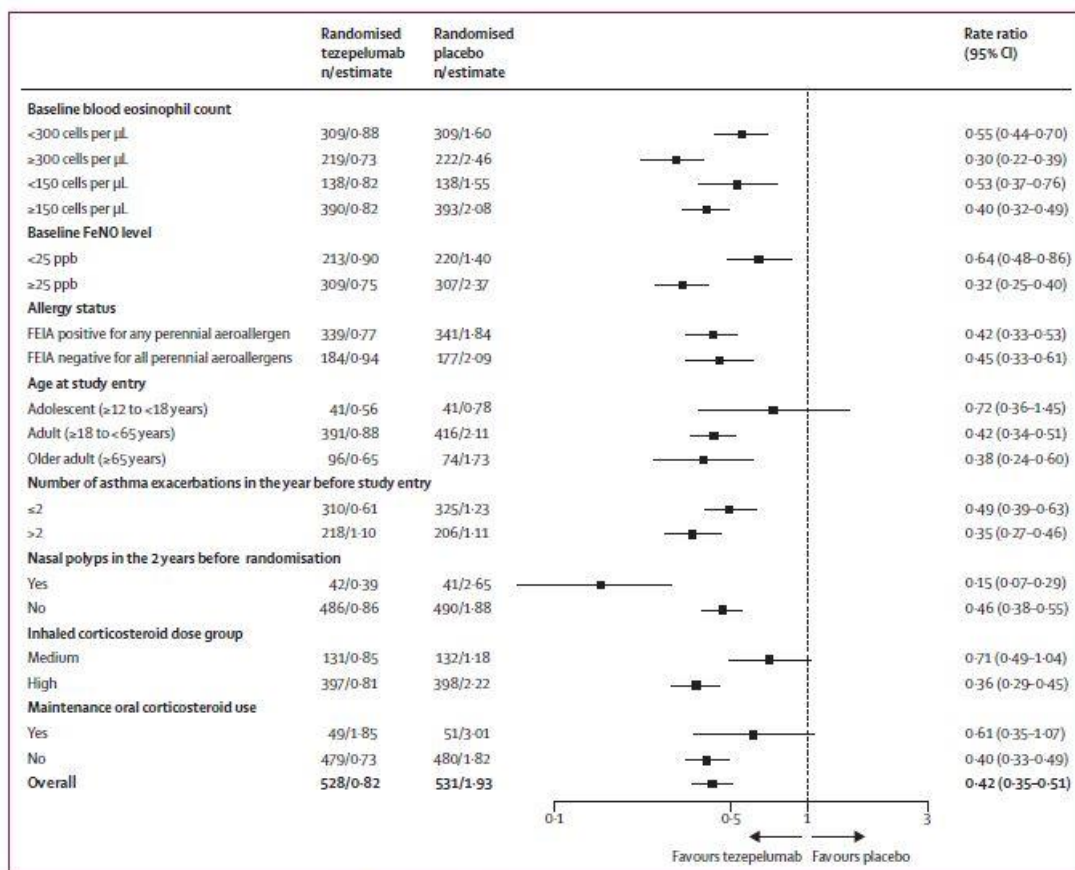
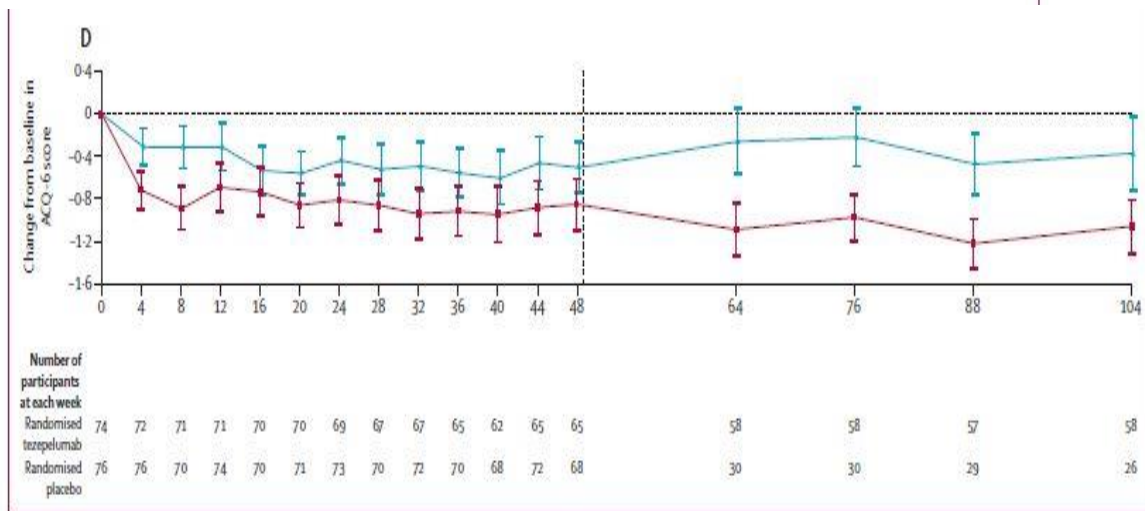
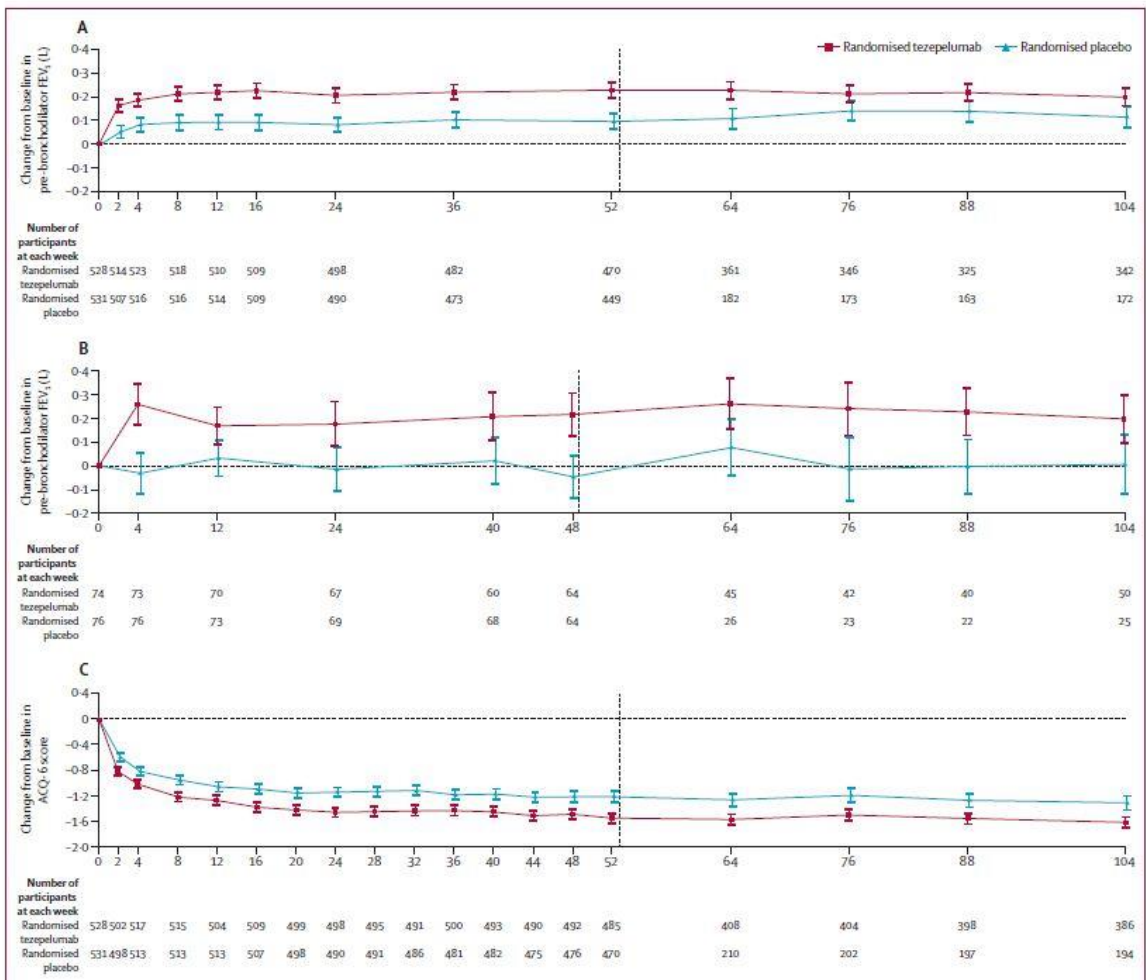


Figure 3: AAER over 104 weeks for participants initially from NAVIGATOR
Data are from the primary full analysis dataset. The randomised tezepelumab group included all participants randomised to tezepelumab in the parent study, and the randomised placebo group included all participants randomised to placebo in the parent study excluding data from the long-term extension period for those re-randomised to receive tezepelumab. AAER=annualised asthma exacerbation rate. FEIA=fluorescence enzyme immunoassay. FeNO=fractional exhaled nitric oxide.

In participants initially from NAVIGATOR, the annualised asthma exacerbation rate was consistently lower in the randomised tezepelumab group than in the randomised placebo group, irrespective of baseline inflammatory biomarkers and other clinical characteristics over 104 weeks (figure 3); time-to-first asthma exacerbation in these individuals was longer in the randomised tezepelumab group than in the randomised placebo group (hazard ratio 0.64, 95% CI 0.54–0.75; appendix p 38). Asthma exacerbations, including those associated with hospitalisation or an emergency department visit, were lower in the first year than those recorded in the 12 months before study entry across both treatment arms, with greater reductions in asthma exacerbations observed in the tezepelumab only group than in the placebo only group (appendix pp 39–41). During the second year, which included the beginning of the COVID-19 pandemic, asthma exacerbations were further reduced, with lower rates observed in the tezepelumab only group than in the placebo only group. Improvements in pre-bronchodilator FEV1, ACQ-6 score, and SGRQ score were sustained throughout the treatment period in the randomised tezepelumab group compared with the randomised placebo group in participants from both parent studies (appendix p 32; figure 4A–F). Results were similar in the supportive long-term extension analysis set (appendix p 42).

Reductions from baseline in blood eosinophil counts and FeNO concentrations were seen early and were sustained to week 104 in the randomised tezepelumab group (appendix pp 43–45). There was a progressive reduction in serum total IgE concentrations to week 104 in the randomised tezepelumab group (appendix pp 43–45). Results were similar in the supportive long-term extension analysis set (appendix p 33).

Results among the placebo then tezepelumab group were similar to the placebo only group during the parent study and similar to the tezepelumab only group during the second year (appendix pp 33, 39–42).



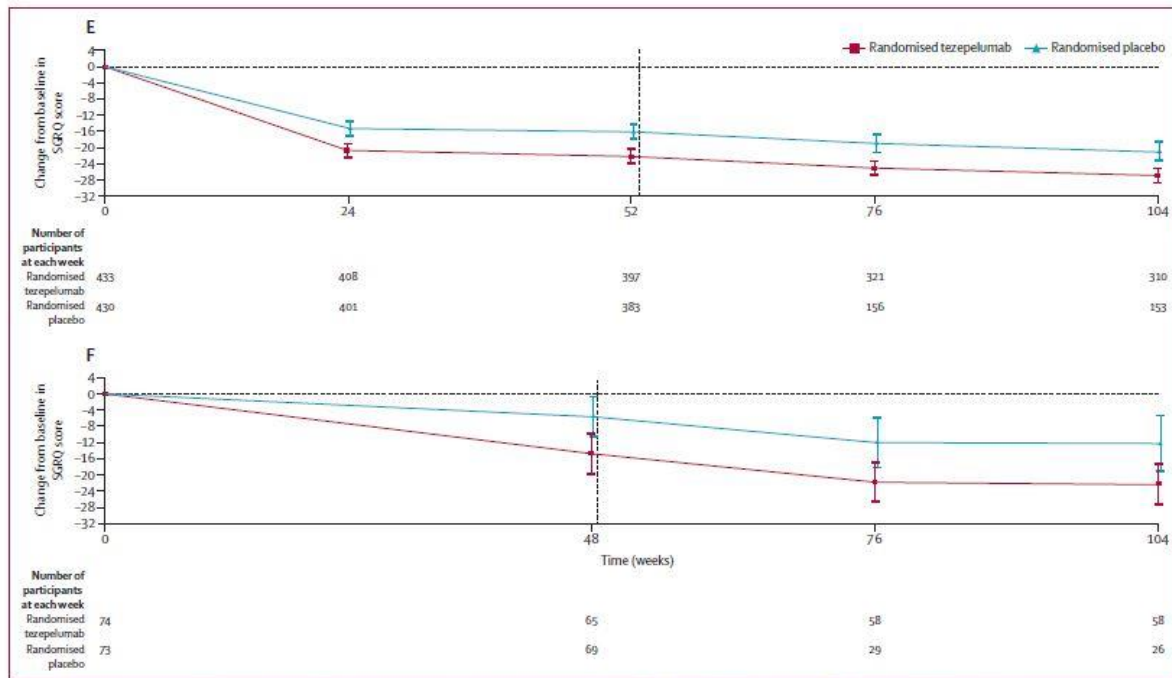


Figure 4: Change over time in pre-bronchodilator FEV₁, ACQ-6 score, and SGRQ score in participants initially from NAVIGATOR (A, C, and E) and SOURCE (B, D, and F). Data are adjusted means and 95% CIs from the primary full analysis dataset. The randomised tezepelumab group included all participants randomised to tezepelumab in the parent study. The randomised placebo group included all participants randomised to placebo in the parent study excluding data from the long-term extension period for those re-randomised to receive tezepelumab. ACQ-6=Asthma Control Questionnaire-6. SGRQ=St George's respiratory questionnaire.

Discussion

Tezepelumab was well tolerated in individuals with severe, uncontrolled asthma over 104 weeks of treatment. The exposure-adjusted incidence of adverse events and serious adverse events was lower with tezepelumab than with placebo. These findings following long-term exposure to tezepelumab are consistent with the favourable safety profile found in previous studies.^{5,7–9,14,15} DESTINATION also further confirmed the long-term benefits of tezepelumab in reducing exacerbations and improving lung function, asthma control, and health-related quality of life.

Within individual MedDRA-coded categories of serious adverse events, there was a lower incidence of respiratory, thoracic, and mediastinal disorder system organ class serious adverse events in the randomised tezepelumab group than in the randomised placebo group, but there was a higher incidence of cardiac disorder system organ class serious adverse events in participants receiving tezepelumab than in those receiving placebo. The reason for this imbalance in cardiac serious adverse events is not understood. There is no known biological mechanism by which blocking TSLP with tezepelumab would lead to cardiac pathophysiology, and the very low expression of TSLP and TSLP receptor mRNA in cardiac tissue suggests that signalling via the TSLP receptor pathway in these tissues is unlikely.¹⁶ The incidence of cardiac disorder adverse events was similar between tezepelumab and placebo recipients, with very few events independently adjudicated as major adverse cardiovascular events or cardiovascular deaths observed. No patterns were identified in the causes of cardiac serious adverse events among tezepelumab-treated individuals or in the timing of the cardiac serious adverse events in relation to tezepelumab dosing. Additionally, no cardiac serious adverse event was causally attributed to tezepelumab by either the investigator or a masked independent adjudication committee. All participants who had a cardiac disorder serious adverse event had at least two risk factors at baseline and 44% had a cardiac disorder at baseline. Imbalances in cardiac serious adverse events have not been observed in previous multidose studies of tezepelumab of up to 1 year of treatment.^{5,7,8,14,15,17} No causal relationship between tezepelumab and these events has been established, nor has a patient population at risk of these events been identified.

The incidence of cardiac serious adverse events in tezepelumab-treated participants in DESTINATION is similar to those estimated from publicly available data of other biologics for severe asthma.^{18–21} In the phase 3 Liberty Asthma QUEST study, a similar imbalance was observed, with cardiac serious adverse events reported in 14 dupilumab recipients but no placebo recipients, with similar rates of major adverse cardiovascular events and cardiovascular deaths between treatment groups.²² The incidence of cardiac serious adverse events in the placebo group in DESTINATION was substantially lower than the incidence in studies of other biologics for severe asthma.^{18–21} Asthma is associated with an increased risk of cardiovascular disorders, with hazard ratios for individuals with asthma reported to be between 1·1 and 3·2 times that of an individual without asthma.^{23–25} In these epidemiological studies, as in DESTINATION, the increased risk encompassed many different types of cardiovascular disorders.

The incidence of severe infection, including pneumonia, was similar between treatment groups, which suggests that tezepelumab's mechanism of action does not predispose users to infections. A similar finding was observed with malignancies. Tezepelumab recipients group did not have a higher rate of COVID-19-related infections or deaths than placebo recipients. The incidence of injection-site reactions with tezepelumab administration was low and similar to that of placebo. No cases of anaphylaxis related to tezepelumab were reported.

Tezepelumab treatment resulted in clinically meaningful reductions in asthma exacerbations compared with placebo over 2 years. Previous studies of biologics for severe asthma have also shown a reduction in exacerbation rates over time. However, these studies lacked a placebo control group, making these changes difficult to interpret.^{2–4,26}

Asthma exacerbation rates in the second year were in part reduced due to the COVID-19 pandemic and related social distancing.²⁷ Nevertheless, exacerbations and hospitalisations were reduced in the tezepelumab group compared with placebo during the second year.

Reductions in exacerbations occurred irrespective of baseline levels of inflammatory biomarkers and other clinical characteristics. The magnitude of reductions in exacerbations versus placebo was greater among those with high levels of type 2 inflammatory biomarkers or with nasal polyps compared with those with low levels of type 2 inflammatory biomarkers or without nasal polyps. This difference confirms findings from PATHWAY and NAVIGATOR^{5,7} that tezepelumab consistently shows clinically meaningful reductions in exacerbations in users across the spectrum of type 2 inflammation, with an enhanced effect in individuals with high type 2 biomarker levels. Although clinically meaningful reductions in exacerbations were observed in adolescents, greater reductions were seen in adults. The estimate of efficacy among adolescent participants is imprecise due to the small number of adolescents and the low exacerbation rate among adolescents in the placebo group.

Improvements from baseline in pre-bronchodilator FEV₁, ACQ-6 score, and SGRQ score were observed in the tezepelumab group as early as the first post-baseline assessment and were maintained up to week 104. Rapid and sustained reductions in blood eosinophil counts and FeNO concentrations were observed in the tezepelumab group compared with the placebo group, along with a progressive reduction in serum total IgE concentrations through week 104. Similar findings were seen in participants who switched from placebo in the parent study to tezepelumab in DESTINATION.

A strength of DESTINATION is the large number of patient-years of exposure to tezepelumab. The robustness of the dataset is shown by high roll-over rates of eligible individuals from the parent studies, low discontinuation rates within DESTINATION, and high treatment adherence. The data robustness allowed DESTINATION to rigorously address the question regarding the safety and efficacy of tezepelumab in patients treated for up to 2 years. DESTINATION also included individuals receiving tezepelumab during the COVID-19 pandemic: no evidence of an increased risk of severe COVID-19 disease was identified, while continued efficacy was observed despite a reduced incidence of exacerbations due to social distancing and other behavioural changes.

A limitation of DESTINATION was the imbalance in exposure between tezepelumab and placebo during the long-term extension period. Although the analysis accounted for these differences in exposure, the model assumed a constant risk through the observation periods, which might not have been true for some adverse events. The overall environment for the study, including non-confirmed COVID-19 illness, societal and health-care disruptions, and participant stress during the pandemic, was not consistent between years 1 and 2, and this might have had unrecognised consequences on the incidence of safety events. The safety and effectiveness of tezepelumab will continue to be assessed in ongoing and future studies.

In conclusion, DESTINATION showed that tezepelumab treatment was well tolerated for up to 2 years and resulted in sustained, clinically meaningful reductions in asthma exacerbations, with improved lung function, asthma control, and health-related quality of life in individuals with severe, uncontrolled asthma, consistent with results from NAVIGATOR and SOURCE. The incidence of adverse events was similar in the second year of treatment compared with the first, and the efficacy of tezepelumab was sustained over 2 years. These findings further show the safety and efficacy of tezepelumab in this population.

Contributors

All authors contributed to the study design, data interpretation, and drafting of the manuscript with support from a medical writer funded by the sponsors. All authors provided critical feedback and final approval for submission and vouch for the completeness and accuracy of the data and analyses and the adherence of the trial to the protocol. All authors had full access to and verified the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AM-G has attended advisory board meetings for AstraZeneca, GlaxoSmithKline, Novartis, Regeneron, Sanofi, and Teva Pharmaceuticals; has received speaker fees from AstraZeneca, Novartis, Sanofi, and Teva Pharmaceuticals; has participated in research with AstraZeneca, for which his institution has been remunerated; has attended international conferences with Teva Pharmaceuticals; and has consultancy agreements with AstraZeneca and Sanofi. MEW is an employee of National Jewish Health and has received consultancy fees from AstraZeneca, Equillium, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, resTORbio, Sanofi, and Teva Pharmaceuticals. CEB has received consultancy fees and grants from 4D Pharma, AstraZeneca, Chiesi, Genentech, GlaxoSmithKline, Mologic, Novartis, Regeneron, Roche, and Sanofi. SK has received fees for lectures or advisory board meetings from AstraZeneca, GlaxoSmithKline, Novartis, Roche, Sanofi Aventis, and Teva Pharmaceuticals. JC has received grants and personal fees from AstraZeneca, Genentech, and Vectura and has received grants from Optinose, Sanofi, and Teva Pharmaceuticals. EI has served as a consultant to and received personal fees from 4D Pharma, AB Science, Amgen, AstraZeneca, Avillion, Biometry, Cowen, Equillium, Genentech, GlaxoSmithKline, Merck, Novartis, Pneuma Respiratory, PPS Healthcare, Regeneron Pharmaceuticals, Sanofi, Sienna Biopharmaceuticals, and Teva Pharmaceuticals; has received non-financial support from Circassia, Teva Pharmaceuticals, and Vorso Corp; and has received clinical research grants from AstraZeneca, Avillion, Genentech, Gossamer Bio, Novartis, and Sanofi. GCh has received speaker and consultancy fees from Amgen, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and Teva Pharmaceuticals. AB, SP, GA, MG, KB, and GCo are employees of AstraZeneca and might own stock or stock options in AstraZeneca. SC is an employee of Amgen and owns stock in Amgen. LS is a consultant to AstraZeneca. KL is an employee of Cytel.

Data sharing

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

Acknowledgments

This study was funded by AstraZeneca and Amgen. We thank the study participants and their families, the investigators, and the site staff. Medical writing support was provided by Madeleine Wynn of PharmaGenesis London, London, UK, with funding from AstraZeneca and Amgen.

Funding:

AstraZeneca and Amgen.

Conflict of interest statement

Declaration of interests AM-G has attended advisory board meetings for AstraZeneca, GlaxoSmithKline, Novartis, Regeneron, Sanofi, and Teva Pharmaceuticals; has received speaker fees from AstraZeneca, Novartis, Sanofi, and Teva Pharmaceuticals; has participated in research with AstraZeneca, for which his institution has been remunerated; has attended international conferences with Teva Pharmaceuticals; and has consultancy agreements with AstraZeneca and Sanofi. MEW is an employee of National Jewish Health and has received consultancy fees from AstraZeneca, Equillium, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, resTORbio, Sanofi, and Teva Pharmaceuticals. CEB has received consultancy fees and grants from 4D Pharma, AstraZeneca, Chiesi, Genentech, GlaxoSmithKline, Mologic, Novartis, Regeneron, Roche, and Sanofi. SK has received fees for lectures or advisory board meetings from AstraZeneca, GlaxoSmithKline, Novartis, Roche, Sanofi Aventis, and Teva Pharmaceuticals. JC has received grants and personal fees from AstraZeneca, Genentech, and Vectura and has received grants from Optinose, Sanofi, and Teva Pharmaceuticals. EI has served as a consultant to and received personal fees from 4D Pharma, AB Science, Amgen, AstraZeneca, Avillion, Biometry, Cowen, Equillium, Genentech, GlaxoSmithKline, Merck, Novartis, Pneuma Respiratory, PPS Healthcare, Regeneron Pharmaceuticals, Sanofi, Sienna Biopharmaceuticals, and Teva Pharmaceuticals; has received non-financial support from Circassia, Teva Pharmaceuticals, and Vorso Corp; and has received clinical research grants from AstraZeneca, Avillion, Genentech, Gossamer Bio, Novartis, and Sanofi. GCh has received speaker and consultancy fees from Amgen, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and Teva Pharmaceuticals. AB, SP, GA, MG, KB, and GCo are employees of AstraZeneca and might own stock or stock options in AstraZeneca. SC is an employee of Amgen and owns stock in Amgen. LS is a consultant to AstraZeneca. KL is an employee of Cytel.

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