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

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Summary

Background. Tezepelumab is a human monoclonal antibody that blocks thymic stromal lymphopoietin.

Methods. DESTINATION was a phase 3, multicentre, randomised, double-blind, placebo-controlled, long-term extension study evaluating the safety and efficacy of tezepelumab 210 mg subcutaneously every 4 weeks in adults and adolescents with severe, uncontrolled asthma who completed treatment in the phase 3 NAVIGATOR (NCT03347279) or SOURCE (NCT03406078) studies. Randomisation was stratified by the parent study. Patients, investigators, and site staff were masked to treatment assignment. Exposure-adjusted incidence (patients with event/total exposure) of adverse events (AEs) and serious AEs (SAEs) (primary endpoints) and the annualised asthma exacerbation rate (AAER) (secondary endpoint) were assessed from week 0 of the parent studies through week 104 of DESTINATION.

Findings. In patients who initially received tezepelumab (n=528) or placebo (n=531) in NAVIGATOR, incidence per 100 patient-years (95% confidence interval [CI]) over 104 weeks were 49·62 (45·16, 54·39) and 62·66 (56·93, 68·81) for AEs (difference tezepelumab vs placebo, −13·04; 95% CI −17·83, −8·18), and 7·85 (95% CI 6·14, 9·89) and 12·45 (9·97, 15·35) for SAEs (difference −4.59; 95% CI −7.69, −1.65), respectively. In those who initially received tezepelumab (n=74) or placebo (n=76) in SOURCE, incidence (95% CI) were 47·15 (36·06, 60·56) and 69·97 (54·54, 88·40) for AEs (difference −22·82; 95% CI −34·77, −10·01), and 13·14 (7·65, 21·04) and 17·99 (10·66, 28·44) for SAEs (difference −4.85; 95% CI −14.88, 4.53), respectively. Tezepelumab reduced the AAER over 104 weeks compared with placebo. In patients initially from NAVIGATOR, the AAER ratio over 104 weeks was 0·42 (95% CI 0·35, 0·51). In patients initially from SOURCE, the AAER ratio over 104 weeks was 0·61 (95% CI 0·38, 0·96).

Interpretation. Tezepelumab treatment was well tolerated for up to 2 years and resulted in sustained, clinically meaningful reductions in asthma exacerbations in patients with severe,

uncontrolled asthma. These findings are consistent with prior randomized, placebo-controlled studies and demonstrate the long-term safety and sustained efficacy of tezepelumab in patients with severe, uncontrolled asthma.

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Research in context

Evidence before this study

Tezepelumab has been approved by the US Food and Drug Administration and European Medicines Agency as a biologic treatment for severe asthma with no biomarker or phenotypic restrictions, based on data from the phase 2b PATHWAY study and the phase 3 NAVIGATOR and SOURCE studies. These studies assessed tezepelumab treatment for up to 1 year as an add-on therapy for severe, uncontrolled asthma. However, patients typically receive treatment with biologics for longer periods than 1 year. A PubMed search of all entries before June 24, 2021, for English language primary publications using the terms “tezepelumab” and “long-term extension study” returned no relevant data from clinical trials.

Added value of this study

DESTINATION was a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, long-term extension study enrolling patients who had completed treatment in the 52-week NAVIGATOR study or the 48-week SOURCE study. It is the first long-term extension study of a biologic for severe asthma to include a placebo group. Patients received treatment for up to 104 weeks. There were high roll-over rates of eligible patients from the parent studies into DESTINATION, low discontinuation rates and high treatment adherence rates. Tezepelumab was well-tolerated for up to 2 years, with lower incidences of adverse events (AEs) and serious adverse events (SAEs) with tezepelumab than with placebo. The incidence per 100 patient-years of SAEs that were categorized as respiratory, thoracic and mediastinal disorders in the Medical Dictionary for Regulatory Activities

(MedDRA) system organ class was lower in those who received tezepelumab than those who received placebo. The incidence of SAEs categorized as cardiac disorders in the MedDRA system organ class was higher in those who received tezepelumab than placebo. The incidence of cardiac disorder AEs were similar between tezepelumab and placebo recipients. The incidence of independently adjudicated major adverse cardiovascular events and cardiovascular deaths were similar between tezepelumab and placebo recipients, with very few events observed. Serious cardiac events will continue to be assessed in ongoing and future studies. Tezepelumab treatment was associated with clinically meaningful reductions in asthma exacerbations, and improved lung function, asthma control and health-related quality of life, which were sustained for up to 2 years.

Implications of all the available evidence

Multiple randomized, placebo-controlled studies have demonstrated that tezepelumab is well tolerated and support the long-term efficacy of tezepelumab in a broad patient population.

Introduction

Biologics are recommended as add-on therapy in patients with severe, uncontrolled asthma. Approval of these drugs is usually based on 1-year safety and efficacy studies, but these therapies are typically used by patients for longer periods.[1] Long-term extension (LTE) studies for biologics in severe asthma have been performed.[2-4] However, these lack a placebo group to provide context for the safety and efficacy data.

Tezepelumab, a human monoclonal antibody (immunoglobulin [Ig] G2λ), binds specifically to thymic stromal lymphopoietin (TSLP) and prevents it from interacting with its heterodimeric receptor.[5] TSLP, an epithelial cytokine, plays 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 hyperresponsiveness.[6]

Tezepelumab reduced the annualised asthma exacerbation rate (AAER) and improved lung function, asthma control, and health-related quality of life (HRQoL) in patients with severe, uncontrolled asthma in the phase 2b PATHWAY (ClinicalTrials.gov identifier: 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 (OCS) reduction was not met, tezepelumab reduced the AAER and improved lung function, asthma control and HRQoL compared with placebo in patients with OCS-dependent asthma.[8] Based on 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 biologic treatment for severe asthma with no biomarker or phenotypic restrictions.[9] The 2022 Global Initiative for Asthma (GINA) guidelines recommend anti-TSLP therapy for patients with and without evidence of type 2 (T2) inflammation.[1]

Here, we report results from DESTINATION (NCT03706079), a long-term, randomised, placebo-controlled extension study that enrolled patients 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 through 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 LTE study to evaluate the safety and efficacy of tezepelumab 210 mg subcutaneously every 4 weeks in patients who completed treatment in the 52-week NAVIGATOR study or the 48-week SOURCE study (**Figure S1**). Full details have been published previously.[10]

The study protocol is included in the Supplementary Appendix. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. Approvals from independent ethics committees were obtained, and all patients provided written informed consent in accordance with local requirements.

Patients

Patients were aged 12–80 years old with severe, uncontrolled asthma and received medium- to high-dose inhaled corticosteroids (ICS), with at least one additional asthma controller medication with or without OCS. 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 patient (**Table S1**).

Randomisation and masking

DESTINATION randomisation was stratified by the parent study (see Supplementary Appendix for stratification factors in NAVIGATOR and SOURCE). All patients were re-randomised to maintain masking and assigned new enrolment codes. Patients who were previously randomised to receive tezepelumab in either parent study continued tezepelumab 210 mg subcutaneously every four weeks (Q4W). Patients who were previously randomised to receive placebo in either parent study were re-randomised 1:1 to receive either tezepelumab 210 mg Q4W or placebo every four weeks using a randomisation list prepared by a computerised system (Calyx Clinical Research Solutions). The resulting overall patient distribution in the LTE period was approximately 3:1 (tezepelumab:placebo). Patients, investigators, and site staff were masked to treatment assignment, which was assigned using an interactive voice/web response system.

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, patients received either tezepelumab 210 mg or placebo every 4 weeks subcutaneously for 52 weeks and 56 weeks for those who previously completed NAVIGATOR and SOURCE, respectively, resulting in a total of 104 weeks of treatment. Patients 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.

Patients who completed the treatment period in DESTINATION entered one of two follow-up periods without treatment (**Figure S1**). Patients 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. Patients recruited from SOURCE were only eligible to enter the 12-week follow-up period. Patients

continued to receive their prescribed controller medications throughout the study. Step-down of OCS and/or ICS could be performed at the discretion of the study physician using the protocol guidance for changes to background asthma medication, adapted from GINA 2018.[11]

Outcomes

The primary endpoints were exposure-adjusted incidence of adverse events (AEs) and serious AEs (SAEs) over 104 weeks, including the treatment duration of the parent studies. The secondary endpoint was the AAER over 104 weeks. This was also assessed in subgroups of patients initially from NAVIGATOR, as described in the Supplementary Appendix.

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 or an emergency department (ED) visit over 104 weeks. Other exploratory outcomes included change from baseline to week 104 in pre-bronchodilator forced expiratory volume in 1 second (FEV_1; clinically relevant difference, 0.1 L),[12] Asthma Control Questionnaire score (ACQ-6; range, 0 [no impairment] to 6 [maximum impairment]; minimum clinically important difference [MCID], 0.5 points),[11] St George's Respiratory Questionnaire score (SGRQ; range, 0 [no impairment] to 100 [maximum impairment]; MCID, 4 points),[13] and T2 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 (i.e., none of the analyses included type I error control). The primary safety and primary full analysis datasets comprised all patients 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 'rand teze'

and 'rand pbo' and are defined in **Figure S2**. Safety analyses were also conducted in an additional group, the 'all teze' group, which comprised patients randomised to tezepelumab in the parent study, plus data from the LTE period from patients 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 Supplementary Appendix.

The supportive LTE and supportive full analysis datasets only included patients who were enrolled in DESTINATION (**Figure S2**). Patients were grouped as follows: (i) patients who received tezepelumab in the parent study and in DESTINATION ('teze+teze'), (ii) patients who received placebo in the parent study and switched to tezepelumab in DESTINATION ('pbo+teze'), and (iii) patients who received placebo in the parent study and in DESTINATION ('pbo+pbo').

On-treatment AEs and SAEs were summarised for the safety analysis set over the 104-week study period using exposure-adjusted incidence to account for variability in follow-up. Incidence per 100 patient-years were calculated as the number of patients reporting AEs or SAEs divided by total exposure duration across all patients in the given treatment group, multiplied by 100. 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 LTE period as a response variable. Full statistical analyses for safety and efficacy related endpoints are described in the Supplementary Appendix.

Role of the funding source

The funders of the study (AstraZeneca and Amgen) contributed to the study design and data interpretation. The study sponsor (AstraZeneca) conducted the study, coordinated the data management, and performed the statistical analysis in collaboration with investigators at the academic centres, all of whom had access to the final study data.

Results

Patients were enrolled in NAVIGATOR from November 23, 2017 and in SOURCE from March 5, 2018. The first patient was enrolled in DESTINATION on January 7, 2019, and the last end-of-treatment visit was October 26, 2021.

The primary dataset included 1059 patients from NAVIGATOR ('rand teze', n=528; 'rand pbo', n=531) and 150 patients from SOURCE ('rand teze', n=74; 'rand pbo', n=76). Roll over rates into DESTINATION were high from both studies. In total, 951 patients (827 from NAVIGATOR and 124 from SOURCE) were randomised into DESTINATION at 182 sites across 18 countries. Patients from Japanese sites in NAVIGATOR (n=59 for tezepelumab and n=38 for placebo) did not participate in DESTINATION. Of the patients who completed treatment in the parent studies and enrolled in countries other than Japan, 95% (827/874) of NAVIGATOR patients and 91% (124/137) of SOURCE patients entered DESTINATION. Subsequently, 94% (775/827) of patients initially from NAVIGATOR and 94% (117/124) of patients initially from SOURCE who enrolled in DESTINATION completed treatment in the LTE period (**Figure 1**).

Among patients from both parent studies, baseline demographics and clinical characteristics were generally well balanced between treatment groups (**Table 1**). The patient demographics and clinical characteristics for the supportive LTE analysis dataset were generally similar to those of the primary analysis dataset (**Table S2**). Among patients initially from NAVIGATOR, a smaller proportion of patients in the supportive LTE analysis dataset were receiving maintenance OCS than in the primary analysis dataset.

Due to the randomization scheme at the start of the LTE period, total exposure time (time at risk) was greater in the 'rand teze' group than in the 'rand pbo' group, with more exposure time for the 'rand teze' group occurring during the COVID-19 pandemic (**Figure S3**). The exposure-adjusted incidence of any AEs, any SAEs, and any AE leading to treatment discontinuation in the on-treatment period were lower in the 'rand teze' group than in the

'rand pbo' group across both parent studies (**Table 2**). In the primary safety analysis set, the most common AEs (occurring in ≥10% of patients) across treatment groups from both parent studies were nasopharyngitis, upper respiratory tract infection, headache, and asthma. Similar AEs were observed in the supportive LTE analysis set (**Table S3**).

The on-study pooled incidence of deaths were 0·80 and 0·58 per 100 patient-years in the 'all teze' and 'rand pbo' groups, respectively (difference, 0·22 [95% CI −0·61, 0·94]), with 11 deaths in patients receiving tezepelumab and five deaths in those receiving placebo (**Table S4** and **Table S5**). 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 (**Table S5**). One death was considered causally related to tezepelumab by the investigator, but not by the adjudication committee, because of the patient's medical history. The patient 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 SAEs categorized in the Medical Dictionary for Regulatory Activities (MedDRA) respiratory, thoracic, and mediastinal disorder system organ class in the 'rand teze' group than in the 'rand pbo' group (incidence of 1·74 *vs* 6·29 per 100 patient-years among patients initially from NAVIGATOR, difference −4·55 [95% CI −6·73, −2·68], and 2·32 *vs* 10·00 per 100 patient-years among patients initially from SOURCE, difference −7.68 [95% CI −15.39, −1.75]); **Table S6**). This was largely due to fewer asthma exacerbations associated with hospitalisation or an ED visit in the 'rand teze' group than in the 'rand pbo' group.

The incidence of an SAE categorized in the MedDRA cardiac disorder system organ class during the on-treatment period was higher in the 'rand teze' group than in the 'rand pbo' group (0·87 *vs* 0 per 100 patient-years among patients initially from NAVIGATOR [difference 0·87; 95% CI 0·32, 1·71] and 3·09 *vs* 0 per 100 patient-years among patients initially from

SOURCE [difference 3·09; 95% CI −0·67, 7·69]; **Table S6**). Including on-treatment events in the 'pbo+teze' group and on-study events in both treatment arms, the pooled on-study incidence of SAEs categorized as cardiac disorders were 1.30 *vs* 0.23 per 100 patient-years for the 'all teze' and 'rand pbo' groups, respectively (**Tables S7 and S8**). No pattern in either the cause of the cardiac SAEs or the timing of the cardiac SAEs in relation to study drug administration was identified. All patients with a cardiac disorder SAE had at least two risk factors at baseline and 44% (8/18) had a cardiac disorder that may have contributed to these events (**Table S9**). Neither investigators nor a masked independent adjudication committee attributed causality to tezepelumab for any cardiac SAE (**Table S8**). Cardiac disorder system organ class AEs occurred at similar rates in the 'rand teze' and 'rand pbo' groups during the on-study period (**Table S10**). Analysis of major adverse cardiovascular events (MACE) by a blinded, independent adjudication committee was prespecified in the study protocol and prospectively evaluated. The incidence of MACE were similar between groups, with few events observed: 0·65 and 0·46 per 100 patient-years for the 'all teze' group and the 'rand pbo' group, respectively (difference 0·19 per 100 patient-years [95% CI −0·58, 0·85]) (**Table S11**). Despite no on-treatment SAEs within the cardiac disorder system organ class being reported among placebo recipients, there were 4 adjudicated MACE among placebo recipients: one cerebrovascular SAE, 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 SAEs in the infections and infestations system organ class was balanced between treatment groups (**Table S6**). A *post hoc* analysis of COVID-19-related AEs was performed, adjusting only for exposure after the start of the pandemic (**Figure S3**). No increase in rates of COVID-19-related AEs, SAEs, and fatal AEs with tezepelumab compared with placebo was observed (**Table S12**); fatal COVID AEs occurred in two tezepelumab recipients and one placebo recipient. There were similar rates of on-treatment pneumonia SAEs in the 'rand teze' group and the 'rand pbo' group (0·76 *vs* 1·29

per 100 patient-years, respectively, difference −0.52 [95% CI −1.74, 0.47], for patients initially in NAVIGATOR, and 3·09 *vs* 2·00 per 100 patient-years, respectively, difference 1.09 [95% CI −4.23, 5.99], for patients initially in SOURCE).

The on-treatment incidence of injection-site reactions was low and similar in the 'rand teze' and 'rand pbo' groups (2·40 *vs* 2·15 per 100 patient-years, respectively, difference 0.25 [95% CI −1.33, 1.73], for patients initially in NAVIGATOR, and 0·00 *vs* 1·00 per 100 patient-years, respectively, difference −1.00 [95% CI −5.46, 1.91], for patients initially in SOURCE). On-treatment malignancies were balanced between treatment groups (**Table S13**). Among patients initially from NAVIGATOR, the on-treatment incidence of hypersensitivity SAEs was 0·33 and 0·29 per 100 patient-years in the 'rand teze' and 'rand pbo' groups, respectively (difference 0.04 [95% CI −0.74, 0.71]); there were no hypersensitivity SAEs among patients from SOURCE. On-treatment hypersensitivity was reported by three patients in the 'rand teze' group (immune thrombocytopenia, drug hypersensitivity, and contact dermatitis) and two patients in the 'rand pbo' group (anaphylactic reaction and rash). No cases of anaphylaxis were observed in the 'rand teze' group.

Tezepelumab reduced the AAER over 104 weeks compared with placebo. In patients initially from NAVIGATOR, the AAER over 104 weeks in the 'rand teze' group was 0·82 (95% CI 0·71, 0·95) compared with 1·93 (95% CI 1·70, 2·20) in the 'rand pbo' group (rate ratio 0·42; 95% CI 0·35, 0·51; **Figure 2a**). In patients initially from SOURCE, the AAER over 104 weeks in the 'rand teze' group was 1·07 (95% CI 0·76, 1·51) compared with 1·76 (95% CI 1·27, 2·45) in the 'rand pbo' group (rate ratio 0·61; 95% CI 0·38, 0·96; **Figure 2b**). Findings were similar in patients initially from NAVIGATOR and SOURCE in the supportive LTE analysis set (**Figure 2c** and **Figure 2d**). Across patients from both parent studies, tezepelumab reduced the annualised rate of asthma exacerbations that were associated with hospitalisation or an ED visit over 104 weeks compared with placebo (**Figure 2e–h**).

In patients initially from NAVIGATOR, the AAER was consistently lower in the 'rand teze' group than in the 'rand pbo' group, irrespective of baseline inflammatory biomarkers and

other clinical characteristics over 104 weeks (**Figure 3**); time-to-first asthma exacerbation in these patients was longer in the 'rand teze' group than in the 'rand pbo' group (hazard ratio 0·64; 95% CI 0·54, 0·75; **Figure S4).** Asthma exacerbations, including those associated with hospitalisation or an ED 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 'teze+teze' group than in the 'pbo+pbo' group (**Figure S5**). During the second year (which included the beginning of the COVID-19 pandemic), asthma exacerbations were further reduced, with lower rates observed in the 'teze+teze' group than in the 'pbo+pbo' group. Improvements in pre-bronchodilator FEV_1, ACQ-6 score, and SGRQ score were sustained throughout the treatment period in the 'rand teze' group compared with the 'rand pbo' group in patients from both parent studies (**Table S14, Figure 4a–f**). Results were similar in the supportive LTE analysis set (**Figure S6**).

Reductions from baseline in blood eosinophil counts and FeNO levels were seen early and were sustained to week 104 in the 'rand teze' group (**Figures S7** and **S8**). There was a progressive reduction in serum total IgE levels to week 104 in the 'rand teze' group (**Figures S7** and **S8**). Results were similar in the supportive LTE analysis set (**Table S15**).

Results among the 'pbo+teze' group were generally similar to the 'pbo+pbo' group during the parent study and generally similar to the 'teze+teze' group during the second year (**Figure S5, Figure S6,** and **Table S15**).

Discussion

Tezepelumab was well-tolerated in patients with severe, uncontrolled asthma over 104 weeks of treatment. The exposure-adjusted incidence of AEs and SAEs were 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 HRQoL.

Within individual MedDRA-coded categories of SAEs, there was a lower incidence of respiratory, thoracic, and mediastinal disorder system organ class SAEs in the 'rand teze' group than in the 'rand pbo' group, but there was a higher incidence of cardiac disorder system organ class SAEs in patients receiving tezepelumab than in patients receiving placebo. The reason for this imbalance in cardiac SAEs 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 AEs were similar between tezepelumab and placebo recipients, with very few events independently adjudicated as MACE or cardiovascular deaths observed. No patterns were identified in the cause of cardiac SAEs among tezepelumab-treated patients or in the timing of the cardiac SAEs in relation to tezepelumab dosing. Additionally, no cardiac SAE was causally attributed to tezepelumab by either the investigator or a masked independent adjudication committee. All patients who experienced a cardiac disorder SAE had at least two risk factors at baseline and nearly half had a cardiac disorder at baseline. Imbalances in cardiac SAEs 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 SAEs in tezepelumab-treated patients 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 SAEs reported in 14 dupilumab recipients but zero placebo recipients, with similar rates of MACE and cardiovascular deaths between treatment groups.[22] The incidence of cardiac SAEs 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 reported to be 1·1-fold to 3·2-

fold higher in patients with asthma than in healthy individuals.[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, were similar between treatment groups, which suggests that the mechanism of action of tezepelumab does not predispose patients to infections. A similar finding was observed with malignancies. The tezepelumab group did not have a higher rate of COVID-19-related infections or deaths than the placebo group. 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 hospitalizations 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 T2 inflammatory biomarkers or with nasal polyps compared with those with low levels of T2 inflammatory biomarkers or without nasal polyps. This confirms findings from PATHWAY and NAVIGATOR[5,7] that tezepelumab consistently demonstrates clinically meaningful reductions in exacerbations in patients across the spectrum of T2 inflammation, with an enhanced effect in patients with high T2 biomarker levels. Although clinically meaningful reductions in exacerbations were observed in adolescents, greater reductions were seen in adults. The estimate of efficacy

among adolescent patients 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 FEV_1, 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 levels were observed in the tezepelumab group compared with the placebo group, as well as a progressive reduction in serum total IgE levels through week 104. Similar findings were seen in patients 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 demonstrated by high roll-over rates of eligible patients from the parent studies, low discontinuation rates within DESTINATION, and high treatment adherence. This allowed DESTINATION to rigorously address the question of 'What is the safety and efficacy of tezepelumab in patients treated for up to 2 years?' DESTINATION also included patients 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 LTE period. Although the analysis accounted for these differences in exposure, the model assumed a constant risk through the observation periods, which may not have been true for some AEs. The overall environment for the study, including non-confirmed COVID-19 illness, as well as societal and healthcare disruptions and patient stress during the pandemic, was not consistent between years 1 and 2, and this may have had unrecognised consequences on the incidence of safety events.

In conclusion, DESTINATION demonstrated 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 HRQoL in patients with severe, uncontrolled asthma, consistent with results from NAVIGATOR and SOURCE. The incidence of AEs 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 demonstrate 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 they 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 they had final responsibility for the decision to submit for publication.

Declaration of interests

AMG 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 and/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 may 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, Inc. and does not own stock in AstraZeneca.

Data sharing

This study is registered at ClinicalTrials.gov with the identifier NCT03706079. 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.

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***Table 1*: Baseline demographics and clinical characteristics of patients (primary safety analysis set)**

Parent study	**NAVIGATOR**		**SOURCE**	
Characteristics	**'Rand teze' (n=528)**	**'Rand pbo' (n=531)**	**'Rand teze' (n=74)**	**'Rand pbo' (n=76)**
Age, mean (SD), years	49·9 (16·3)	49·0 (15·9)	53·5 (12·1)	53·4 (11·9)
Female, n (%)	335 (63·4)	337 (63·5)	49 (66·2)	45 (59·2)
BMI, mean (SD), kg/m^2	28·7 (7·1)	28·3 (6·9)	29·3 (6·7)	29·4 (7·4)
Race, n (%)				
White	332 (62·9)	327 (61·6)	62 (83·8)	64 (84·2)
Black or African American	30 (5·7)	31 (5·8)	1 (1·4)	0 (0·0)
Asian	146 (27·7)	149 (28·1)	11 (14·9)	11 (14·5)
Native Hawaiian or other Pacific Islander	1 (0·2)	0 (0·0)	0 (0·0)	0 (0·0)
American Indian or Alaska Native	0 (0·0)	1 (0·2)	0 (0·0)	0 (0·0)
Other	19 (3·6)	23 (4·3)	0 (0·0)	1 (1·3)
Ethnicity, n (%)				
Hispanic or Latino	83 (15·7)	81 (15·3)	10 (13·5)	14 (18·4)
Not Hispanic or Latino	445 (84·3)	450 (84·7)	64 (86·5)	62 (81·6)
ICS dose group, n (%)*				
Low	0 (0·0)	1 (0·2)	0 (0·0)	0 (0·0)
Medium	131 (24·8)	132 (24·9)	1 (1·4)	0 (0·0)
High	397 (75·2)	398 (75·0)	73 (98·6)	76 (100)
Maintenance OCS use, n (%)	49 (9·3)	51 (9·6)	74 (100)	76 (100)
Pre-bronchodilator FEV_1, mean (SD), L	1·83 (0·72)	1·85 (0·71)	1·56 (0·50)	1·59 (0·64)
Pre-bronchodilator FEV_1, mean (SD), % predicted	62·8 (18·0)	62·7 (18·0)	54·3 (18·1)	53·3 (18·4)
Exacerbations in the past 12 months, n (%)				
1	0 (0·0)	1 (0·2)	34 (45·9)	30 (39·5)
2	310 (58·7)	324 (61·0)	27 (36·5)	25 (32·9)
>2	218 (41·3)	206 (38·8)	13 (17·6)	21 (27·6)

FeNO level, ppb				
Mean (SD)	41·38 (36·30)	46·27 (44·73)	38·71 (40·82)	42·35 (37·44)
Median (IQR)	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, ppb, n (%)				
<25, n (%)	213 (40·8)	220 (41·7)	32 (47·1)	26 (37·7)
≥25–<50, n (%)	158 (30·3)	151 (28·7)	20 (29·4)	27 (39·1)
≥50, n (%)	151 (28·9)	156 (29·6)	16 (23·5)	16 (23·2)
Blood eosinophil count, cells/µL				
Mean (SD)	327 (293)	353 (488)	253 (203)	232 (154)
Median (IQR)	250 (140, 410)	250 (140, 430)	215 (100, 370)	200 (115,310)
Blood eosinophil count group, cells/µL, n (%)				
<150	138 (26·1)	138 (26·0)	27 (36·5)	24 (31·6)
150–<300	171 (32·4)	171 (32·2)	19 (25·7)	28 (36·8)
300–<450	99 (18·8)	95 (17·9)	20 (27·0)	16 (21·1)
≥450	120 (22·7)	127 (23·9)	8 (10·8)	8 (10·5)
Serum total IgE, IU/mL				
Mean (SD)	515·68 (959·75)	614·05 (1159·49)	298·71 (576·28)	300·89 (521·39)
Median (IQR)	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, n (%)	339 (64·2)	341 (64·2)	25 (33·8)	34 (44·7)

*Medium-dose ICS: fluticasone propionate 500 µg/day or equivalent; high-dose ICS: fluticasone propionate >500 µg/day or equivalent; there was one patient in the placebo group who received fluticasone propionate <500 µg/day or equivalent.

Data are from the primary safety analysis dataset. The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab.

BMI=body mass index. FEIA=fluorescence enzyme immunoassay. FeNO=fractional exhaled nitric oxide. FEV_1=forced expiratory volume in 1 second. ICS=inhaled corticosteroids. IgE=immunoglobulin E. IQR=interquartile range. OCS=oral corticosteroid. n=number of patients. SD=standard deviation.

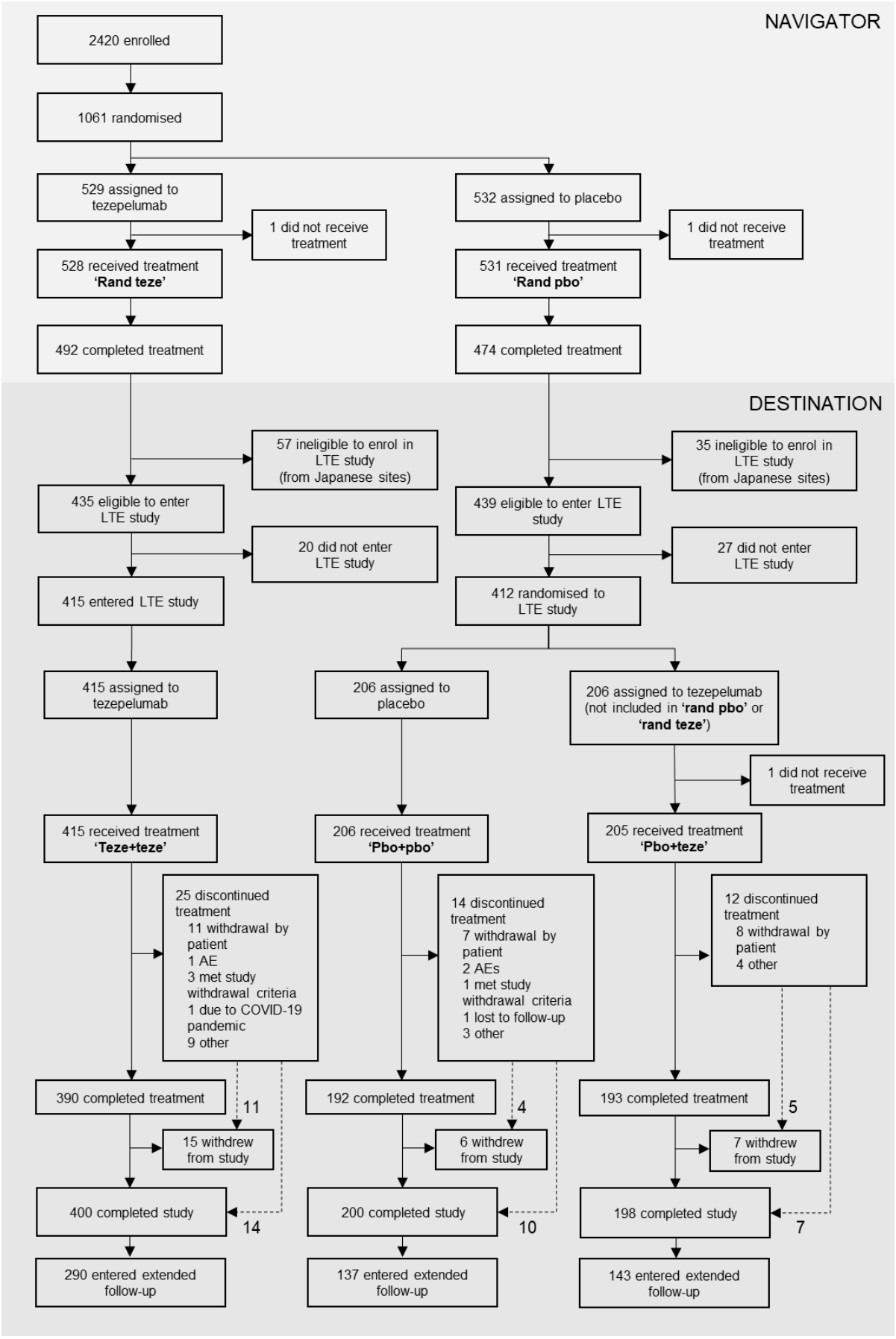
***Table 2*: Summary of on-treatment adverse events (primary safety analysis set)**

Parent study	**NAVIGATOR**		**SOURCE**	
	'Rand teze' (n=528)	**'Rand pbo' (n=531)**	**'Rand teze' (n=74)**	**'Rand pbo' (n=76)**
Total time at risk across all patients (years)	917·0	699·0	129·4	100·0
Any AE				
n (%)	455 (86·2)	438 (82·5)	61 (82·4)	70 (92·1)
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)
Incidence difference (95% CI)	−13·04 (−17·83, −8·18)		−22·82 (−34·77, −10·01)	
Any AE resulting in death				
n (%)	7 (1·3)	1 (0·2)	2 (2·7)	0 (0·0)
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)
Incidence difference (95% CI)	0.62 (−0.10, 1.44)		1.55 (−2.19, 5.47)	
Any SAE				
n (%)	72 (13·6)	87 (16·4)	17 (23·0)	18 (23·7)
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)
Incidence difference (95% CI)	−4.59 (−7.69, −1.65)		−4.85 (−14.88, 4.53)	
Any AE leading to discontinuation of treatment				
n (%)	15 (2·8)	21 (4·0)	2 (2·7)	2 (2·6)
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)
Incidence difference (95% CI)	−1.37 (−3.05, 0.08)		−0.45 (−5.62, 3.74)	
Most common AEs,* n (%)				
Nasopharyngitis	129 (24·4)	123 (23·2)	17 (23·0)	22 (28·9)
Upper respiratory tract infection	71 (13·4)	88 (16·6)	12 (16·2)	8 (10·5)
Headache	56 (10·6)	53 (10·0)	9 (12·2)	10 (13·2)
Asthma	27 (5·1)	61 (11·5)	8 (10·8)	14 (18·4)
Bronchitis bacterial	30 (5·7)	18 (3·4)	8 (10·8)	7 (9·2)

*AEs that occurred in ≥10% of patients in any treatment group, irrespective of causality.

Data are from the primary safety analysis dataset. The ‘rand teze’ group included all patients randomised to tezepelumab in the parent study, and the ‘rand pbo’ group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab.
AE=adverse event. SAE=serious adverse event. n=number of patients.

a)


NAVIGATOR
2420 enrolled
1061 randomised
529 assigned to tezepelumab
1 did not receive treatment
528 received treatment 'Rand teze'
492 completed treatment
532 assigned to placebo
1 did not receive treatment
531 received treatment 'Rand pbo'
474 completed treatment
DESTINATION
57 ineligible to enrol in LTE study (from Japanese sites)
435 eligible to enter LTE study
20 did not enter LTE study
415 entered LTE study
35 ineligible to enrol in LTE study (from Japanese sites)
439 eligible to enter LTE study
27 did not enter LTE study
412 randomised to LTE study
415 assigned to tezepelumab
206 assigned to placebo
206 assigned to tezepelumab (not included in 'rand pbo' or 'rand teze')
1 did not receive treatment
415 received treatment 'Teze+teze'
206 received treatment 'Pbo+pbo'
205 received treatment 'Pbo+teze'
25 discontinued treatment
11 withdrawal by patient
1 AE
3 met study withdrawal criteria
1 due to COVID-19 pandemic
9 other
14 discontinued treatment
7 withdrawal by patient
2 AEs
1 met study withdrawal criteria
1 lost to follow-up
3 other
12 discontinued treatment
8 withdrawal by patient
4 other
390 completed treatment
11
15 withdrew from study
192 completed treatment
4
6 withdrew from study
193 completed treatment
5
7 withdrew from study
400 completed study
14
200 completed study
10
198 completed study
7
290 entered extended follow-up
137 entered extended follow-up
143 entered extended follow-up

b)

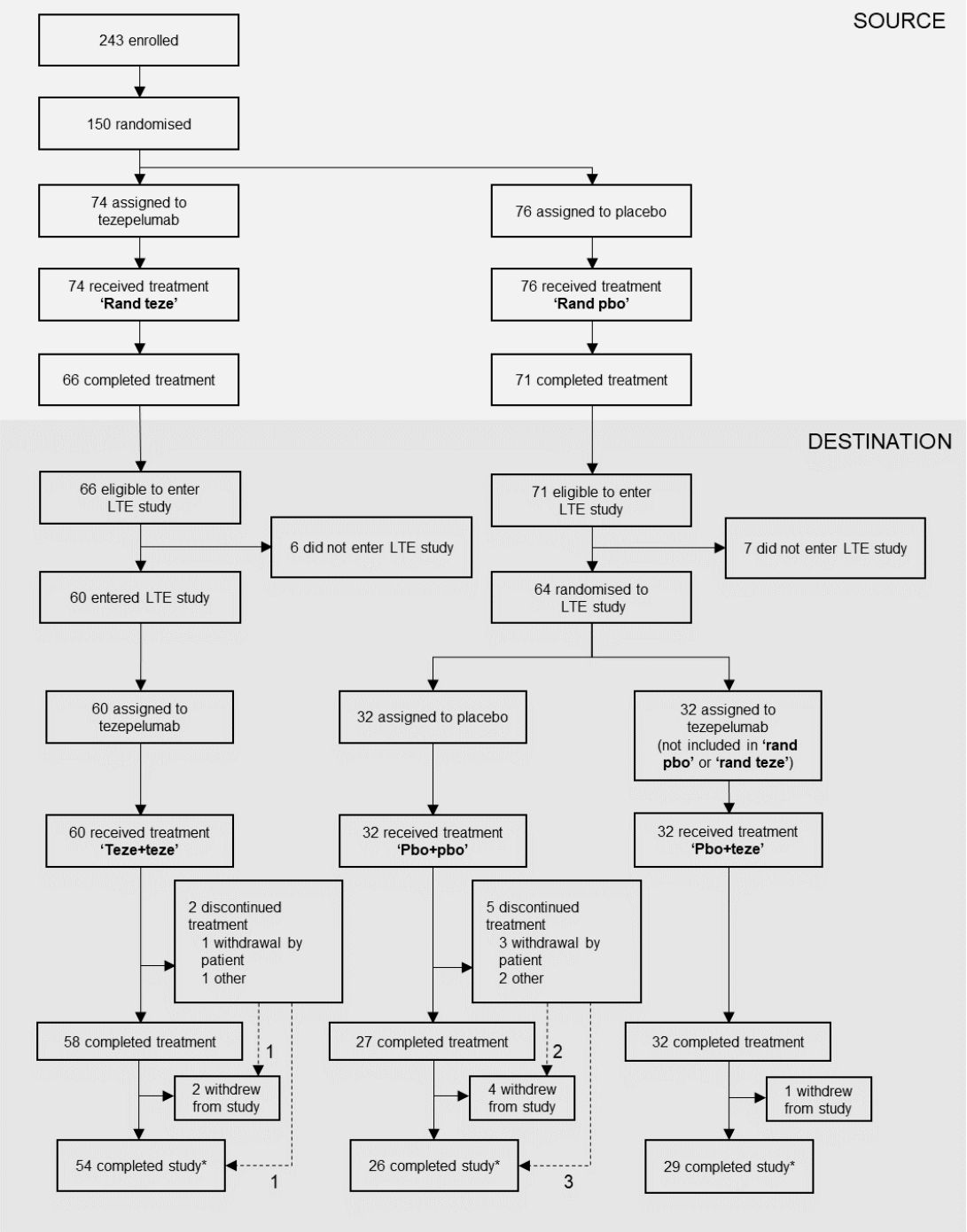


***Figure 1*: Study profile for patients initially from NAVIGATOR (a) and SOURCE (b)**

Treatment groups for the primary analysis set ('rand teze', 'rand pbo') and supportive LTE analysis set ('teze+teze', 'pbo+pbo', 'pbo+teze') are indicated.

*Eight patients were still in the safety follow-up at the time of database lock (four patients in the 'teze+teze' group, two in the 'pbo+pbo' group and two in the 'pbo+teze' group).

LTE=long-term extension.

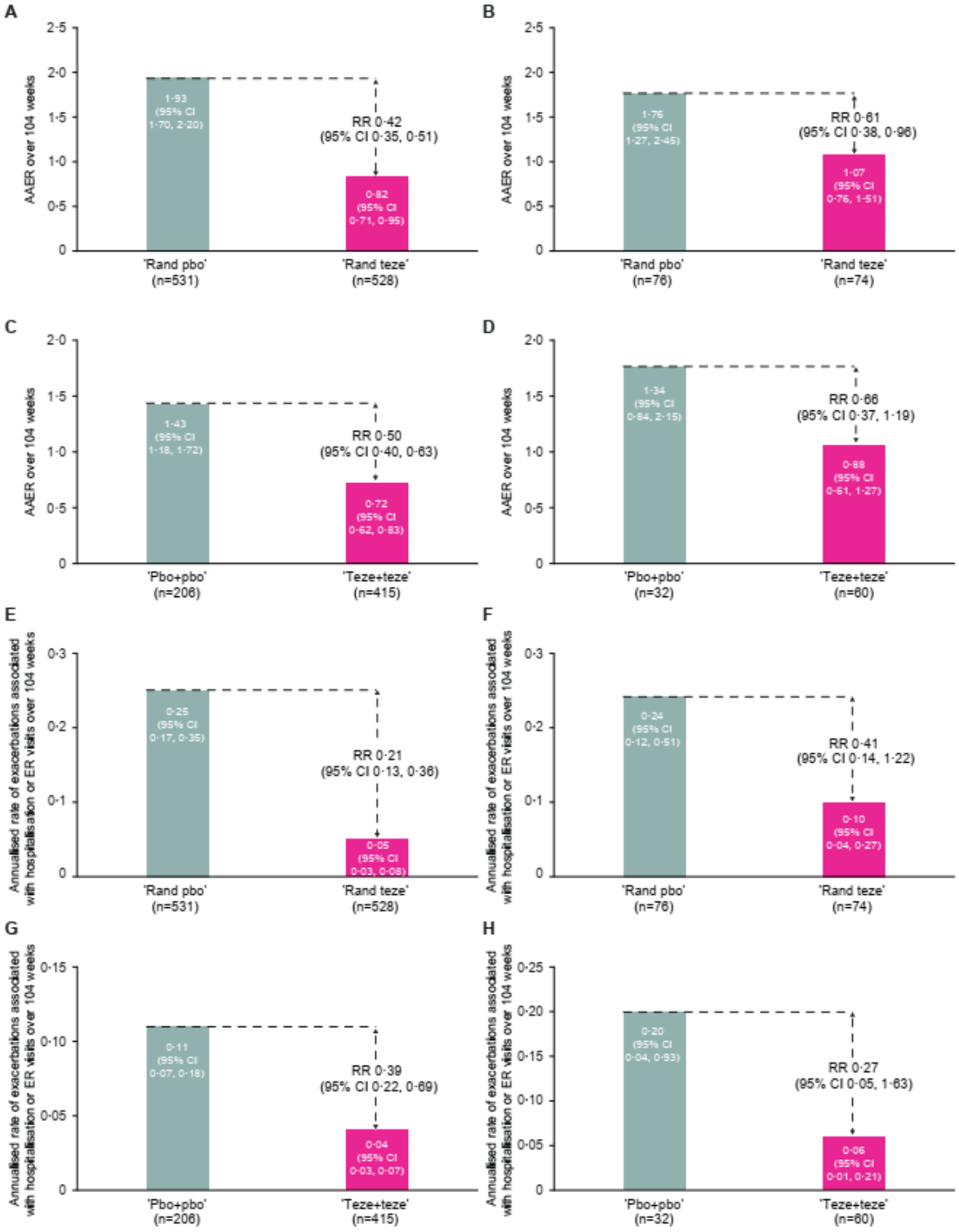


***Figure 2*: AAER and the annualised rate of asthma exacerbations that were associated with hospitalisation or an ED visit over 104 weeks**

Adjusted AAER from the primary full analysis dataset in patients initially from NAVIGATOR (a) and SOURCE (b); adjusted AAER from the supportive LTE analysis dataset in patients initially from NAVIGATOR (c), and SOURCE (d); adjusted annualised rate of asthma

exacerbations associated with hospitalisation or an ED visit from the primary full analysis dataset in patients initially from NAVIGATOR (e) and SOURCE (f); adjusted annualised rate of asthma exacerbations associated with hospitalisation or an ED visit from the supportive LTE analysis dataset in patients initially from NAVIGATOR (g) and SOURCE (h).

AAER=annualised asthma exacerbation rate. CI=confidence interval. ED=emergency department. LTE=long-term extension. RR=rate ratio.

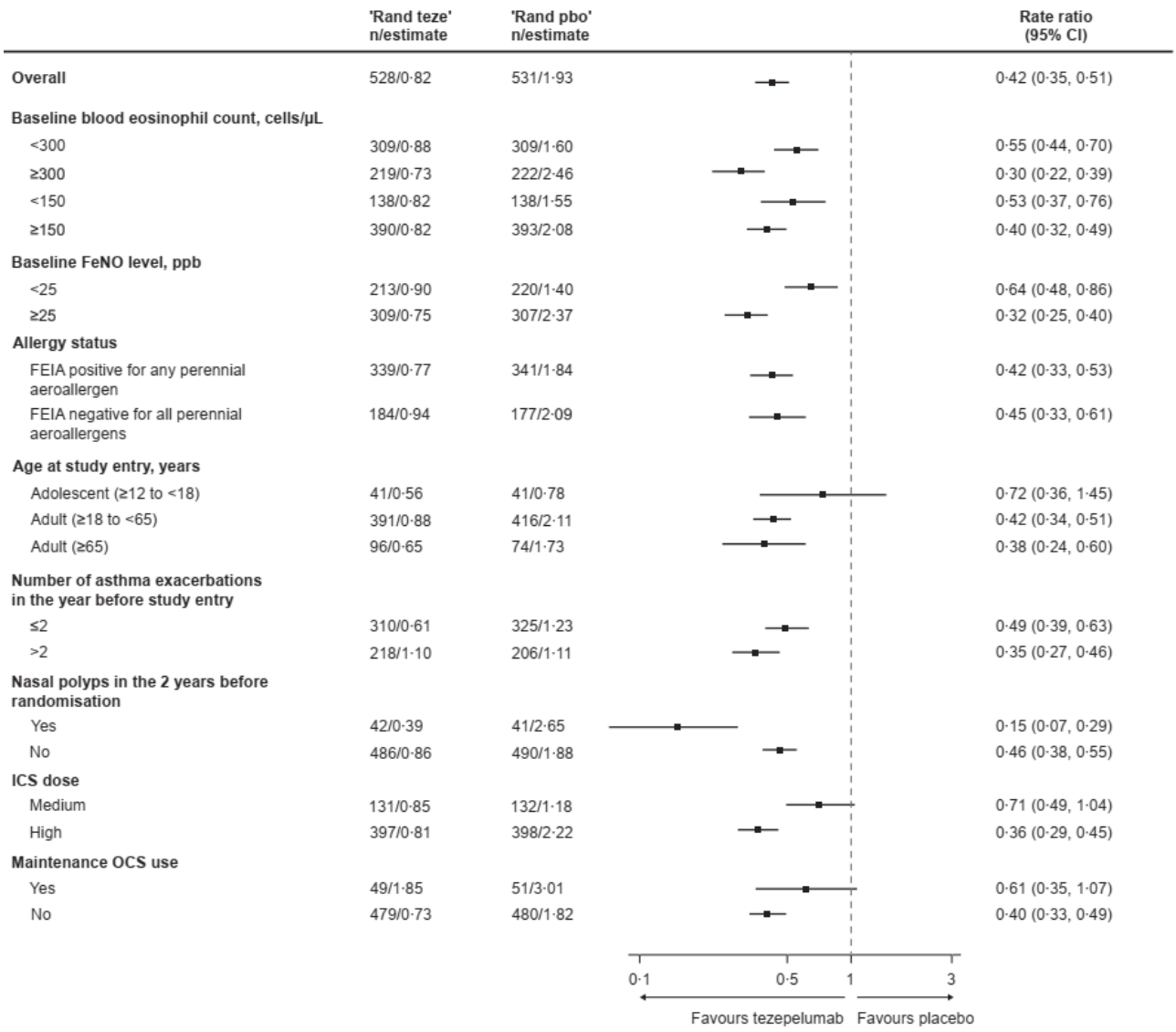
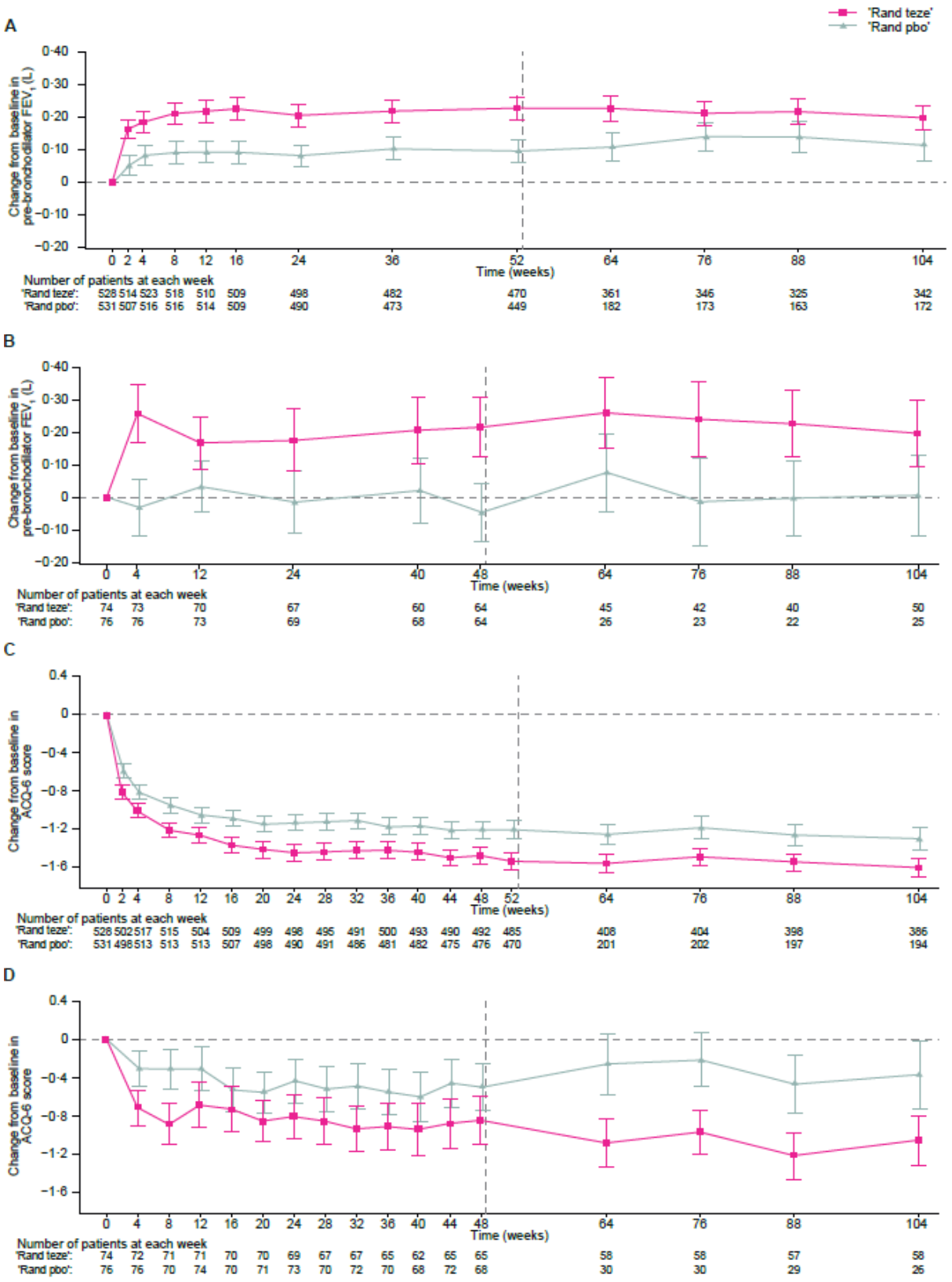


***Figure 3*: AAER over 104 weeks for patients initially from NAVIGATOR**

Data are from the primary full analysis dataset. The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab.

AAER=annualised asthma exacerbation rate. CI=confidence interval. FEIA=fluorescence enzyme immunoassay; FeNO=fractional exhaled nitric oxide. ICS=inhaled corticosteroids. IgE=immunoglobulin E. LTE=long-term extension. OCS=oral corticosteroids.


A
'Rand teze'
'Rand pbo'
Change from baseline in pre-bronchodilator FEV1 (L)
0·40
0·30
0·20
0·10
0
−0·10
−0·20
0 2 4 8 12 16 24 36 52 64 76 88 104
Time (weeks)
Number of patients at each week
'Rand teze': 528 514 523 518 510 509 498 482 470 361 345 325 342
'Rand pbo': 531 507 516 516 514 509 490 473 449 182 173 163 172
B
Change from baseline in pre-bronchodilator FEV1 (L)
0·40
0·30
0·20
0·10
0
−0·10
−0·20
0 4 12 24 40 48 64 76 88 104
Time (weeks)
Number of patients at each week
'Rand teze': 74 73 70 67 60 64 45 42 40 50
'Rand pbo': 76 76 73 69 68 64 26 23 22 25
C
Change from baseline in ACQ-6 score
0·4
0
−0·4
−0·8
−1·2
−1·6
0 2 4 8 12 16 20 24 28 32 36 40 44 48 52 64 76 88 104
Time (weeks)
Number of patients at each week
'Rand teze': 528 502 517 515 504 509 499 498 495 491 500 493 490 492 485 408 404 398 386
'Rand pbo': 531 498 513 513 513 507 498 490 491 486 481 482 475 476 470 201 202 197 194
D
Change from baseline in ACQ-6 score
0·4
0
−0·4
−0·8
−1·2
−1·6
0 4 8 12 16 20 24 28 32 36 40 44 48 64 76 88 104
Time (weeks)
Number of patients at each week
'Rand teze': 74 72 71 71 70 70 69 67 67 65 62 65 65 58 58 57 58
'Rand pbo': 76 76 70 74 70 71 73 70 72 70 68 72 68 30 30 29 26

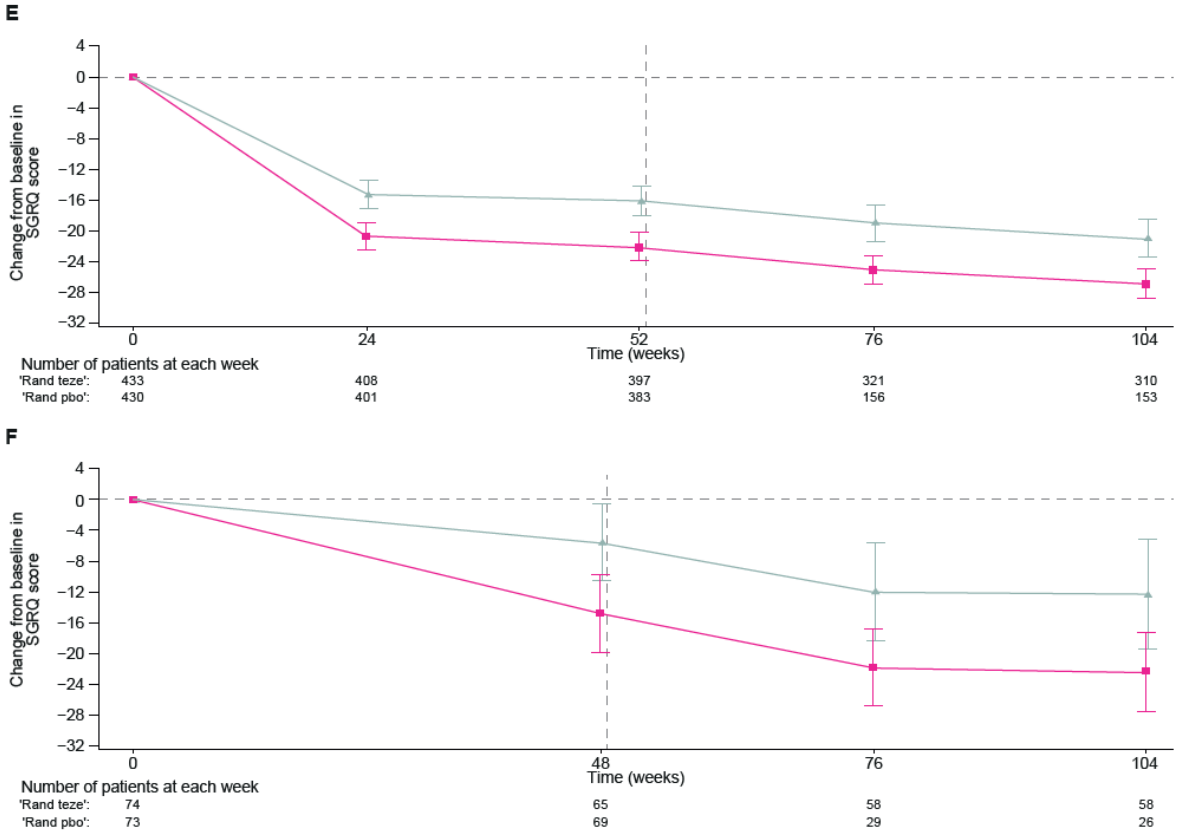


***Figure 4*: Change over time in pre-bronchodilator FEV_1, ACQ-6 score, and SGRQ score in patients initially from NAVIGATOR (a, c and e) and SOURCE (b, d and f)**

Data are adjusted means and 95% CIs from the primary full analysis dataset. The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab.

ACQ-6=Asthma Control Questionnaire-6. BD=bronchodilator. CI=confidence interval. FEV_1=forced expiratory volume in 1 second. LTE=long-term extension. SGRQ=St George's respiratory questionnaire.

SUPPLEMENTARY APPENDIX

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

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Major protocol amendments

The protocol was amended after the start of patient recruitment to account for the COVID-19 pandemic. Patients aiming to enrol in the DESTINATION study who were not able to attend an onsite end of treatment visit in either parent study continued to participate in the 12-week safety follow-up period of either NAVIGATOR or SOURCE until on-site randomisation and administration of the first dose of study treatment in DESTINATION could be conducted.

A 36-week extended follow-up period was also added after the start of recruitment, to evaluate the persistence of the clinical and pharmacodynamic effects of tezepelumab for up to 40 weeks after final dose. Only patients initially from the NAVIGATOR parent study were eligible for the extended follow-up. These results are not included in the current publication.

Randomisation
In NAVIGATOR, patients were stratified according to geographic region (Asia–Pacific, central and eastern Europe, western Europe and Australia, North America, South America, or the rest of the world) and age (adults or adolescents). In SOURCE, patients were stratified by region. Following entry into DESTINATION, patients were stratified by parent study.

Subgroup analyses
As part of a pre-specified exploratory analysis, the annualised asthma exacerbation rate over 104 weeks was assessed in subgroups of patients initially from NAVIGATOR, grouped by baseline blood eosinophil count, fractional exhaled nitric oxide (FeNO) level, perennial allergic status (positive or negative for perennial aeroallergen sensitivity), age, number of exacerbations in the year before study, history of nasal polyps, inhaled corticosteroid dose, and maintenance oral corticosteroid use.

Blood eosinophil count was determined at a centralised laboratory using a standard clinical haematology analyser with automated or manual differentials using Wright–Giemsa stains. FeNO was measured using a NIOX VERO airway inflammation monitor (Circassia Pharmaceuticals Inc.) to perform a standardised single-breath test, per American Thoracic Society recommendations.[28] Immunoassays (Phadia™) were performed at a centralised laboratory to determine serum total immunoglobulin (Ig)E levels.

Perennial allergen sensitivity was determined according to a positive (≥0.35 kilo units of allergen-specific IgE per litre) or negative fluorescence enzyme immunoassay (ImmunoCAP™, Thermo Fisher Scientific) test result for a specific serum IgE against the following perennial aeroallergens: animal (cat dander, dog dander), insects (cockroach, dust mite [*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*]), and mould mix. A patient was considered to have a perennial allergy if they had a positive fluorescence immunoassay test result for at least one of these allergens. A patient without perennial allergy had a negative fluorescence immunoassay test result for all of these allergens.

Statistical analyses
The on-treatment period started on the date of randomisation in the parent study (for efficacy endpoints) or the date of the first dose of tezepelumab or placebo (for safety endpoints) and ended on the date of the last dose of tezepelumab or placebo + 33 days, the date of death, the date of study withdrawal, or the day before the start date of another biologic that impacts asthma control (whichever was first). The on-study period started on the date of randomisation in the parent studies (for efficacy endpoints) or the date of the first dose of tezepelumab or placebo (for safety endpoints) and ended on the study completion or withdrawal date (this was the later date if a patient completed the parent study and enrolled in DESTINATION).

The sample size for enrolment into DESTINATION was determined by the number of patients who completed the parent studies and decided to continue in the LTE study. Unless stated otherwise, safety and efficacy data were analysed and reported separately by parent study.

On-treatment adverse events (AEs) and serious adverse events (SAEs) were summarised for the safety analysis set over the 104-week study period using exposure-adjusted incidence to account for variability in follow-up. Incidence per 100 patient-years were calculated as the number of patients reporting AEs or SAEs divided by total exposure duration across all patients in the given treatment group, multiplied by 100. As a prespecified measure to confirm the details of observed cardiac events, a masked independent adjudication committee reviewed all cardiac disorder SAEs to assess agreement with the investigator-reported AE term, diagnosis of major adverse cardiac events, relation of the event to COVID-19, whether the event resulted in death, and AE causality to treatment. The categories of causality were certain, probably/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable. A *post hoc* analysis assessed AEs or SAEs related to COVID-19. Incidence per 100 patient-years were calculated as the number of patients reporting COVID-19-related AEs or SAEs divided by total exposure duration after 11 March 2020 across all patients in the given treatment group, multiplied by 100. Two-sided 95% confidence intervals (CI) for incidence were calculated using a chi-square distribution (where incidence was 0, a one-sided CI was used). CIs for the incidence difference between the tezepelumab and placebo groups were calculated using the Miettinen-Nurminen score method in SAS.

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 LTE period as a response variable. Treatment, region, and history of exacerbations (≤2 or >2) were included as covariates in the model. For NAVIGATOR analyses, age group (adolescents or adults) was also included in the model. For subgroup analyses in patients initially from NAVIGATOR, subgroup and treat-by-subgroup interaction were also included

in the model. Time at risk was used as an offset variable in the model to adjust for patients' having different follow-up times during which the events occurred. Time-to-first asthma exacerbation over 104 weeks was summarised using Kaplan-Meier estimates, and analysed using a Cox proportional hazards model with factors for treatment, region, age (for NAVIGATOR analyses only), and history of exacerbations (≤2 or >2 in the previous 12 months). A negative binomial regression analysis was used to estimate the annualised rate of exacerbations that were associated with hospitalisation or an ED visit over 104 weeks. Treatment, region, age (for NAVIGATOR analyses only), and history of exacerbations were included as covariates in the model. The logarithm of the time at risk was used as an offset variable.

Change from baseline to week 104 in exploratory endpoints were estimated using a model for repeated measures with unstructured covariance. Biomarker data were log-transformed prior to analyses. The response variable in the model was change from baseline at each scheduled post-randomisation visit up to and including week 104, and irrespective of whether the patient remained on treatment and/or took other treatments, with the exception of other biologics that impact asthma control data (data beyond this were not used). Treatment, region, age (for NAVIGATOR analyses only), visit, visit-by-treatment interaction, and the baseline value (log of the baseline value for biomarker data) of the corresponding endpoint were included as covariates in the model. For biomarker data, the anti-log of the result is reported. The patient was included in the model using the REPEATED statement (not the RANDOM statement) in SAS, with an unstructured covariance that was assumed to model the relationship between pairs of response variables taken at different visits on the same patient. The Kenward-Roger approximation to estimating the degrees of freedom was used for tests of fixed effects derived from the model. Missing data were modelled based on what was observed during the study, using direct likelihood approaches.

While the clinical study protocol indicated that an interim analysis may be performed according to regulatory and other requirements, no interim analyses occurred.

Important protocol deviations

The majority of DESTINATION participants were ongoing in the study during the COVID-19 pandemic: 98.9% of patients originally from NAVIGATOR and 98.4% of patients originally from SOURCE. Amongst these patients, 323 (39.1%) originally from NAVIGATOR had at least one disruption owing to the COVID-19 pandemic (156 [37.6%] in the 'teze+teze' group, 75 [36.4%] in the 'pbo+pbo' group, 92 [44.9%] in the 'pbo+teze' group). Among patients originally from SOURCE, 73 (58.9%) had at least one disruption owing to the COVID-19 pandemic (37 [61.7%] in the 'teze+teze' group, 16 [50.0%] in the 'pbo+pbo' group, 20 [62.5%] in the 'pbo+teze' group). The highest number of disruptions were due to the changed format of scheduled visits, including partially completed visits and remote visits.

The most common important protocol deviation, not related to COVID-19, in patients originally from NAVIGATOR was receiving prohibited concomitant medication, reported for 31 (3.8%) of patients overall (19 [4.6%] in the 'teze+teze' group, 8 [3.9%] in the 'pbo+pbo' group and 4 [2.0%] in the 'pbo+teze' group). For patients originally from SOURCE, the most common important protocol deviations observed overall were receiving prohibited concomitant medication and investigational product (IP) management (i.e. IP dosing missed at least twice), each reported for 6 (4.8%) patients. Receipt of prohibited concomitant medication was reported for 3 (5.0%) patients in the 'teze+teze' group and 3 (9.4%) in the 'pbo+pbo' group (none in the 'pbo+teze' group). IP management was reported for 3 (5.0%) patients in the 'teze+teze' group, 2 (6.3%) in the 'pbo+pbo' group and 1 (3.1%) in the 'pbo+teze' group.

***Table S1*: Key study inclusion and exclusion criteria**

The phase 3 SOURCE study	The phase 3 NAVIGATOR study	The phase 3 DESTINATION study
Key inclusion criteria • Men or women, 18–80 years old, weight ≥40 kg at visit 1 • Documented physician-diagnosed asthma for ≥12 months before visit 1, and receiving medium- or high-dose ICS (as per GINA 2017 guidelines) for 12 months before visit 1 • Documented physician-prescribed LABA and high-dose ICS (total daily dose corresponding to fluticasone propionate >500 µg dry powder formulation equivalent) for ≥3 months before visit 1 • Additional maintenance asthma controller medications (e.g. LAMA, LTRA, theophylline, secondary ICS and cromones) are permitted if documented for ≥3 months before visit 1 • Received OCS for the treatment of asthma for ≥6 months before visit 1 and receiving a stable dose of prednisone or prednisolone 7.5–30 mg daily or daily equivalent for ≥1 month before visit 1 • Morning pre-bronchodilator FEV_1 <80% predicted at either visit 1 or visit 2 • Documented historical FEV_1 reversibility of ≥12% and ≥200 mL (15–30 min after administration of four puffs of albuterol/salbutamol) in the 12 months before visit 1 or at visit 1 or visit 2 • History of ≥1 asthma exacerbation event ≤12 months before visit 1 • Received optimized OCS dose for ≥2 weeks before randomization **Key exclusion criteria** • Any clinically important pulmonary disease, other than asthma, associated with high peripheral eosinophil counts	**Key inclusion criteria** • Male or female, 12–80 years old, weight ≥40 kg at visit 1 • Documented physician-diagnosed asthma for ≥12 months before visit 1, and receiving medium- or high-dose ICS (as per GINA 2017 guidelines) for 12 months before visit 1 • Documented treatment with ICS (total daily dose corresponding to fluticasone propionate ≥500 µg dry powder formulation equivalent) plus at least one additional maintenance asthma controller medication (e.g. LABA, LTRA, theophylline) for ≥3 months before visit 1 • Morning pre-bronchodilator FEV1 <80% predicted normal (<90% for patients 12–17 years old) at either visit 2 or visit 2a • Documented historical FEV1 reversibility of ≥12% and ≥200 mL in the 12 months before visit 1 OR post-bronchodilator (albuterol/salbutamol) FEV1 reversibility ≥12% and ≥200 mL at visit 2 or visit 2a • ACQ-6 score ≥1.5 at screening and at randomization **Key exclusion criteria** • Any clinically important pulmonary disease, other than asthma, associated with high peripheral eosinophil counts • Any disorder that could, in the opinion of the investigator, affect the safety of the patient or influence the study findings • Any clinically significant infection requiring antibiotic or antiviral • treatment in the 2 weeks before visit 1 or during the run-in period	**Key inclusion criteria at randomization** • Female or male patients who have not met tezepelumab discontinuation criteria and have attended the end of treatment visit in either the NAVIGATOR study or the SOURCE study **Key exclusion criteria at randomization** • Pregnant, breastfeeding or lactating • Any clinically important pulmonary disease other than asthma associated with elevated peripheral eosinophil counts • Any disorder that could, in the opinion of the investigator, affect the safety of the patient throughout the study, influence the study findings or their interpretation, or impede the patient's ability to complete the study • Current malignancy or malignancy that developed during a predecessor study[a] • Treatment with systemic immunosuppressive/immunomodulating drugs (e.g. methotrexate, cyclosporine) in the 12 weeks before randomization, with the exception of oral corticosteroids used in the treatment of asthma/asthma exacerbations • Concurrent enrolment in another clinical study involving an investigational product • Any clinically meaningful abnormal finding during the predecessor study (demonstrated by physical examination, vital signs, ECG, haematology, clinical chemistry or urinalysis) that could, in the opinion of the investigator, affect the safety of the patient throughout the study, influence the study findings or their interpretation, or impede the patient's ability to complete the study

• Any disorder that could, in the opinion of the investigator, affect the safety of the patient or influence study findings • Any clinically significant infection requiring antibiotic or antiviral treatment in the 2 weeks before visit 1 or during the enrolment period • Helminth or parasitic infection diagnosed in the 6 months before visit 1 that has not been treated with, or is unresponsive to, standard-of-care therapy • History of cancer, HIV, or hepatitis B or C • Current smokers or patients with a smoking history of ≥10 pack-years • History of chronic alcohol or drug abuse ≤12 months before visit 1 • Tuberculosis requiring treatment ≤12 months before visit 1 • Use of any marked or investigational biologic agent in the 4 months or 5 half-lives before visit 1, or any investigational non-biologic agent in the 30 days or 5 half-lives before visit 1 • Use of any immunosuppressive medication in the 12 weeks before randomization • History of anaphylaxis after biologic therapy • Pregnant, breastfeeding or lactating • If, during the optimization period, asthma control requires an OCS dose <7.5 mg or >30 mg and/or if asthma control is still maintained after three consecutive OCS dose reductions	• Helminth or parasitic infection diagnosed in the 6 months before visit 1 that has not been treated with, or is unresponsive to, standard-of-care therapy • History of cancer, HIV or hepatitis B or C • Current smokers or patients with a smoking history of ≥10 pack-years • Use of any marketed or investigational biologic agent in the 4 months or 5 half-lives before visit 1, or any investigational non-biologic agent in the 30 days or 5 half-lives before visit 1 • Use of any immunosuppressive medication in the 12 weeks before randomization • History of anaphylaxis after biologic therapy • Pregnant, breastfeeding or lactating	• Patients with important protocol deviations in either of the predecessor studies, assessed at the discretion of the sponsor

ACQ-6=Asthma Control Questionnaire-6. *ECG*=electrocardiogram. FEV1=Forced expiratory volume in 1 s. GINA=Global Initiative for Asthma. HIV=Human immunodeficiency virus. ICS=Inhaled corticosteroids. LABA=Long-acting β2 agonist. LAMA=Long-acting muscarinic antagonist. LTRA=Leukotriene receptor antagonist. OCS=Oral corticosteroid.

[a]Patients with a basal cell carcinoma or a localized squamous cell carcinoma of the skin that was resected for cure were not excluded

Table S2: Characteristics of patients at baseline (supportive LTE analysis set)

Parent study	**NAVIGATOR**			**SOURCE**		
Characteristics	**Teze+teze (n=415)**	**Pbo+pbo (n=206)**	**Pbo+teze (n=205)**	**Teze+teze (n=60)**	**Pbo+pbo (n=32)**	**Pbo+teze (n=32)**
Age, mean (SD), years	49·7 (16·5)	48·4 (16·7)	48·2 (16·4)	53·0 (11·9)	52·6 (11·9)	54·3 (39·9)
Female, n (%)	260 (62·7)	129 (62·6)	131 (63·9)	41 (68·3)	19 (59·4)	19 (59·4)
BMI, mean (SD), kg/m^2	29·1 (7·2)	28·6 (7·3)	28·7 (6·8)	29·2 (6·7)	29·5 (8·0)	29·6 (7·8)
ICS dose group, n (%)*						
Low	0 (0·0)	1 (0·5)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Medium	103 (24·8)	53 (25·7)	58 (28·3)	1 (1·7)	0 (0·0)	0 (0·0)
High	312 (75·2)	152 (73·8)	147 (71·7)	59 (98·3)	32 (100)	32 (100)
Maintenance OCS use, n (%)	29 (7·0)	13 (6·3)	15 (7·3)	60 (100)	32 (100)	32 (100)
Pre-bronchodilator FEV_1, mean (SD), L	1·83 (0·70)	1·84 (0·69)	1·90 (0·75)	1·63 (0·49)	1·54 (0·64)	1·67 (0·68)
Pre-bronchodilator FEV_1, mean (SD), % predicted	62·5 (17·3)	62·3 (16·8)	63·7 (18·4)	56·5 (18·0)	50·7 (18·8)	56·2 (19·8)
Exacerbations in the past 12 months, n (%)						
1	0 (0·0)	0 (0·0)	0 (0·0)	25 (41·7)	14 (43·8)	11 (34·4)
2	253 (61·0)	132 (64·1)	127 (62·0)	24 (40·0)	10 (31·3)	10 (31·3)
>2	162 (39·0)	74 (35·9)	78 (38·0)	11 (18·3)	8 (25·0)	11 (34·4)
FeNO level, ppb						
Mean (SD)	39·94 (34·22)	42·31 (44·71)	44·75 (41·82)	38·52 (42·30)	44·18 (40·12)	39·84 (33·16)
Median (IQR)	29·00 (16·00, 54·00)	26·50 (15·00, 51·50)	29·00 (18·00, 56·50)	24·50 (15·50, 49·50)	30·50 (16·50, 46·50)	27·00 (21·00, 48·00)
FeNO group, ppb, n (%)						
<25, n (%)	177 (43·3)	96 (47·1)	84 (41·2)	28 (50·0)	9 (32·1)	13 (41·9)
≥25–<50, n (%)	115 (28·1)	54 (26·5)	63 (30·9)	14 (25·0)	13 (46·4)	11 (35·5)
≥50, n (%)	117 (28·6)	54 (26·5)	57 (27·9)	14 (25·0)	6 (21·4)	7 (22·6)

Parent study	NAVIGATOR			SOURCE		
Characteristics	**Teze+teze (n=415)**	**Pbo+pbo (n=206)**	**Pbo+teze (n=205)**	**Teze+teze (n=60)**	**Pbo+pbo (n=32)**	**Pbo+teze (n=32)**
Blood eosinophil count, cells/µL						
Mean (SD)	322 (300)	298 (225)	368 (678)	260 (189)	246 (161)	203 (146)
Median (IQR)	250 (140, 400)	230 (130, 410)	240 (140, 390)	240 (105,380)	195 (130,330)	165 (95,300)
Blood eosinophil count group, cells/µL, n (%)						
<150	106 (25·5)	57 (27·7)	54 (26·3)	19 (31·7)	9 (28·1)	13 (40·6)
150–<300	142 (34·2)	68 (33·0)	74 (36·1)	15 (25·0)	13 (40·6)	9 (28·1)
300–<450	81 (19·5)	38 (18·4)	36 (17·6)	19 (31·7)	6 (18·8)	8 (25·0)
≥450	86 (20·7)	43 (20·9)	41 (20·0)	7 (11·7)	4 (12·5)	2 (6·3)
Serum total IgE, IU/mL						
Mean (SD)	516·33 (969·56)	545·60 (954·47)	701·65 (1415·15)	224·54 (401·25)	344·42 (625·38)	295·23 (491·92)
Median (IQR)	204·70 (52·80, 566·30)	173·75 (53·00, 572·40)	204·80 (52·10, 597·00)	109·70 (32·30, 242·50)	85·35 (45·75, 399·00)	127·20 (22·10, 300.35)
FEIA positive for any perennial aeroallergen, n (%)	263 (63·4)	130 (63·1)	134 (65·4)	21 (35·0)	16 (50·0)	12 (37·5)

*Medium-dose ICS: fluticasone propionate 500 µg/day or equivalent; high-dose ICS: fluticasone propionate >500 µg/day or equivalent; there was one patient in the placebo group who received fluticasone propionate <500 µg/day or equivalent.

Data are from the supportive full LTE analysis dataset. The 'teze+teze' group included patients who received tezepelumab in both the parent study and in DESTINATION, and the 'pbo+pbo' group included patients who received placebo in both the parent study and in DESTINATION.

BMI=body mass index. FEIA=fluorescence enzyme immunoassay. FeNO=fractional exhaled nitric oxide. FEV_1=forced expiratory volume in 1 second. ICS=inhaled corticosteroids. IgE=immunoglobulin E. IQR=interquartile range. LTE=long-term extension. OCS=oral corticosteroid. SD=standard deviation.

***Table S3*: Summary of on-treatment adverse events (supportive LTE analysis set)**

Parent study	**NAVIGATOR**						**SOURCE**					
	Teze+teze (n=415)		**Pbo+pbo (n=206)**		**Pbo+teze (n=205)**		**Teze+teze (n=60)**		**Pbo+pbo (n=32)**		**Pbo+teze (n=32)**	
AE category/preferred term	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**
Overall												
Total time at risk across all patients (years)		824·2		406·6				120·2		61·7		
Any AE	359 (86·5)	43·56	178 (86·4)	43·78			52 (86·7)	43·25	31 (96·9)	50·21		
Any AE resulting in death	7 (1·7)	0·85	1 (0·5)	0·25			1 (1·7)	0·83	0 (0·0)	0·00		
Any SAE	58 (14·0)	7·04	37 (18·0)	9·10			14 (23·3)	11·64	7 (21·9)	11·34		
Any AE leading to discontinuation of treatment	4 (1·0)	0·49	2 (1·0)	0·49			0 (0·0)	0·00	0 (0·0)	0·00		
Most common AEs*												
Nasopharyngitis	95 (22·9)	11·53	51 (24·8)	12·54			16 (26·7)	13·31	11 (34·4)	17·82		
Upper respiratory tract infection	60 (14·5)	7·28	40 (19·4)	9·84			9 (15·0)	7·48	4 (12·5)	6·48		
Headache	49 (11·8)	5·95	29 (14·1)	7·13			9 (15·0)	7·48	6 (18·8)	9·72		
Asthma	24 (5·8)	2·91	22 (10·7)	5·41			7 (11·7)	5·82	5 (15·6)	8·10		

***Table S3*: Summary of on-treatment adverse events (supportive LTE analysis set) (continued)**

Parent study	**NAVIGATOR**						**SOURCE**					
	Teze+teze (n=415)		**Pbo+pbo (n=206)**		**Pbo+teze (n=205)**		**Teze+teze (n=60)**		**Pbo+pbo (n=32)**		**Pbo+teze (n=32)**	
AE category/preferred term	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**
During parent study												
Total time at risk across all patients (years)		417·3		206·7		206·1		55·6		29·6		29·8
Any AE	313 (75·4)	75·00	162 (78·6)	78·39	161 (78·5)	78·12	44 (73·3)	79·07	26 (81·3)	87·82	29 (90·6)	97·19
Any AE resulting in death	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Any SAE	32 (7·7)	7·67	20 (9·7)	9·68	17 (8·3)	8·25	8 (13·3)	14·38	5 (15·6)	16·89	6 (18·8)	20·11
Any AE leading to discontinuation of treatment	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Most common AEs[a]												
Nasopharyngitis	78 (18·8)	18·69	41 (19·9)	19·84	38 (18·5)	18·44	10 (16·7)	17·97	8 (25·0)	27·02	9 (28·1)	30·16
Upper respiratory tract infection	48 (11·6)	11·50	37 (18·0)	17·90	33 (16·1)	16·01	6 (10·0)	10·78	3 (9·4)	10·13	2 (6·3)	6·70
Headache	37 (8·9)	8·87	20 (9·7)	9·68	15 (7·3)	7·28	3 (5·0)	5·39	4 (12·5)	13·51	3 (9·4)	10·05
Asthma	22 (5·3)	5·27	17 (8·3)	8·23	20 (9·8)	9·70	6 (10·0)	10·78	4 (12·5)	13·51	7 (21·9)	23·46

***Table S3*: Summary of on-treatment adverse events (supportive LTE analysis set) (continued)**

Parent study	**NAVIGATOR**						**SOURCE**					
	Teze+teze (n=415)		**Pbo+pbo (n=206)**		**Pbo+teze (n=205)**		**Teze+teze (n=60)**		**Pbo+pbo (n=32)**		**Pbo+teze (n=32)**	
AE category/preferred term	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**
During LTE												
Total time at risk across all patients (years)		406·8		199·9		201·6		64·6		32·1		34·9
Any AE	277 (66·7)	68·09	147 (71·4)	73·52	144 (70·2)	71·43	43 (71·7)	66·57	22 (68·8)	68·46	24 (75·0)	68·77
Any AE resulting in death	7 (1·7)	1·72	1 (0·5)	0·50	1 (0·5)	0·50	1 (1·7)	1·55	0 (0·0)	0·00	0 (0·0)	0·00
Any SAE	35 (8·4)	8·60	22 (10·7)	11·00	18 (8·8)	8·93	7 (11·7)	10·84	4 (12·5)	12·45	3 (9·4)	8·60
Any AE leading to discontinuation of treatment	4 (1·0)	0·98	2 (1·0)	1·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Most common AEs*												
Nasopharyngitis	43 (10·4)	10·57	23 (11·2)	11·50	21 (10·2)	10·42	9 (15·0)	13·93	6 (18·8)	18·67	7 (21·9)	20·06
Upper respiratory tract infection	24 (5·8)	5·90	15 (7·3)	7·50	6 (2·9)	2·98	4 (6·7)	6·19	1 (3·1)	3·11	0 (0·0)	0·00
Headache	27 (6·5)	6·64	18 (8·7)	9·00	12 (5·9)	5·95	6 (10·0)	9·29	3 (9·4)	9·34	1 (3·1)	2·87
Asthma	4 (1·0)	0·98	11 (5·3)	5·50	7 (3·4)	3·47	1 (1·7)	1·55	2 (6·3)	6·22	0 (0·0)	0·00

*AEs that occurred in ≥10% of patients in any treatment group.

Data are from the supportive full LTE analysis dataset. The 'teze+teze' group included patients who received tezepelumab in both the parent study and in DESTINATION, the 'pbo+pbo' group included patients who received placebo in both the parent study and in DESTINATION, and the 'pbo+teze' group included patients who received placebo in the parent study and tezepelumab in DESTINATION.

AE=adverse event. LTE=long-term extension. n=number of patients. PY=patient-years. SAE=serious adverse event.

***Table S4*: Incidence of fatal adverse events during the on-study period by preferred term**

Parent study	NAVIGATOR						SOURCE					
	'Rand teze' (n=528)		'Rand pbo' (n=531)		'All teze' (n=734)		'Rand teze' (n=74)		'Rand pbo' (n=76)		'All teze' (n=106)	
AE category/preferred term	n (%)	Incidence per 100 PY	n (%)	Incidence per 100 PY	n (%)	Incidence per 100 PY	n (%)	Incidence per 100 PY	n (%)	Incidence per 100 PY	n (%)	Incidence per 100 PY
Total time at risk across all patients (years)		977.5		757·2		1193·0		144·8		111·1		186·5
Any fatal AE	8 (1·5)	0·82	5 (0·9)	0·66	9 (1·2)	0·75	2 (2·7)	1·38	0 (0·0)	0·00	2 (1·9)	1·07
COVID-19 pneumonia	2 (0·4)	0·20	0 (0·0)	0·00	2 (0·3)	0·17	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Pneumonia	1 (0·2)	0·10	0 (0·0)	0·00	1 (0·1)	0·08	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Septic shock	1 (0·2)	0·10	0 (0·0)	0·00	1 (0·1)	0·08	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
COVID-19	0 (0·0)	0·00	1 (0·2)	0·13	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Colorectal cancer	1 (0·2)	0·10	0 (0·0)	0·00	1 (0·1)	0·08	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Ruptured cerebral aneurysm	1 (0·2)	0·10	0 (0·0)	0·00	1 (0·1)	0·08	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Acute left ventricular failure	0 (0·0)	0·00	0 (0·0)	0·00	1 (0·1)	0·08	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Cardiac failure	0 (0·0)	0·00	1 (0·2)	0·13	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Cardiac arrest	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	1 (1·4)	0·69	0 (0·0)	0·00	1 (0·9)	0·54
Myocardial infarction	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	1 (1·4)	0·69	0 (0·0)	0·00	1 (0·9)	0·54
Death	1 (0·2)	0·10	3 (0·6)	0·40	1 (0·1)	0·08	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00
Periprocedural myocardial infarction	1 (0·2)	0·10	0 (0·0)	0·00	1 (0·1)	0·08	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00

The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab. The 'all teze' group consisted of patients randomised to tezepelumab in the parent study, plus patients who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION.

AE=adverse event. LTE=long-term extension. n=number of patients. PY=patient-years.

***Table S5*: Adjudicated fatal adverse events**

Treatment	Parent study	Time period	Occurrence on treatment or during follow up	AE (MedDRA preferred term)	Time from first dose to AE (days)	Time from last dose to death (days)	Time from first dose to death (days)	Reasonable possibility AE causally related to investigational product as assessed by the investigator/ masked independent adjudication committee*
Pbo+noLTE	NAVIGATOR	Parent study	Follow-up	Death	63	35	63	No/unlikely
Pbo+noLTE	NAVIGATOR	Parent study	Follow-up	Cardiac failure	145	61	145	No/unlikely
Pbo+pbo	NAVIGATOR	LTE	Follow-up	COVID-19	815	117	820	No/unlikely
Pbo+pbo	NAVIGATOR	LTE	On-treatment	Death	665	19	665	No/unlikely
Pbo+teze†	NAVIGATOR	Run-in, LTE	Follow-up	Death	374	36	374	No/unlikely
Pbo+teze	NAVIGATOR	LTE	On-treatment	Acute left ventricular failure	437	14	437	No/unlikely
Teze+noLTE	SOURCE	Parent study	On-treatment	Cardiac arrest	181	19	182	No/unlikely
Teze+teze	NAVIGATOR	LTE	On-treatment	COVID-19 pneumonia	668	44	689	No/unlikely
Teze+teze	NAVIGATOR	LTE	Follow-up	Septic shock	558	89	566	No/unlikely
Teze+teze	NAVIGATOR	LTE	On-treatment	COVID-19 pneumonia	683	18	697	No/unlikely
Teze+teze	NAVIGATOR	LTE	On-treatment	Pneumonia	653	15	659	No/unlikely
Teze+teze	NAVIGATOR	LTE	On-treatment	Colorectal cancer	588	115	758	Yes/unlikely
Teze+teze	NAVIGATOR	LTE	On-treatment	Periprocedural myocardial infarction	554	26	564	No/unlikely
Teze+teze	NAVIGATOR	LTE	On-treatment	Ruptured cerebral aneurysm	722	21	731	No/unlikely
Teze+teze	NAVIGATOR	LTE	On-treatment	Death	486	10	486	No/unlikely
Teze+teze	SOURCE	LTE	On-treatment	Myocardial infarction	560	24	560	No/unlikely

*WHO criteria were used to assess whether there was a reasonable possibility that an AE was causally related to the investigational product.

[†]This patient received placebo in NAVIGATOR, was randomised to the tezepelumab group in DESTINATION, but died during the LTE run-in period before receiving tezepelumab. This death was therefore counted as occurring on placebo.

Patients were grouped as follows: patients who received tezepelumab in the parent study and in DESTINATION ('teze+teze'); patients who received placebo in the parent study and switched to tezepelumab in DESTINATION (pbo+teze); patients who received placebo in the parent study and in DESTINATION (pbo+pbo); patients who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION (same as the 'pbo+teze' group); and patients who received tezepelumab in the parent study but did not enter the LTE (teze+noLTE); and patients who received placebo in the parent study but did not enter the LTE (pbo+noLTE).

AE=adverse event. LTE=long-term extension. n=number of patients. NoLTE=no enrolment in long-term extension. MedDRA=Medical Dictionary for Regulatory activities. WHO=World Health Organization.

***Table S6*: On-treatment SAEs by system organ class**

Parent study	NAVIGATOR					SOURCE				
	'Rand teze' (n=528)		'Rand pbo' (n=531)			'Rand teze' (n=74)		'Rand pbo' (n=76)		
SAE category/system organ class	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**
Total time at risk across all patients (years)		917·0		699·0			129·4		100·0	
Any SAE	72 (13·6)	7·85	87 (16·4)	12·45	−4·59 (−7·69, −1·65)	17 (23·0)	13·14	18 (23·7)	17·99	−4·85 (−14·88, 4·53)
Infections and infestations	20 (3·8)	2·18	16 (3·0)	2·29	−0·11 (−1·70, 1·35)	5 (6·8)	3·86	3 (3·9)	3·00	0·87 (−5·02, 6·20)
Neoplasms benign, malignant and unspecified	8 (1·5)	0·87	6 (1·1)	0·86	0·01 (−1·07, 0·98)	2 (2·7)	1·55	0 (0·0)	0·00	1·55 (−2·19, 5·47)
Blood and lymphatic system disorders	1 (0·2)	0·11	0 (0·0)	0·00	0·11 (−0·44, 0·62)	0 (0·0)	0·00	0 (0·0)	0·00	-
Immune system disorders	1 (0·2)	0·11	1 (0·2)	0·14	−0·03 (−0·70, 0·48)	0 (0·0)	0·00	0 (0·0)	0·00	-
Endocrine disorders	1 (0·2)	0·11	0 (0·0)	0·00	0·11 (−0·44, 0·62)	0 (0·0)	0·00	0 (0·0)	0·00	-
Metabolism and nutrition disorders	0 (0·0)	0·00	4 (0·8)	0·57	−0·57 (−1·46, −0·15)	1 (1·4)	0·77	0 (0·0)	0·00	0·77 (−2·95, 4·26)
Psychiatric disorders	2 (0·4)	0·22	0 (0·0)	0·00	0·22 (−0·33, 0·79)	0 (0·0)	0·00	0 (0·0)	0·00	-
Nervous system disorders	5 (0·9)	0·55	5 (0·9)	0·72	−0·17 (−1·17, 0·66)	0 (0·0)	0·00	2 (2·6)	2·00	−2·00 (−7·01, 0·93)
Eye disorders	1 (0·2)	0·11	2 (0·4)	0·29	−0·18 (−0·94, 0·36)	0 (0·0)	0·00	0 (0·0)	0·00	-
Ear and labyrinth disorders	0 (0·0)	0·00	1 (0·2)	0·14	−0·14 (−0·81, 0·27)	0 (0·0)	0·00	0 (0·0)	0·00	-

***Table S6*: On-treatment SAEs by system organ class (continued)**

Parent study	NAVIGATOR					SOURCE				
	'Rand teze' (n=528)		'Rand pbo' (n=531)			'Rand teze' (n=74)		'Rand pbo' (n=76)		
SAE category/system organ class	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**
Cardiac disorders	8 (1·5)	0·87	0 (0·0)	0·00	0·87 (0·32, 1·71)	4 (5·4)	3·09	0 (0·0)	0·00	3·09 (−0·67, 7·69)
Vascular disorders	2 (0·4)	0·22	0 (0·0)	0·00	0·22 (−0·33, 0·79)	0 (0·0)	0·00	1 (1·3)	1·00	−1·00 (−5·46, 1·91)
Respiratory, thoracic, and mediastinal disorders	16 (3·0)	1·74	44 (8·3)	6·29	−4·55 (−6·73, −2·68)	3 (4·1)	2·32	10 (13·2)	10·00	−7·68 (−15·39, −1·75)
Gastrointestinal disorders	7 (1·3)	0·76	5 (0·9)	0·72	0·05 (−0·98, 0·96)	1 (1·4)	0·77	1 (1·3)	1·00	−0·23 (−4·75, 3·36)
Hepatobiliary disorders	2 (0·4)	0·22	2 (0·4)	0·29	−0·07 (−0·84, 0·54)	0 (0·0)	0·00	1 (1·3)	1·00	−1·00 (−5·46, 1·91)
Skin and subcutaneous tissue disorders	1 (0·2)	0·11	1 (0·2)	0·14	−0·03 (−0·70, 0·48)	0 (0·0)	0·00	0 (0·0)	0·00	-
Musculoskeletal and connective tissue disorders	7 (1·3)	0·76	3 (0·6)	0·43	0·33 (−0·56, 1·20)	1 (1·4)	0·77	3 (3·9)	3·00	−2·23 (−7·77, 1·61)
Renal and urinary disorders	1 (0·2)	0·11	2 (0·4)	0·29	−0·18 (−0·94, 0·36)	1 (1·4)	0·77	0 (0·0)	0·00	0·77 (−2·95, 4·26)
Reproductive system and breast disorders	2 (0·4)	0·22	1 (0·2)	0·14	0·08 (−0·60, 0·67)	0 (0·0)	0·00	0 (0·0)	0·00	-
Congenital, familial, and genetic disorders	0 (0·0)	0·00	1 (0·2)	0·14	−0·14 (−0·81, 0·27)	0 (0·0)	0·00	0 (0·0)	0·00	-
General disorders and administration-site conditions	3 (0·6)	0·33	2 (0·4)	0·29	0·04 (−0·74, 0·71)	0 (0·0)	0·00	0 (0·0)	0·00	-
Investigations	0 (0·0)	0·00	1 (0·2)	0·14	−0·14 (−0·81, 0·27)	0 (0·0)	0·00	0 (0·0)	0·00	-
Injury, poisoning, and procedural complications	8 (1·5)	0·87	5 (0·9)	0·72	0·16 (−0·88, 1·10)	1 (1·4)	0·77	3 (3·9)	3·00	−2·23 (−7·77, 1·61)

***Table S6*: On-treatment SAEs by system organ class (continued)**

Parent study	Pooled NAVIGATOR + SOURCE				
	'Rand teze' (n=602)		'Rand pbo' (n=607)		
SAE category/system organ class	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**
Total time at risk across all patients (years)		1046·4		799·0	
Any SAE	89 (14·8)	8·51	105 (17·3)	13·14	−4.64 (−7.60, −1.80)
Infections and infestations	25 (4·2)	2·39	19 (3·1)	2·38	0.01 (−1.50, 1.42)
Neoplasms benign, malignant and unspecified	10 (1·7)	0·96	6 (1·0)	0·75	0.20 (−0.77, 1.11)
Blood and lymphatic system disorders	1 (0·2)	0·10	0 (0·0)	0·00	0.10 (−0.38, 0.54)
Immune system disorders	1 (0·2)	0·10	1 (0·2)	0·13	−0.03 (−0.62, 0.43)
Endocrine disorders	1 (0·2)	0·10	0 (0·0)	0·00	0.10 (−0.38, 0.54)
Metabolism and nutrition disorders	1 (0·2)	0·10	4 (0·7)	0·50	−0.41 (−1.19, 0.10)
Psychiatric disorders	2 (0·3)	0·19	0 (0·0)	0·00	0.19 (−0.29, 0.69)
Nervous system disorders	5 (0·8)	0·48	7 (1·2)	0·88	−0.40 (−1.37, 0.37)
Eye disorders	1 (0·2)	0·10	2 (0·3)	0·25	−0.15 (−0.82, 0.31)
Ear and labyrinth disorders	0 (0·0)	0·00	1 (0·2)	0·13	−0.13 (−0.71, 0.24)
Cardiac disorders	12 (2·0)	1·15	0 (0·0)	0·00	1.15 (0.66, 1.99)
Vascular disorders	2 (0·3)	0·19	1 (0·2)	0·13	0.07 (−0.53, 0.58)
Respiratory, thoracic, and mediastinal disorders	19 (3·2)	1·82	54 (8·9)	6·76	−4.94 (−7.02, −3.13)
Gastrointestinal disorders	8 (1·3)	0·76	6 (1·0)	0·75	0.01 (−0.94, 0.86)
Hepatobiliary disorders	2 (0·3)	0·19	3 (0·5)	0·38	−0.18 (−0.92, 0.37)
Skin and subcutaneous tissue disorders	1 (0·2)	0·10	1 (0·2)	0·13	−0.03 (−0.62, 0.43)
Musculoskeletal and connective tissue disorders	8 (1·3)	0·76	6 (1·0)	0·75	0.01 (−0.94, 0.86)
Renal and urinary disorders	2 (0·3)	0·19	2 (0·3)	0·25	−0.06 (−0.73, 0.47)
Reproductive system and breast disorders	2 (0·3)	0·19	1 (0·2)	0·13	0.07 (−0.53, 0.58)
Congenital, familial, and genetic disorders	0 (0·0)	0·00	1 (0·2)	0·13	−0.13 (−0.71, 0.24)
General disorders and administration-site conditions	3 (0·5)	0·29	2 (0·3)	0·25	0.04 (−0.65, 0.62)
Investigations	0 (0·0)	0·00	1 (0·2)	0·13	−0.13 (−0.71, 0.24)
Injury, poisoning, and procedural complications	9 (1·5)	0·86	8 (1·3)	1·00	−0.14 (−1.19, 0.77)

Data are from the primary safety analysis dataset. The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab. The 95% CI of the incidence difference is based on the Miettinen and Nurminen's score method.
AE=adverse event. LTE=long-term extension. N/A=not applicable. n=number of patients. PY=patient-years. SAE=serious adverse event.

***Table S7*: On-study cardiac SAEs within the cardiac disorders system organ class**

Parent study	**NAVIGATOR**							
	'Rand teze' (n=528)		**'Rand pbo' (n=531)**		**'All teze' (n=734)**		**Incidence difference (95% CI)**	
SAE system organ class/preferred term	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**'Rand teze' vs 'Rand pbo'**	**'All teze' vs 'Rand pbo'**
Total time at risk across all patients (years)		977·5		757·2		1193·0		
Cardiac disorders	9 (1·7)	0·92	2 (0·4)	0·26	14 (1·9)	1·17	0.66 (−0.13, 1.51)	0.91 (0.11, 1.74)
Acute myocardial infarction	2 (0·4)	0·20	0 (0·0)	0·00	2 (0·3)	0·17	0.20 (−0.30, 0.74)	0.17 (−0.34, 0.61)
Cardiac failure congestive	2 (0·4)	0·20	0 (0·0)	0·00	3 (0·4)	0·25	0.20 (−0.30, 0.74)	0.25 (−0.25, 0.74)
Coronary artery disease	2 (0·4)	0·20	0 (0·0)	0·00	3 (0·4)	0·25	0.20 (−0.30, 0.74)	0.25 (−0.25, 0.74)
Aortic valve stenosis	1 (0·2)	0·10	0 (0·0)	0·00	1 (0·1)	0·08	0.10 (−0.40, 0.58)	0.08 (−0.42, 0.47)
Atrial flutter	1 (0·2)	0·10	0 (0·0)	0·00	1 (0·1)	0·08	0.10 (−0.40, 0.58)	0.08 (−0.42, 0.47)
Coronary artery occlusion	1 (0·2)	0·10	0 (0·0)	0·00	1 (0·1)	0·08	0.10 (−0.40, 0.58)	0.08 (−0.42, 0.47)
Ventricular extrasystoles	1 (0·2)	0·10	0 (0·0)	0·00	1 (0·1)	0·08	0.10 (−0.40, 0.58)	0.08 (−0.42, 0.47)
Acute left ventricular failure	0 (0·0)	0·00	0 (0·0)	0·00	1 (0·1)	0·08	-	0.08 (−0.42, 0.47)
Atrial tachycardia	0 (0·0)	0·00	0 (0·0)	0·00	1 (0·1)	0·08	-	0.08 (−0.42, 0.47)
Cardiac failure	0 (0·0)	0·00	1 (0·2)	0·13	0 (0·0)	0·00	−0.13 (−0.74, 0.26)	−0.13 (−0.74, 0.19)
Myocarditis	0 (0·0)	0·00	0 (0·0)	0·00	1 (0·1)	0·08		0.08 (−0.42, 0.47)
Palpitations	0 (0·0)	0·00	1 (0·2)	0·13	0 (0·0)	0·00	−0.13 (−0.74, 0.26)	−0.13 (−0.74, 0.19)
Cardiac arrest	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	-	-
Myocardial infarction	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	-	-
Prinzmetal angina	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	-	-
Supraventricular tachycardia	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0·00	-	-

***Table S7*: On-study cardiac SAEs within the cardiac disorders system organ class (continued)**

Parent study	SOURCE							
	'Rand teze' (n=74)		'Rand pbo' (n=76)		'All teze' (n=106)		Incidence difference (95% CI)	
SAE system organ class/preferred term	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**'Rand teze' vs 'Rand pbo'**	**'All teze' vs 'Rand pbo'**
Total time at risk across all patients (years)		144·8		111·1		186·5		
Cardiac disorders	4 (5·4)	2·76	0 (0·0)	0·00	4 (3·8)	2·14	2.76 (−0.63, 6.90)	2.14 (−1.23, 5.39)
Acute myocardial infarction	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Cardiac failure congestive	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Coronary artery disease	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Aortic valve stenosis	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Atrial flutter	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Coronary artery occlusion	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Ventricular extrasystoles	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Acute left ventricular failure	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Atrial tachycardia	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Cardiac failure	1 (1·4)	0·69	0 (0·0)	0·00	1 (0·9)	0·54	0.69 (−2.67, 3.82)	0.54 (−2.82, 2.98)
Myocarditis	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Palpitations	0 (0·0)	0·00	0 (0·0)	0·00	0 (0·0)	0 (0·0)	-	-
Cardiac arrest	1 (1·4)	0·69	0 (0·0)	0·00	1 (0·9)	0·54	0.69 (−2.67, 3.82)	0.54 (−2.82, 2.98)
Myocardial infarction	1 (1·4)	0·69	0 (0·0)	0·00	1 (0·9)	0·54	0.69 (−2.67, 3.82)	0.54 (−2.82, 2.98)
Prinzmetal angina	1 (1·4)	0·69	0 (0·0)	0·00	1 (0·9)	0·54	0.69 (−2.67, 3.82)	0.54 (−2.82, 2.98)
Supraventricular tachycardia	1 (1·4)	0·69	0 (0·0)	0·00	1 (0·9)	0·54	0.69 (−2.67, 3.82)	0.54 (−2.82, 2.98)

***Table S7*: On-study cardiac SAEs within the cardiac disorders system organ class (continued)**

Parent study	Pooled NAVIGATOR + SOURCE							
	'Rand teze' (n=602)		'Rand pbo' (n=607)		'All teze' (n=1840)		Incidence difference (95% CI)	
SAE system organ class/preferred term	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**'Rand teze' vs 'Rand pbo'**	**'All teze' vs 'Rand pbo'**
Total time at risk across all patients (years)		1122·3		868·3		1379·6		
Cardiac disorders	13 (2·2)	1·16	2 (0·3)	0·23	18 (2·1)	1·3	0.93 (0.20, 1.77)	1.07 (0.35, 1.86)
Acute myocardial infarction	2 (0·3)	0·18	0 (0·0)	0·00	2 (0·2)	0·14	0.18 (−0.26, 0.65)	0.14 (−0.30, 0.53)
Cardiac failure congestive	2 (0·3)	0·18	0 (0·0)	0·00	3 (0·4)	0·22	0.18 (−0.26, 0.65)	0.22 (−0.22, 0.64)
Coronary artery disease	2 (0·3)	0·18	0 (0·0)	0·00	3 (0·4)	0·22	0.18 (−0.26, 0.65)	0.22 (−0.22, 0.64)
Aortic valve stenosis	1 (0·2)	0·09	0 (0·0)	0·00	1 (0·1)	0·07	0.09 (−0.35, 0.50)	0.07 (−0.37, 0.41)
Atrial flutter	1 (0·2)	0·09	0 (0·0)	0·00	1 (0·1)	0·07	0.09 (−0.35, 0.50)	0.07 (−0.37, 0.41)
Coronary artery occlusion	1 (0·2)	0·09	0 (0·0)	0·00	1 (0·1)	0·07	0.09 (−0.35, 0.50)	0.07 (−0.37, 0.41)
Ventricular extrasystoles	1 (0·2)	0·09	0 (0·0)	0·00	1 (0·1)	0·07	0.09 (−0.35, 0.50)	0.07 (−0.37, 0.41)
Acute left ventricular failure	0 (0·0)	0·00	0 (0·0)	0·00	1 (0·1)	0·07	-	0.07 (−0.37, 0.41)
Atrial tachycardia	0 (0·0)	0·00	0 (0·0)	0·00	1 (0·1)	0·07	-	0.07 (−0.37, 0.41)
Cardiac failure	1 (0·2)	0·09	1 (0·2)	0·12	1 (0·1)	0·07	−0.03 (−0.57, 0.40)	−0.04 (−0.58, 0.31)
Myocarditis	0 (0·0)	0·00	0 (0·0)	0·00	1 (0·1)	0·07	-	0.07 (−0.37, 0.41)
Palpitations	0 (0·0)	0·00	1 (0·2)	0·12	0 (0·0)	0·00	−0.12 (−0.65, 0.23)	−0.12 (−0.65, 0.16)
Cardiac arrest	1 (0·2)	0·09	0 (0·0)	0·00	1 (0·1)	0·07	0.09 (−0.35, 0.50)	0.07 (−0.37, 0.41)
Myocardial infarction	1 (0·2)	0·09	0 (0·0)	0·00	1 (0·1)	0·07	0.09 (−0.35, 0.50)	0.07 (−0.37, 0.41)
Prinzmetal angina	1 (0·2)	0·09	0 (0·0)	0·00	1 (0·1)	0·07	0.09 (−0.35, 0.50)	0.07 (−0.37, 0.41)
Supraventricular tachycardia	1 (0·2)	0·09	0 (0·0)	0·00	1 (0·1)	0·07	0.09 (−0.35, 0.50)	0.07 (−0.37, 0.41)

Data are from the primary safety analysis dataset. The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab. The 'all teze' group consisted of patients randomised to tezepelumab in the parent study, plus patients who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION.

LTE=long-term extension. n=number of patients. PY=patient-years. SAE=serious adverse event.

Table S8: **Adjudicated cardiac SAEs**

Treatment grouping	Parent study	Time period	Occurrence on treatment or during follow up	Investigator-reported AE term	Masked independent adjudication committee agreement with term	Independent adjudication committee proposed term	Time from last dose to AE (days)	Time from first dose to AE (days)	Reasonable possibility AE causally related to investigational product as assessed by the investigator/masked independent adjudication committee*	Adjudicated MACE
Pbo+noLTE	NAVIGATOR	Parent study	Follow-up	Heart failure	Y		61	145	No/unlikely	Y
Pbo+pbo	NAVIGATOR	LTE	Follow-up	Cardiac palpitations	Y		38	395	No/possible	N
Pbo+teze	NAVIGATOR	LTE	On-treatment	Inflammatory cardiomyopathia	N	Idiopathic cardiomyopathia	4	510	No/unlikely	N
Pbo+teze	NAVIGATOR	LTE	On-treatment	Tachycardia atrial fibrillation	Y		28	729	No/unlikely	N
Pbo+teze	NAVIGATOR	LTE	On-treatment	Coronary artery disease	Y		23	723	No/unlikely	N
Pbo+teze	NAVIGATOR	LTE	On-treatment	Congestive heart failure	N	Mitral regurgitation	35	538	No/unlikely	N
Pbo+teze	NAVIGATOR	LTE	On-treatment	Acute left ventricular failure	N	Sudden cardiac death	14	437	No/unlikely	Y
Teze+noLTE	NAVIGATOR	Parent study	Follow-up	Aortic valve stenosis	Y		64	400	No/unlikely	N
Teze+noLTE	NAVIGATOR	Parent study	On-treatment	Acute on chronic diastolic congestive heart failure	N	Congestive heart failure	2	178	No/unlikely	N
Teze+noLTE	SOURCE	Parent study	On-treatment	Cardiac decompensation	N	Cardiac arrest	16	100	No/unlikely	N
Teze+noLTE	SOURCE	Parent study	On-treatment	Cardiac arrest	Y		18	181	No/unlikely	Y
Teze+teze	NAVIGATOR	LTE	On-treatment	Killip Kimball inferior T type acute myocardial infarction	N	Non-ST elevation myocardial infarction	16	638	No/unlikely	Y
Teze+teze	NAVIGATOR	LTE	On-treatment	Coronaropathy circumflex coronary artery	N	Coronary artery disease	23	735	No/unlikely	N
Teze+teze	NAVIGATOR	Parent study	On-treatment	Coronary heart disease	N	Coronary artery disease	15	323	No/unlikely	N
Teze+teze	NAVIGATOR	LTE	On-treatment	Non-ST elevation myocardial infarction	Y		12	534	No/unlikely	Y
Teze+teze	NAVIGATOR	LTE	On-treatment	Atypical atrial flutter	Y		7	427	No/unlikely	N

Teze+teze	NAVIGATOR	Parent study	On-treatment	Congestive cardiac failure	N	Congestive heart failure	2	30	No/unlikely	N
Teze+teze	NAVIGATOR	Parent study	On-treatment	Increased premature ventricular contractions	N	Palpitations	10	93	No/unlikely	N
Teze+teze	NAVIGATOR	Parent study	On-treatment	Blocked coronary arteries	N	Coronary artery disease	2	141	No/unlikely	Y
Teze+teze	SOURCE	Parent study	On-treatment	Arrhythmia (paroxysmal supraventricular tachycardia)	Y		9	94	No/unlikely	N
Teze+teze	SOURCE	Parent study	On-treatment	Worsening of arrhythmia (paroxysmal supraventricular tachycardia)	N	Arrhythmia (paroxysmal supraventricular tachycardia)	3	199	No/unlikely	N
Teze+teze	SOURCE	LTE	On-treatment	Myocardial infarction	N	Sudden cardiac death	24	560	No/unlikely	Y
Teze+teze	SOURCE	LTE	On-treatment	Variant angina	N	Unstable angina	16	525	No/unlikely	N

*WHO criteria were used to assess whether there was a reasonable possibility that an AE was causally related to the investigational product.
The 'teze+teze' group included patients who received tezepelumab in the parent study and in DESTINATION. The 'pbo+teze' group included patients who received placebo in the parent study and switched to tezepelumab in DESTINATION. The 'pbo+pbo' group included patients who received placebo in the parent study and in DESTINATION. The 'teze+noLTE' group included patients who received tezepelumab in the parent study but did not enter DESTINATION. The 'pbo+noLTE' group included patients who received placebo in the parent study but did not enter DESTINATION.
AE=adverse event. LTE=long-term extension. WHO=World Health Organization.

***Table S9*: Summary of cardiovascular risks at baseline for patients receiving tezepelumab with a cardiac disorder SAE (on-study; pooled across those initially from NAVIGATOR and SOURCE)**

	'All teze' (n=18)
Any cardiovascular disorder or any other cardiovascular risk factor	18 (100·0)
Any cardiovascular disorder and any other cardiovascular risk factor	8 (44·4)
Any cardiovascular risk factor (excluding cardiovascular disorder)	10 (55·6)
Any cardiovascular disorder (with no other cardiovascular risk factor)	0 (0·0)
≥1 cardiovascular risk factor	18 (100·0)
≥2 cardiovascular risk factors	18 (100·0)
≥3 cardiovascular risk factors	17 (94·4)
≥4 cardiovascular risk factors	16 (88·9)
≥5 cardiovascular risk factors	12 (66·7)
≥6 cardiovascular risk factors	8 (44·4)
≥7 cardiovascular risk factors	5 (27·8)
≥8 cardiovascular risk factors	3 (16·7)
≥9 cardiovascular risk factors	1 (5·6)
With 1 organ systems affected	4 (22·2)
With 2 organ systems affected	1 (5·6)
With 3 organ systems affected	0 (0·0)
Individual risk factors	
BP Grade 1	5 (27·8)
BP Grade 2	0 (0·0)
BP Grade 3	1 (5·6)
Former smoker	5 (27·8)
Diabetes mellitus type 1 or type 2*	6 (33·3)
Obesity†	12 (66·7)
Age ≥50 to 64 years	9 (50·0)
Age ≥65 years	7 (38·9)
Male	11 (61·1)
Hypertension‡	14 (77·8)
Hypercholesterolemia§	1 (5·6)
Total Cholesterol (mmol/L)	
Mean (min, max)	5·161 (2·89, 7·71)
>4 mmol/L	15 (83·3)
>6 mmol/L	5 (27·8)
>8 mmol/L	0 (0·0)

* Includes diabetes reported in medical history or in respiratory history.
†Includes preferred term Obesity reported in medical history or a BMI of ≥30 kg/m² at baseline.
‡Includes hypertension reported in medical history or in respiratory history.
§Includes hypercholesterolemia reported in medical history or as pre-treatment AE.
The 'all teze' group consisted of patients randomised to tezepelumab in the parent study plus patients who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION.
AE=adverse event. BP=blood pressure. SAE=serious adverse event. Teze=Tezepelumab.

***Table S10*: On-study cardiac AEs within the cardiac disorders system organ class**

Parent study	NAVIGATOR					SOURCE				
	'Rand teze' (n=528)		'Rand pbo' (n=531)			'Rand teze' (n=74)		'Rand pbo' (n=76)		
AE category/system organ class/preferred term	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**
Total time at risk across all patients (years)		977.5		757.2			144.8		111.1	
Cardiac disorders	25 (4·7)	2·56	20 (3·8)	2·64	−0·08 (−1·71, 1·43)	6 (8·1)	4·14	6 (7·9)	5·40	−1·26 (−7·61, 4·20)
Coronary artery disease	4 (0·8)	0·41	0 (0·0)	0·00	0·41 (−0·10, 1·05)	0 (0·0)	0·00	0 (0·0)	0·00	-
Tachycardia	4 (0·8)	0·41	1 (0·2)	0·13	0·28 (−0·36, 0·93)	0 (0·0)	0·00	2 (2·6)	1·80	−1·80 (−6·34, 0·82)
Ventricular extrasystoles	4 (0·8)	0·41	1 (0·2)	0·13	0·28 (−0·36, 0·93)	0 (0·0)	0·00	0 (0·0)	0·00	-
Angina pectoris	3 (0·6)	0·31	2 (0·4)	0·26	0·04 (−0·68, 0·67)	0 (0·0)	0·00	1 (1·3)	0·90	−0·90 (−4·93, 1·71)
Palpitations	3 (0·6)	0·31	2 (0·4)	0·26	0·04 (−0·68, 0·67)	0 (0·0)	0·00	0 (0·0)	0·00	-
Supraventricular extrasystoles	3 (0·6)	0·31	0 (0·0)	0·00	0·31 (−0·20, 0·90)	0 (0·0)	0·00	0 (0·0)	0·00	-
Acute myocardial infarction	2 (0·4)	0·20	0 (0·0)	0·00	0·20 (−0·30, 0·74)	0 (0·0)	0·00	0 (0·0)	0·00	-
Aortic valve incompetence	2 (0·4)	0·20	1 (0·2)	0·13	0·07 (−0·55, 0·63)	0 (0·0)	0·00	0 (0·0)	0·00	-
Cardiac failure congestive	2 (0·4)	0·20	1 (0·2)	0·13	0·07 (−0·55, 0·63)	0 (0·0)	0·00	0 (0·0)	0·00	-
Left ventricular failure	2 (0·4)	0·20	0 (0·0)	0·00	0·20 (−0·30, 0·74)	0 (0·0)	0·00	0 (0·0)	0·00	-
Mitral valve incompetence	2 (0·4)	0·20	0 (0·0)	0·00	0·20 (−0·30, 0·74)	0 (0·0)	0·00	1 (1·3)	0·90	−0·90 (−4·93, 1·71)
Aortic valve stenosis	1 (0.2)	0.10	0 (0.0)	0.00	0·10 (−0·40, 0·58)	0 (0.0)	0.00	0 (0.0)	0.00	-
Atrial fibrillation	1 (0·2)	0·10	6 (1·1)	0·79	−0·69 (−1·63, −0·11)	1 (1·4)	0·69	0 (0·0)	0·00	0·69 (−2·67, 3·82)
Atrial flutter	1 (0·2)	0·10	0 (0·0)	0·00	0·10 (−0·40, 0·58)	0 (0·0)	0·00	0 (0·0)	0·00	-
Cardiomegaly	1 (0·2)	0·10	0 (0·0)	0·00	0·10 (−0·40, 0·58)	0 (0·0)	0·00	0 (0·0)	0·00	-
Congestive cardiomyopathy	1 (0·2)	0·10	0 (0·0)	0·00	0·10 (−0·40, 0·58)	0 (0·0)	0·00	0 (0·0)	0·00	-
Coronary artery occlusion	1 (0·2)	0·10	1 (0·2)	0·13	−0·03 (−0·65, 0·46)	0 (0·0)	0·00	0 (0·0)	0·00	-
Dilatation atrial	1 (0·2)	0·10	0 (0·0)	0·00	0·10 (−0·40, 0·58)	0 (0·0)	0·00	0 (0·0)	0·00	-
Dilatation ventricular	1 (0·2)	0·10	0 (0·0)	0·00	0·10 (−0·40, 0·58)	0 (0·0)	0·00	0 (0·0)	0·00	-
Pericardial effusion	1 (0·2)	0·10	0 (0·0)	0·00	0·10 (−0·40, 0·58)	0 (0·0)	0·00	0 (0·0)	0·00	-
Pulmonary valve incompetence	1 (0·2)	0·10	0 (0·0)	0·00	0·10 (−0·40, 0·58)	0 (0·0)	0·00	0 (0·0)	0·00	-
Sinus tachycardia	1 (0·2)	0·10	2 (0·4)	0·26	−0·16 (−0·86, 0·34)	0 (0·0)	0·00	2 (2·6)	1·80	−1·80 (−6·34, 0·82)
Tricuspid valve incompetence	1 (0·2)	0·10	1 (0·2)	0·13	−0·03 (−0·65, 0·46)	0 (0·0)	0·00	0 (0·0)	0·00	-
Right ventricular hypertrophy	0 (0·0)	0·00	1 (0·2)	0·13	−0·13 (−0·74, 0·26)	0 (0·0)	0·00	0 (0·0)	0·00	-

***Table S10*: On-study cardiac AEs within the cardiac disorders system organ class (continued)**

Parent study	NAVIGATOR					SOURCE				
	'Rand teze' (n=528)		'Rand pbo' (n=531)			'Rand teze' (n=74)		'Rand pbo' (n=76)		
AE category/system organ class/preferred term	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**
Total time at risk across all patients (years)		977.5		757.2			144.8		111.1	
Sinus node dysfunction	0 (0·0)	0·00	1 (0·2)	0·13	−0·13 (−0·74, 0·26)	0 (0·0)	0·00	0 (0·0)	0·00	-
Ventricular remodelling	0 (0·0)	0·00	1 (0·2)	0·13	−0·13 (−0·74, 0·26)	0 (0·0)	0·00	0 (0·0)	0·00	-
Bradyarrhythmia	0 (0·0)	0·00	0 (0·0)	0·00	-	1 (1·4)	0·69	0 (0·0)	0·00	0·69 (−2·67, 3·82)
Cardiac arrest	0 (0·0)	0·00	0 (0·0)	0·00	-	1 (1·4)	0·69	0 (0·0)	0·00	0·69 (−2·67, 3·82)
Cardiac failure	0 (0·0)	0·00	3 (0·6)	0·40	−0·40 (−1·16, −0·00)	1 (1·4)	0·69	0 (0·0)	0·00	0·69 (−2·67, 3·82)
Myocardial infarction	0 (0·0)	0·00	0 (0·0)	0·00	-	1 (1·4)	0·69	0 (0·0)	0·00	0·69 (−2·67, 3·82)
Prinzmetal angina	0 (0·0)	0·00	0 (0·0)	0·00	-	1 (1·4)	0·69	0 (0·0)	0·00	0·69 (−2·67, 3·82)
Supraventricular tachycardia	0 (0·0)	0·00	0 (0·0)	0·00	-	1 (1·4)	0·69	0 (0·0)	0·00	0·69 (−2·67, 3·82)
Arrhythmia	0 (0·0)	0·00	0 (0·0)	0·00	-	0 (0·0)	0·00	1 (1·3)	0·90	−0·90 (−4·93, 1·71)
Tachycardia paroxysmal	0 (0·0)	0·00	0 (0·0)	0·00	-	0 (0·0)	0·00	1 (1·3)	0·90	−0·90 (−4·93, 1·71)

***Table S10*: On-study cardiac AEs within the cardiac disorders system organ class (continued)**

Parent study	Pooled NAVIGATOR + SOURCE				
	'Rand teze' (n=602)		'Rand pbo' (n=607)		
AE category/system organ class/preferred term	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Incidence difference (95% CI)**
Total time at risk across all patients (years)		1122·3		868·3	
Cardiac disorders	31 (5·1)	2·76	26 (4·3)	2·99	−0·23 (−1·81, 1·24)
Coronary artery disease	4 (0·7)	0·36	0 (0·0)	0·00	0·36 (−0·08, 0·91)
Tachycardia	4 (0·7)	0·36	3 (0·5)	0·35	0·01 (−0·69, 0·61)
Ventricular extrasystoles	4 (0·7)	0·36	1 (0·2)	0·12	0·24 (−0·32, 0·81)
Angina pectoris	3 (0·5)	0·27	3 (0·5)	0·35	−0·08 (−0·77, 0·48)
Palpitations	3 (0·5)	0·27	2 (0·3)	0·23	0·04 (−0·59, 0·58)
Supraventricular extrasystoles	3 (0·5)	0·27	0 (0·0)	0·00	0·27 (−0·17, 0·78)
Acute myocardial infarction	2 (0·3)	0·18	0 (0·0)	0·00	0·18 (−0·26, 0·65)
Aortic valve incompetence	2 (0·3)	0·18	1 (0·2)	0·12	0·06 (−0·48, 0·55)
Atrial fibrillation	2 (0·3)	0·18	6 (1·0)	0·69	−0·51 (−1·34, 0·06)
Cardiac failure congestive	2 (0·3)	0·18	1 (0·2)	0·12	0·06 (−0·48, 0·55)
Left ventricular failure	2 (0·3)	0·18	0 (0·0)	0·00	0·18 (−0·26, 0·65)
Mitral valve incompetence	2 (0·3)	0·18	1 (0·2)	0·12	0·06 (−0·48, 0·55)
Aortic valve stenosis	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Atrial flutter	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Bradyarrhythmia	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Cardiac arrest	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Cardiac failure	1 (0·2)	0·09	3 (0·5)	0·35	−0·26 (−0·93, 0·19)
Cardiomegaly	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Congestive cardiomyopathy	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Coronary artery occlusion	1 (0·2)	0·09	1 (0·2)	0·12	−0·03 (−0·57, 0·40)
Dilatation atrial	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Dilatation ventricular	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Myocardial infarction	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Pericardial effusion	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Prinzmetal angina	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Pulmonary valve incompetence	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Sinus tachycardia	1 (0·2)	0·09	4 (0·7)	0·46	−0·37 (−1·10, 0·10)
Supraventricular tachycardia	1 (0·2)	0·09	0 (0·0)	0·00	0·09 (−0·35, 0·50)
Tricuspid valve incompetence	1 (0·2)	0·09	1 (0·2)	0·12	−0·03 (−0·57, 0·40)
Arrhythmia	0 (0·0)	0·00	1 (0·2)	0·12	−0·12 (−0·65, 0·23)
Right ventricular hypertrophy	0 (0·0)	0·00	1 (0·2)	0·12	−0·12 (−0·65, 0·23)
Sinus node dysfunction	0 (0·0)	0·00	1 (0·2)	0·12	−0·12 (−0·65, 0·23)
Ventricular remodelling	0 (0·0)	0·00	1 (0·2)	0·12	−0·12 (−0·65, 0·23)
Tachycardia paroxysmal	0 (0·0)	0·00	1 (0·2)	0·12	−0·12 (−0·65, 0·23)

Data are from the primary safety analysis dataset. The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab.
AE=adverse event. CI=confidence interval. LTE=long-term extension. PY=patient-years.

Table S11: **Adjudicated on-study MACE in patients from NAVIGATOR and SOURCE parent studies combined**

	'Rand teze' (N=602)		**'Rand pbo' (N=607)**		**'All teze' (N=840)**		**Incidence difference (95% CI)**	
	n (%)	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**n (%)**	**Incidence per 100 PY**	**Rand teze vs Rand pbo**	**All teze vs Rand pbo**
Total time at risk across all patients (years)		1122·3		868·3		1379·6		
Events assessed as MACE by the Independent Adjudication Committee*	8 (1·3)	0·71	4 (0·7)	0·46	9 (1·1)	0·65	0·25 (–0·54, 1·00)	0·19 (–0·58, 0·85)
Cardiovascular death	5 (0·8)	0·45	3 (0·5)	0·35	6 (0·7)†	0·43	0·10 (–0·61, 0·74)	0·09 (–0·61, 0·66)
Non-fatal myocardial infarction	3 (0·5)	0·27	0 (0·0)	0·00	3 (0·4)	0·22	0·27 (–0·17, 0·78)	0·22 (–0·22, 0·64)
Non-fatal stroke	0 (0·0)	0·00	1 (0·2)	0·12	0 (0·0)	0·00	–0·12 (–0·65, 0·23)	–0·12 (–0·65, 0·16)

*The independent adjudication committee's adjudication was based on the definition of MACE in the Adjudication Charter, namely stroke, myocardial infarction and unstable angina. MACE events that resulted in death were categorized as cardiovascular deaths within the MACE category.

†Excludes 1 patient/event in the 'all teze' group who had a fatal AE (sudden death unknown cause) during the EFU period (167 days after the last dose) that was determined by the Independent Adjudication Committee to be a MACE (cardiovascular death).

The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab. The 'all teze' group consisted of patients randomised to tezepelumab in the parent study plus patients who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION.

AE=adverse event. CI=confidence interval. EFU=extended follow=up. LTE=long-term extension. MACE, major adverse cardiovascular events. MedRA=Medical Dictionary For Regulatory Activities Terminology. n=number of patients. PY=patient-years.

***Table S12*: On-study COVID-19-related AEs, SAEs, and AEs with a fatal outcome after the start of COVID-19 pandemic (pooled across those initially from NAVIGATOR and SOURCE)**

AE category	'Rand teze' (n=602)		'Rand pbo' (n=607)		'All teze' (n=840)	
	n (%)	Incidence per 100 PY	n (%)	Incidence per 100 PY	n (%)	Incidence per 100 PY
AEs						
Total time at risk across all patients (years)		343·6		188·1		501·0
Patients with any AE, n (%)	24 (4·0)	6·98	17 (2·8)	9·04	39 (4·6)	7·78
SAEs						
Total time at risk across all patients (years)		343·6		188·1		501·0
Patients with any SAE, n (%)	9 (1·5)	2·62	5 (0·8)	2·66	9 (1·1)	1·80
AEs with a fatal outcome						
Total time at risk across all patients (years)		343·6		188·1		501·0
Patients with any AE, n (%)	2 (0·3)	0·58	1 (0·2)	0·53	2 (0·2)	0·40

The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab. The 'all teze' group consisted of patients randomised to tezepelumab in the parent study, plus patients who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION.

AE=adverse event. LTE=long-term extension. n=number of patients. PY=patient-years. SAE=severe adverse event.

***Table S13*: Malignancies by system organ class and preferred term (on-treatment)**

Parent study	NAVIGATOR					SOURCE				
	'Rand teze' (n=528)		'Rand pbo' (n=531)		Incidence difference (95% CI)	'Rand teze' (n=74)		'Rand pbo' (n=76)		Incidence difference (95% CI)
System organ class/preferred term	n (%)	Incidence per 100 PY	n (%)	Incidence per 100 PY		n (%)	Incidence per 100 PY	n (%)	Incidence per 100 PY	
Total time at risk across all patients (years)		917·0		699·0			129·4		100·0	
Patients with any malignancy	6 (1·1)	0·65	5 (0·9)	0·72	–0.06 (–1.07, 0.81)	1 (1·4)	0·77	0 (0·0)	0·00)	0.77 (–2.95, 4.26)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	6 (1·1)	0·65	5 (0·9)	0·72	–0.06 (–1.07, 0.81)	1 (1·4)	0·77	0 (0·0)	0·00)	0.77 (–2.95, 4.26)
Malignant melanoma in situ	2 (0·4)	0·22	0 (0·0)	0·00	0.22 (–0.33, 0.79)	0 (0·0)	0·00	0 (0·0)	0·00	-
Basal cell carcinoma	1 (0·2)	0·11	2 (0·4)	0·29	–0.18 (–0.94, 0.36)	0 (0·0)	0·00	0 (0·0)	0·00	-
Colon cancer stage IV	1 (0·2)	0·11	0 (0·0)	0·00	0.11 (–0.44, 0.62)	0 (0·0)	0·00	0 (0·0)	0·00	-
Colorectal cancer	1 (0·2)	0·11	0 (0·0)	0·00	0.11 (–0.44, 0.62)	0 (0·0)	0·00	0 (0·0)	0·00	-
Prostate cancer	1 (0·2)	0·11	0 (0·0)	0·00	0.11 (–0.44, 0.62)	0 (0·0)	0·00	0 (0·0)	0·00	-
Squamous cell carcinoma	1 (0·2)	0·11	1 (0·2)	0·14	–0.03 (–0.70, 0.48)	0 (0·0)	0·00	0 (0·0)	0·00	-
Endometrial cancer	0 (0·0)	0·00	1 (0·2)	0·14	–0.14 (–0.81, 0.27)	0 (0·0)	0·00	0 (0·0)	0·00	-
Squamous cell carcinoma of the oral cavity	0 (0·0)	0·00)	1 (0·2)	0·14	–0.14 (–0.81, 0.27)	0 (0·0)	0·00	0 (0·0)	0·00	-
Invasive breast cancer	0 (0·0)	0·00	0 (0·0)	0·00		1 (1·4)	0·77	0 (0·0)	0·00)	0.77 (–2.95, 4.26)

Data are from the primary safety analysis dataset. The 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab.
LTE=long-term extension. n=number of patients. PY=patient-years.

***Table S14*: Change from baseline to week 104 in pre-bronchodilator FEV_1, ACQ-6 score, and SGRQ score**

Parent study	NAVIGATOR		SOURCE	
	'Rand teze' (n=528)	'Rand pbo' (n=531)	'Rand teze' (n=74)	'Rand pbo' (n=76)
Pre-bronchodilator FEV_1, L				
Mean baseline (SD)	2·07 (0·77)	2·1 (0·76)	1·80 (0·54)	1.81 (0.73)
Change from baseline at week 104				
n1	527	531	73	76
n2	342	172	50	25
LS mean (SE)	0·20 (0·02)	0·12 (0·02)	0·20 (0·05)	0.01 (0.06)
LS mean difference versus placebo (95% CI)				
	0·08 (0·02, 0·15)		0·19 (0·03, 0·35)	
ACQ-6 score*				
Mean baseline (SD)	2·82 (0·81)	2·79 (0·82)	2·48 (1·07)	2.46 (1.03)
Change from baseline at week 104				
n1	527	531	72	76
n2	386	194	58	26
LS mean (SE)	−1·61 (0·05)	−1·31 (0·06)	−1·06 (0·13)	−0.37 (0.18)
LS mean difference versus placebo (95% CI)				
	−0·30 (−0·45, −0·15)		−0·69 (−1·12, −0·25)	
SGRQ score†				
Mean baseline (SD)	55·17 (19·51)	52·81 (19·00)	56·71 (20·61)	58.67 (18.50)
Change from baseline at week 104				
n1	417	413	66	69
n2	310	153	58	26
LS mean (SE)	−26·97 (0·96)	−20·92 (1·25)	−22·29 (2·55)	−12.25 (3.55)
LS mean difference versus placebo (95% CI)				
	−6·05 (−9·15, −2·94)		−10·04 (−18·73, −1·36)	

*Scores range from 0 (no impairment) to 6 (maximum impairment), with lower scores indicating better disease control. Scores higher than 1.5 indicate inadequately controlled asthma. Scores lower than 0.75 indicate well-controlled asthma. The minimum clinically important difference is 0.5 points. †Scores range from 0 to 100, with higher scores indicating more limitations. The minimum clinically important difference is 4 points.

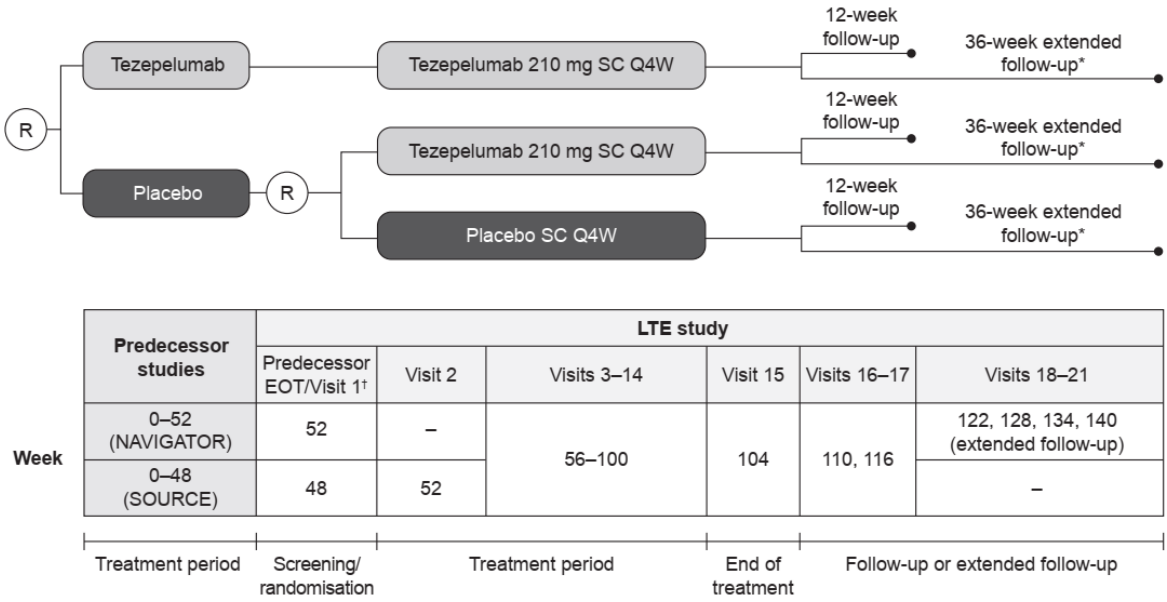
Data are from the primary full analysis dataset. The 'rand teze' group included all patients randomised to tezepelumab in the parent study and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab.

ACQ-6=Asthma Control Questionnaire-6. CI=confidence interval. FEV_1=forced expiratory volume in 1 second. LS=least squares. n1=number of patients included in the analysis (i.e. the number of patients with at least one change from baseline value at any post baseline visit). n2=number of patients with a change from baseline value at each timepoint. SD=standard deviation. SE=standard error. SGRQ=St George's Respiratory Questionnaire score.

***Table S15*: Change in inflammatory biomarkers over time (supportive LTE dataset)**

Parent study	NAVIGATOR			SOURCE		
	Teze+teze (n=415)	**Pbo+pbo (n=206)**	**Pbo+teze (n=205)**	**Teze+teze (n=60)**	**Pbo+pbo (n=32)**	**Pbo+teze (n=32)**
FeNO, ppb						
Mean baseline (SD)	39·94 (34·22)	42·31 (44·71)	44·75 (41·82)	38·52 (42·30)	44·18 (40·12)	39·84 (33·16)
Change from baseline at end of parent study (SD)	–16·35 (27·99)	–3·49 (32·31)	–4·46 (31·98)	–12·83 (26·20)	0·62 (31·58)	–0·88 (26·58)
Change from baseline at week 104 (SD)	–14·53 (30·52)	–6·07 (27·46)	–22·18 (36·40)	–14·05 (31·10)	–3·20 (31·91)	–9·68 (14·55)
Blood eosinophil count, cells/μL						
Mean baseline (SD)	322 (300)	298 (225)	368 (678)	260 (189)	246 (161)	203 (146)
Change from baseline at end of parent study (SD)	–159 (270)	–30 (190)	–36 (524)	–97 (161)	22 (175)	60 (148)
Change from baseline at week 104 (SD)	–167 (280)	–11 (238)	–152 (366)	–80 (161)	70 (236)	–80 (122)
Serum total IgE, IU/mL						
Mean baseline (SD)	516·33 (969·56)	545·60 (954·47)	701·65 (1415·15)	224·54 (401·25)	344·42 (625·38)	295·23 (491·92)
Change from baseline at end of parent study (SD)	–166·22 (521·67)	79·02 (1090·11)	–22·09 (635·86)	–48·42 (123·91)	–49·40 (239·84)	103·09 (493·30)
Change from baseline at week 104 (SD)	–205·48 (691·20)	30·10 (989·45)	–247·51 (926·05)	–76·40 (226·16)	–41·66 (298·51)	–71·07 (156·88)

Data are from the supportive LTE analysis dataset that only included patients who were enrolled in DESTINATION. For the supportive dataset, the 'teze+teze' group included patients who received tezepelumab in both the parent study and in DESTINATION, and the pbo+pbo group included patients who received placebo in both the parent study and in DESTINATION. Patients in the 'pbo+teze' group received placebo in the parent study and tezepelumab in the LTE.
FeNO=fractional exhaled nitric oxide. IgE=immunoglobulin E. LTE=long-term extension. SD=standard deviation.



	Predecessor studies	LTE study					
		Predecessor EOT/Visit 1†	Visit 2	Visits 3–14	Visit 15	Visits 16–17	Visits 18–21
Week	0–52 (NAVIGATOR)	52	–	56–100	104	110, 116	122, 128, 134, 140 (extended follow-up)
	0–48 (SOURCE)	48	52				–
		Treatment period	Screening/ randomisation	Treatment period		End of treatment	Follow-up or extended follow-up

***Figure S1*: Study design**
Figure reproduced from Menzies-Gow and colleagues.[10]
*Only patients initially from the NAVIGATOR parent study were eligible for a 36-week extended follow-up (results not included in the current publication).
†The protocol was amended in light of the COVID-19 pandemic. Patients aiming to enrol in the DESTINATION study who were not able to attend an onsite end of treatment visit in either parent study continued to participate in the 12-week safety follow-up period of either NAVIGATOR or SOURCE until on-site randomisation and administration of the first dose of study treatment in DESTINATION could be conducted.
EOT=end of treatment. LTE=long-term extension. Q4W=every 4 weeks. R=randomisation. SC=subcutaneously.

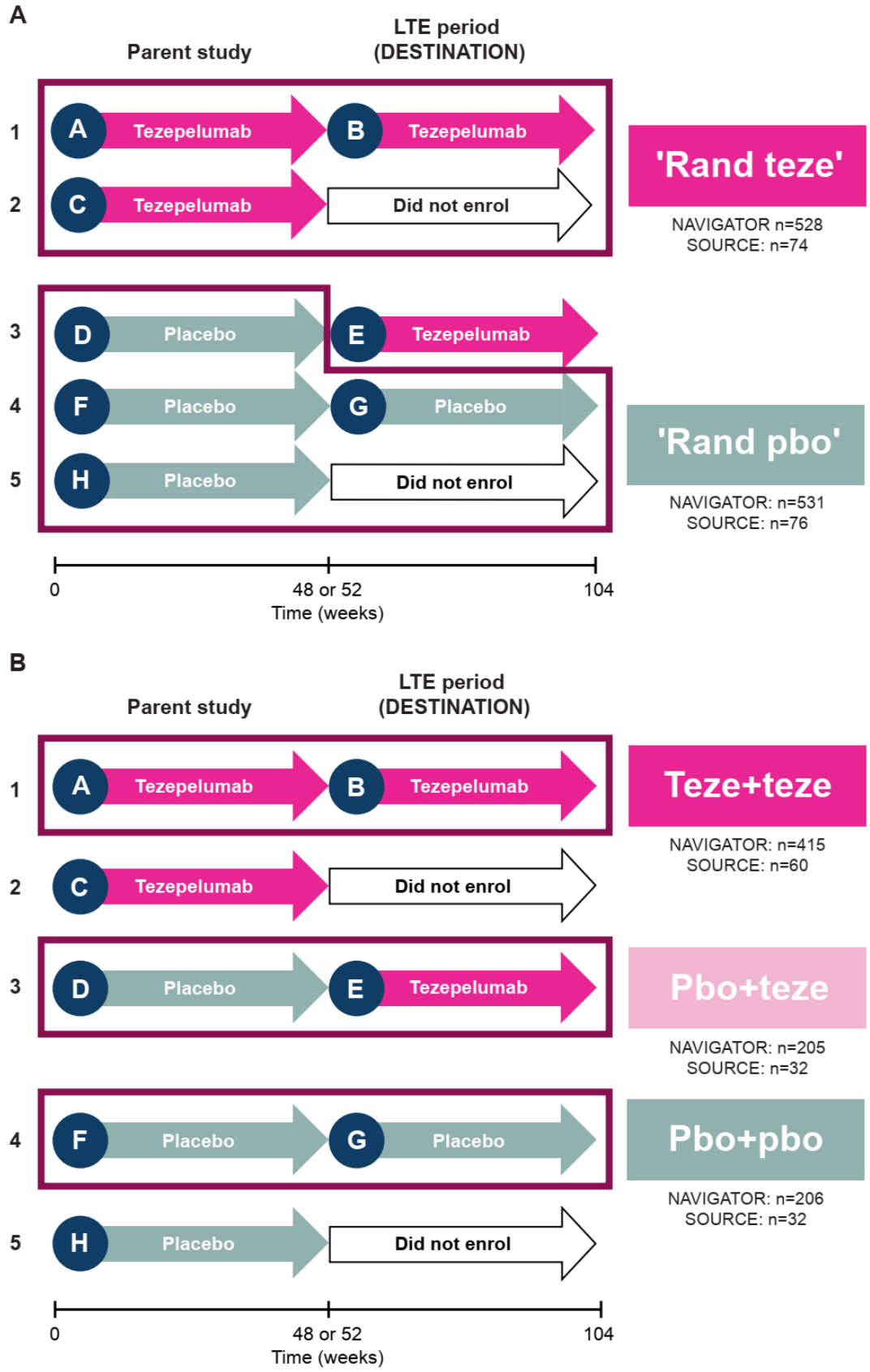


***Figure S2*: Primary (a) and supportive LTE (b) analysis sets**

The 'rand teze' group in the primary safety and full analysis datasets included patients who received tezepelumab in the parent study, and the dataset consisted of all data from the beginning of the parent study until the end of DESTINATION (A, B and C). The 'rand pbo' group in the primary safety and full analysis datasets included patients who received placebo in the parent study, and the dataset consisted of all data from the

beginning of the parent study until switch to tezepelumab (for patients who were randomised to tezepelumab in DESTINATION [D]) or the end of DESTINATION (for patients who continued on placebo [F, G]) or until the end of the parent trial (for patients who did not enrol in DESTINATION [H]). The supportive safety and full analysis datasets only included patients who were enrolled in DESTINATION. Patients were grouped as follows: patients who received tezepelumab in the parent study and in DESTINATION ('teze+teze'; A and B); patients who received placebo in the parent study and switched to tezepelumab in DESTINATION (pbo+teze; D and E); patients who received placebo in the parent study and in DESTINATION ('pbo+pbo'; F and G). The 'all teze' group consisted of patients randomised to tezepelumab in the parent study (E; data from D were not included), plus patients who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION (same as the 'pbo+teze' group).
LTE=long-term extension.

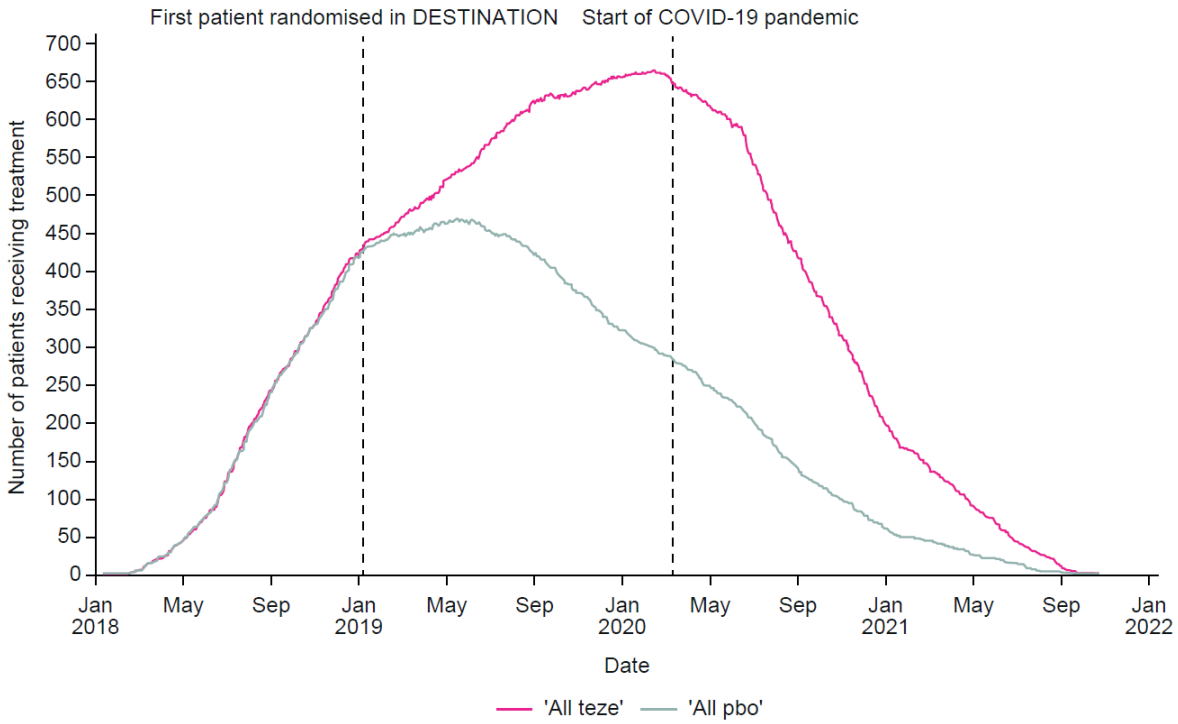


***Figure S3*: Exposure to tezepelumab and placebo over 104 weeks**
The 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab. The 'all teze' group consisted of patients randomised to tezepelumab in the parent study, plus patients who received placebo in the parent study and were re-randomised to receive tezepelumab in DESTINATION (data following re-randomisation only).

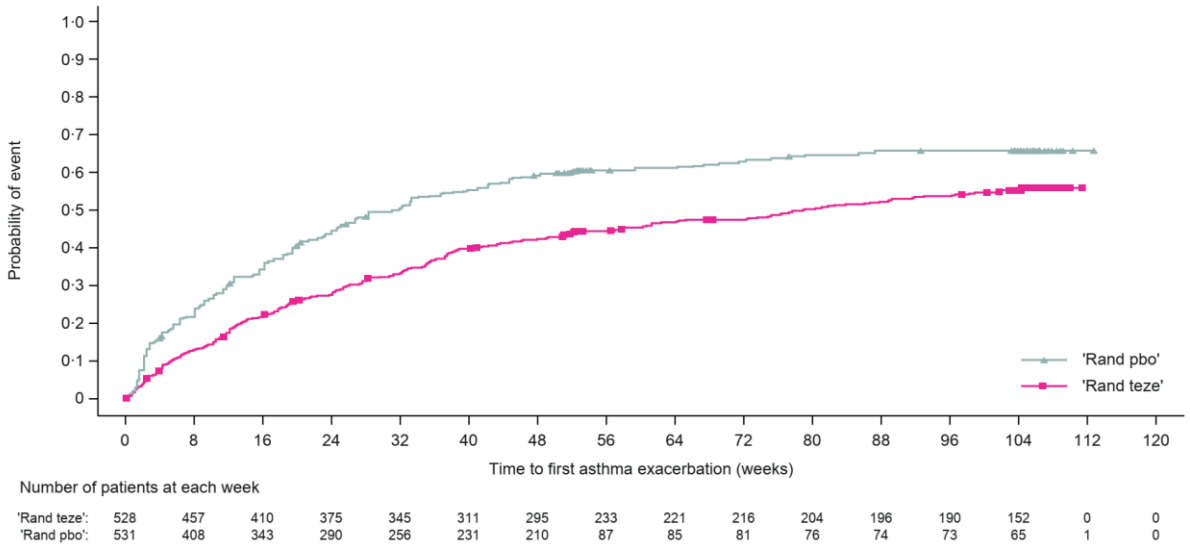


***Figure S4*: Time-to-first asthma exacerbation over 104 weeks among patients initially from NAVIGATOR**

Censoring symbols indicate time when a patient completed their planned treatment or withdrew from the study during planned treatment without an asthma exacerbation. Data are from the primary full analysis dataset. The tezepelumab group included all patients randomised to tezepelumab in the parent study, and the placebo group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab.

LTE=long-term extension.

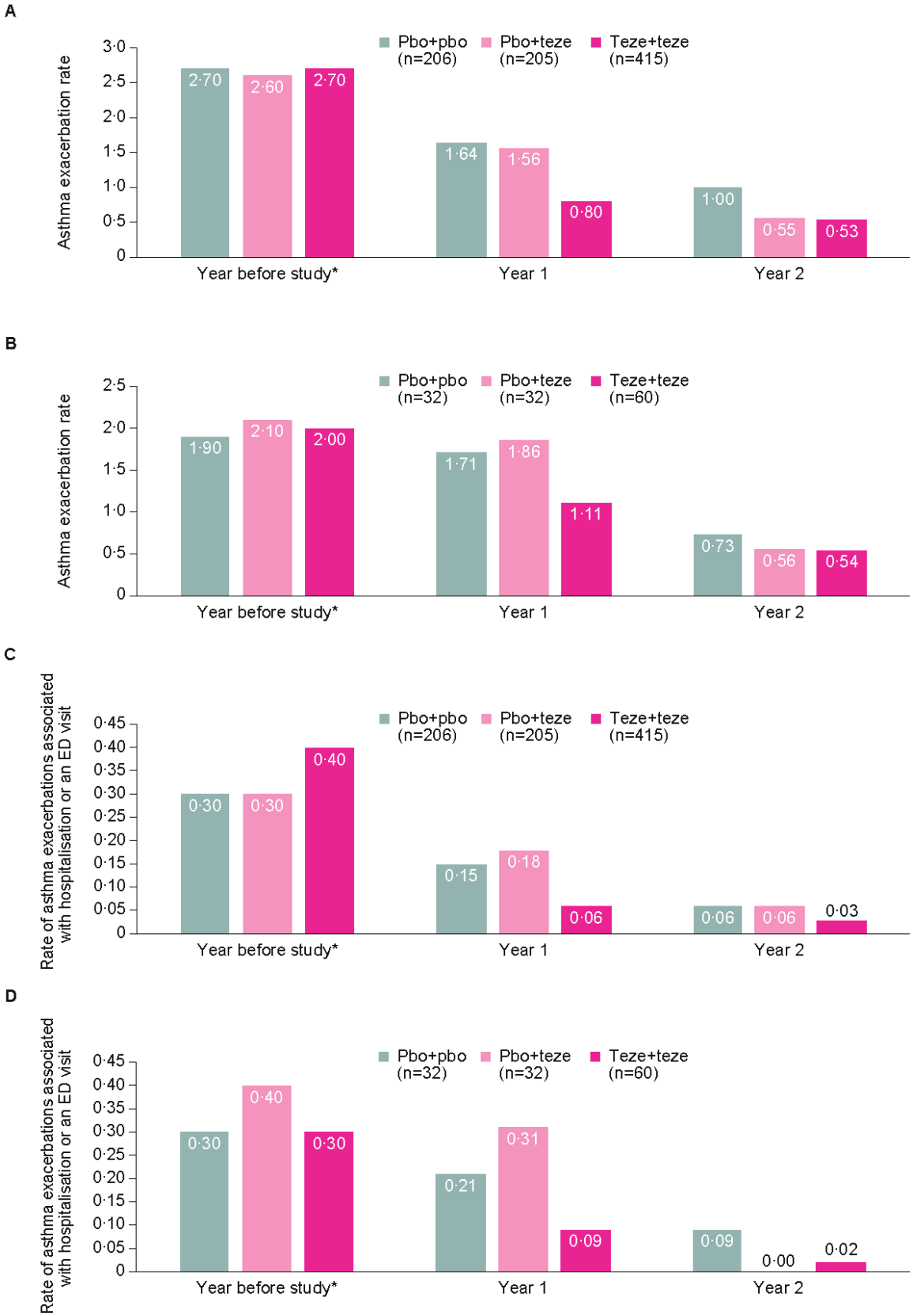
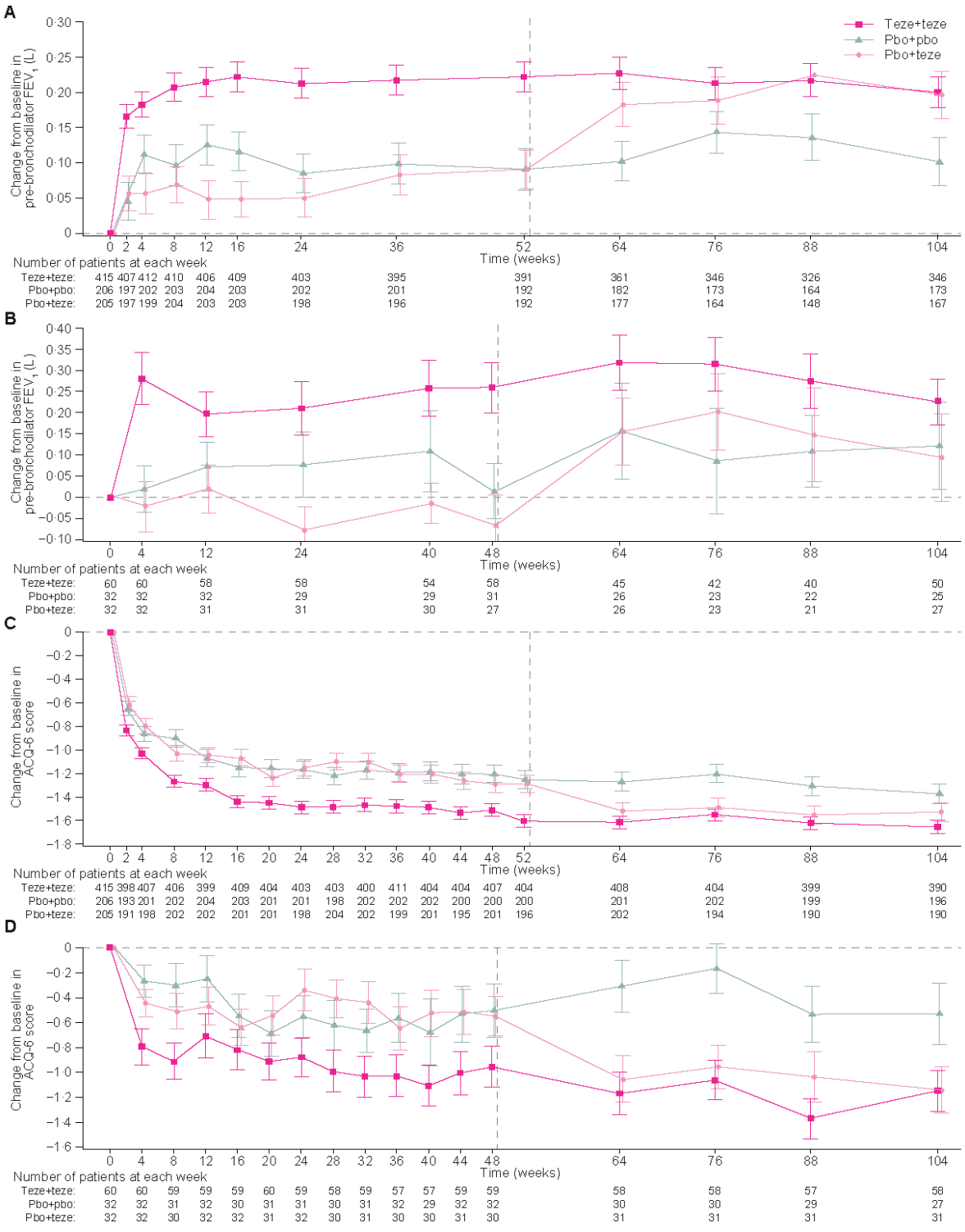


***Figure S5*: Asthma exacerbations overall among patients initially from NAVIGATOR (a) and SOURCE (b), and asthma exacerbations associated with hospitalisation or ED visits among patients originally from NAVIGATOR (c) and SOURCE (d)**

*Data from the 12 months before enrolment into the parent studies show the mean number of exacerbations over 12 months, rather than the asthma exacerbation rate (number of exacerbations/total time at-risk).

The supportive full LTE analysis dataset only included patients who were enrolled in DESTINATION. The 'teze+teze' group shown included patients who received tezepelumab in both the parent study and in DESTINATION, and the 'pbo+pbo' group included patients who received placebo in both the parent study and in DESTINATION. Patients in the 'pbo+teze' group received placebo in the parent study and tezepelumab in the LTE.
ED=emergency department. LTE=long-term extension.


A
Change from baseline in pre-bronchodilator FEV1 (L)
Teze+teze
Pbo+pbo
Pbo+teze
Time (weeks)
Number of patients at each week
Teze+teze: 415 407 412 410 406 409 403 395 391 361 346 326 346
Pbo+pbo: 206 197 202 203 204 203 202 201 192 182 173 164 173
Pbo+teze: 205 197 199 204 203 203 198 196 192 177 164 148 167
B
Change from baseline in pre-bronchodilator FEV1 (L)
Time (weeks)
Number of patients at each week
Teze+teze: 60 60 58 58 54 58 45 42 40 50
Pbo+pbo: 32 32 32 29 29 31 26 23 22 25
Pbo+teze: 32 32 31 31 30 27 26 23 21 27
C
Change from baseline in ACQ-6 score
Time (weeks)
Number of patients at each week
Teze+teze: 415 398 407 406 399 409 404 403 403 400 411 404 404 407 404 408 404 399 390
Pbo+pbo: 206 193 201 202 204 203 201 201 198 202 202 202 200 200 200 201 202 199 196
Pbo+teze: 205 191 198 202 202 201 201 198 204 202 199 201 195 201 196 202 194 190 190
D
Change from baseline in ACQ-6 score
Time (weeks)
Number of patients at each week
Teze+teze: 60 60 59 59 59 60 59 58 59 57 57 59 59 58 58 57 58
Pbo+pbo: 32 32 31 32 30 31 31 30 31 32 29 32 32 30 30 29 27
Pbo+teze: 32 32 30 32 32 31 32 30 31 30 30 31 30 31 31 31 31

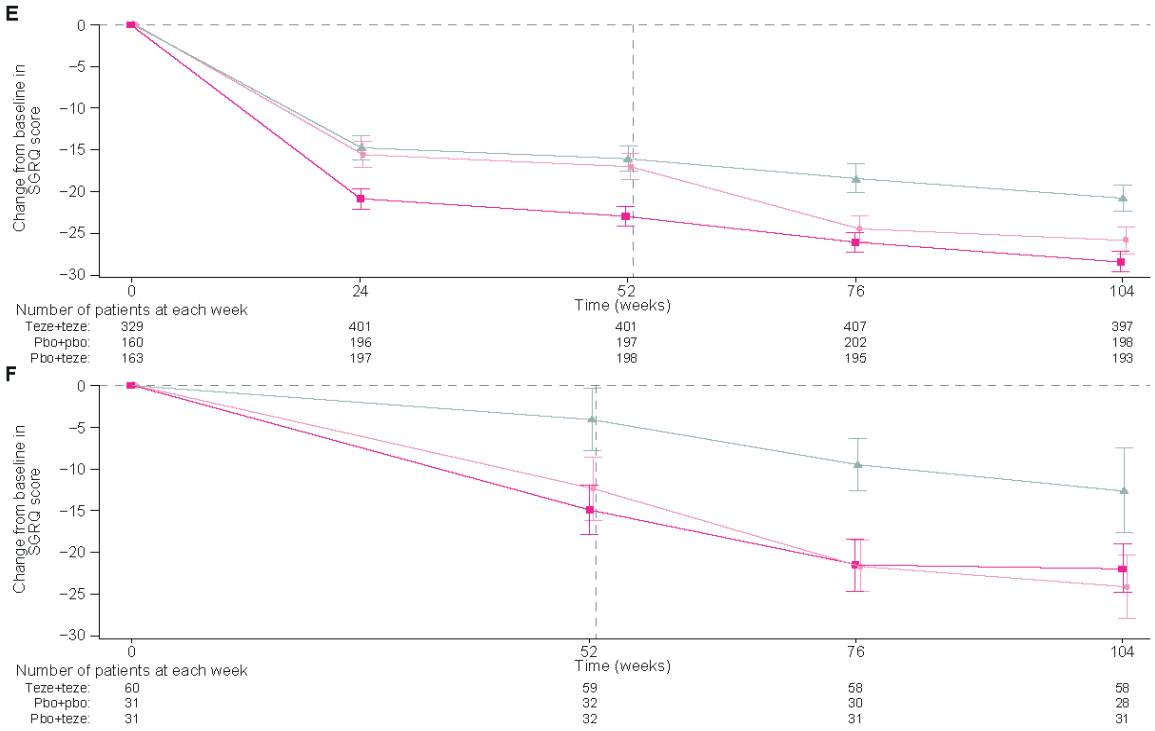
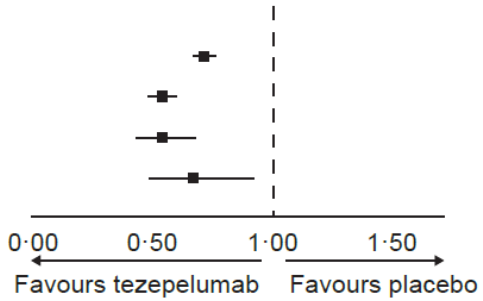
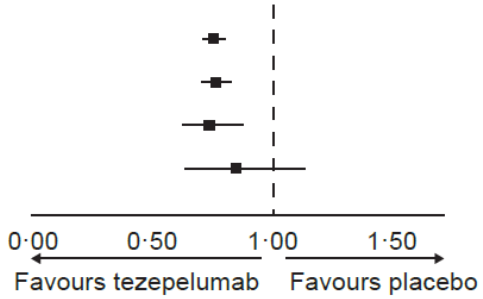


***Figure S6*: Change from baseline in pre-bronchodilator FEV_1, ACQ-6 score, and SGRQ score in patients initially from NAVIGATOR (a, c and e) and SOURCE (b, d and f) (supportive LTE analysis set)**
Data are unadjusted means and standard errors. Data are from the supportive LTE analysis dataset that only included patients who were enrolled in DESTINATION. For the supportive dataset, the 'teze+teze' group included patients who received tezepelumab in both the parent study and in DESTINATION, and the 'pbo+pbo' group included patients who received placebo in both the parent study and in DESTINATION. Patients in the 'pbo+teze' group received placebo in the parent study and tezepelumab in the LTE.
ACQ=Asthma Control Questionnaire. BD=bronchodilator. FEV_1=forced expiratory volume in 1 second. LTE=long-term extension. SGRQ=St George's Respiratory Questionnaire.

Biomarker	Parent study	Week	Geometric LS mean (95% CI) difference from baseline/n 'Rand teze'	Geometric LS mean (95% CI) difference from baseline/n 'Rand pbo'	Geometric LS mean (95% CI) difference versus placebo
Blood eosinophil count, cells/µL	NAVIGATOR	2	0·71 (0·68, 0·74)/527	1·00 (0·95, 1·04)/531	0·71 (0·67, 0·76)
		104	0·53 (0·50, 0·57)/527	0·99 (0·90, 1·08)/531	0·54 (0·48, 0·60)
	SOURCE	4	0·62 (0·53, 0·73)/73	1·15 (0·98, 1·34)/76	0·54 (0·43, 0·68)
		104	0·77 (0·65, 0·91)/73	1·14 (0·88, 1·48)/76	0·67 (0·49, 0·92)
FeNO, ppb	NAVIGATOR	2	0·73 (0·70, 0·76)/521	0·98 (0·94, 1·02)/527	0·74 (0·70, 0·78)
		104	0·66 (0·62, 0·70)/521	0·87 (0·81, 0·94)/527	0·76 (0·69, 0·83)
	SOURCE	4	0·76 (0·67, 0·85)/67	1·03 (0·92, 1·16)/69	0·73 (0·62, 0·87)
		104	0·76 (0·64, 0·90)/67	0·90 (0·71, 1·15)/69	0·84 (0·63, 1·13)
Serum total IgE, IU/mL	NAVIGATOR	2	0·94 (0·92, 0·97)/527	0·99 (0·96, 1·01)/531	0·96 (0·92, 0·99)
		104	0·58 (0·54, 0·61)/527	0·95 (0·87, 1·04)/531	0·60 (0·54, 0·67)
	SOURCE	4	0·91 (0·85, 0·97)/72	0·98 (0·92, 1·05)/76	0·92 (0·84, 1·02)
		104	0·62 (0·51, 0·74)/72	0·90 (0·72, 1·13)/76	0·69 (0·51, 0·92)





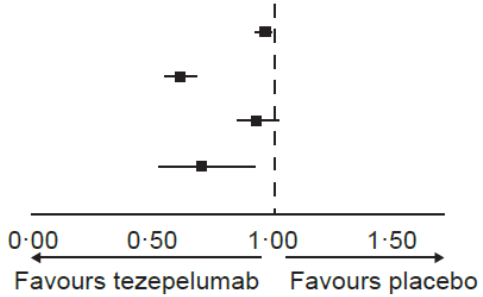
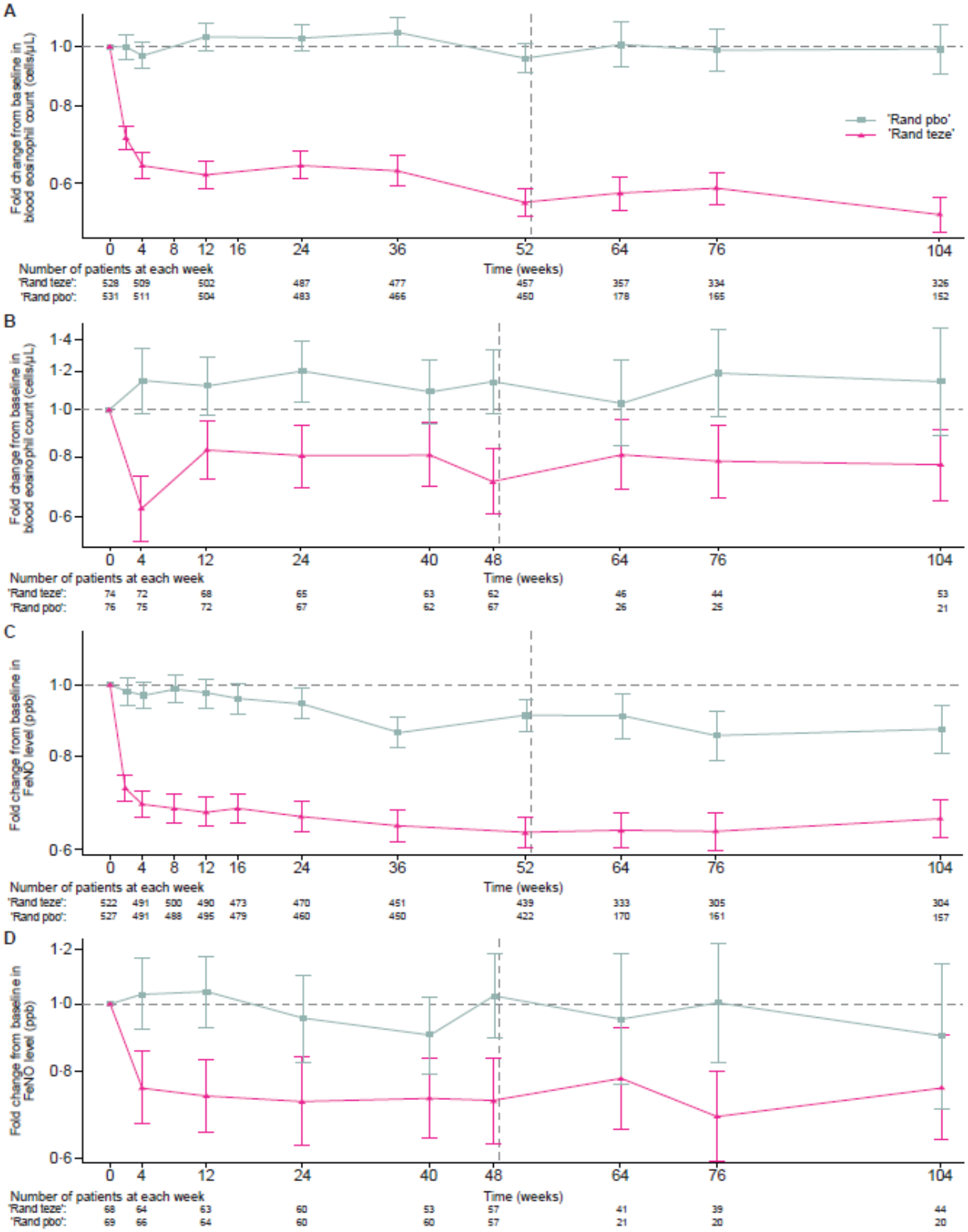


***Figure S7*: Change from baseline to week 104 in inflammatory biomarkers**

Data are from the primary full analysis dataset, in which the 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab.

CI=confidence interval. FeNO=fractional exhaled nitric oxide. IgE=immunoglobulin E. LS=least squares. LTE=long term extension. SE=standard error.


A
Fold change from baseline in blood eosinophil count (cells/µL)
1·0
0·8
0·6
'Rand pbo'
'Rand teze'
0 4 8 12 16 24 36 52 64 76 104
Time (weeks)
Number of patients at each week
'Rand teze': 528 509 502 487 477 457 357 334 326
'Rand pbo': 531 511 504 483 466 450 178 165 152
B
Fold change from baseline in blood eosinophil count (cells/µL)
1·4
1·2
1·0
0·8
0·6
0 4 12 24 40 48 64 76 104
Time (weeks)
Number of patients at each week
'Rand teze': 74 72 68 65 63 62 46 44 53
'Rand pbo': 76 75 72 67 62 67 26 25 21
C
Fold change from baseline in FeNO level (ppb)
1·0
0·8
0·6
0 4 8 12 16 24 36 52 64 76 104
Time (weeks)
Number of patients at each week
'Rand teze': 522 491 500 490 473 470 451 439 333 305 304
'Rand pbo': 527 491 488 495 479 460 450 422 170 161 157
D
Fold change from baseline in FeNO level (ppb)
1·2
1·0
0·8
0·6
0 4 12 24 40 48 64 76 104
Time (weeks)
Number of patients at each week
'Rand teze': 68 64 63 60 53 57 41 39 44
'Rand pbo': 69 66 64 60 60 57 21 20 20

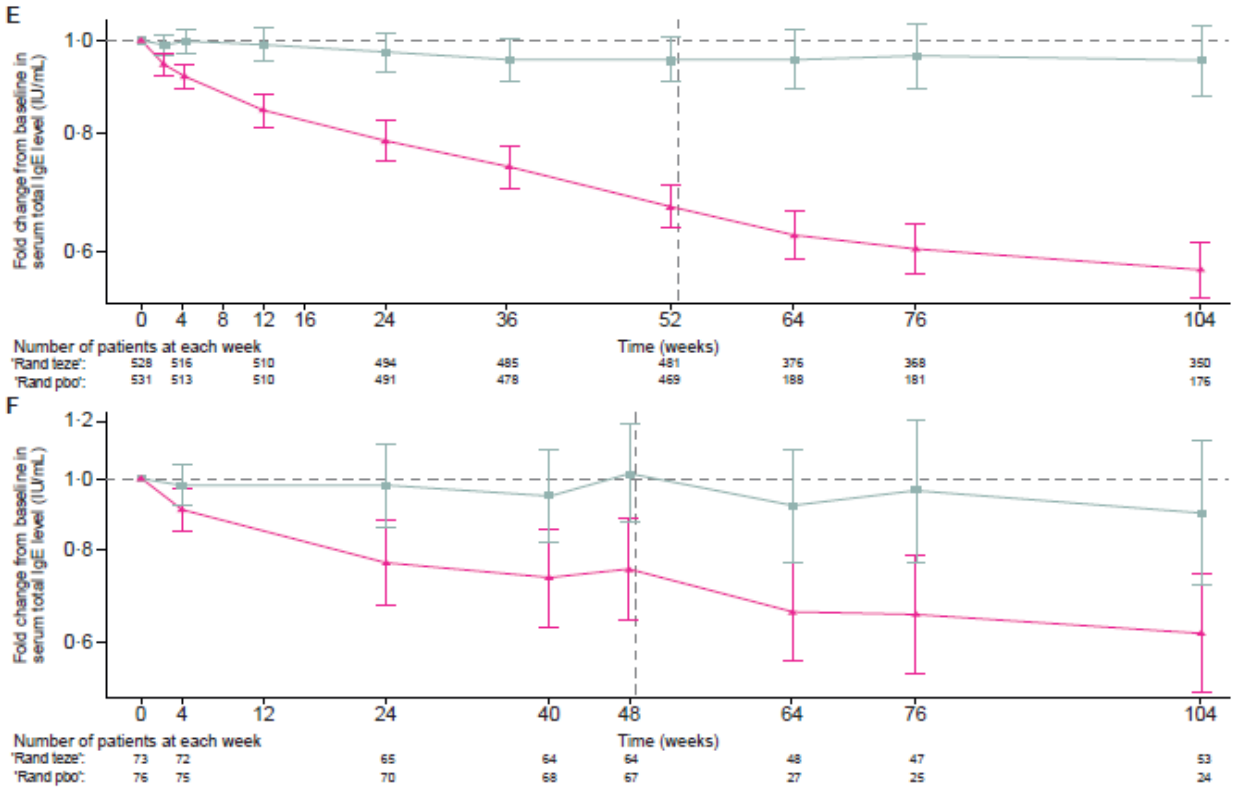


***Figure S8*: Fold change from baseline in inflammatory biomarkers over time in patients initially from NAVIGATOR (a, c and e) and SOURCE (b, d and f)**

Data are adjusted means and 95% CIs. Data are from the primary full analysis dataset, in which the 'rand teze' group included all patients randomised to tezepelumab in the parent study, and the 'rand pbo' group included all patients randomised to placebo in the parent study excluding data from the LTE period for patients re-randomised to receive tezepelumab. Baseline is defined as the last non-missing measurement recorded before randomisation in the parent study.

CI=confidence interval. FeNO=fractional exhaled nitric oxide. IgE=immunoglobulin E. LTE=long-term extension.