Clinical Study Report Synopsis	
Drug Substance	Tezepelumab
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A Multicentre, Double-blind, Randomised, Placebo Controlled, Parallel Group, Phase 3, Safety Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma (DESTINATION)

Study dates: First subject enrolled: 07 January 2019
Last subject last visit: 26 October 2021 (last subject last visit for primary database lock)
The analyses presented in this synopsis are based on a clinical database lock of 09 December 2021

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator: Andrew Menzies-Gow, PhD, FRCP
Royal Brompton Hospital
Sydney Street
London, United Kingdom
SW3 6NP

Sponsor's Responsible Medical Officer: PPD
AstraZeneca Gaithersburg
101 ORD Building
Gaithersburg, MD 20878, US

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study Centre(s)

Subjects were enrolled and randomised at 182 centres in 18 countries.

Publications

Menzies-Gow A, Ponnarambil S, Downie J, Bowen K, Hellqvist A, Colice G. DESTINATION: a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial to evaluate the long-term safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res. 2020;21(1):279. doi: 10.1186/s12931-020-01541-7.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objectives [a]			Outcome Variable [b]
Priority	**Type**	**Description**	**Description**
Primary	Safety	To evaluate the long-term safety and tolerability of tezepelumab in severe asthma subjects	Exposure-adjusted incidence rates of AEs/SAEs over 104 weeks
Secondary	Efficacy	To assess the long-term effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent subjects with severe uncontrolled asthma compared with placebo	AAER over 104 weeks (Baseline is Week 0 in predecessor study)
CCI [redacted]			

Table S1 Objectives and Outcome Variables

Objectives [a]			Outcome Variable [b]
Priority	**Type**	**Description**	**Description**
CCI			

a CCI

b Unless otherwise stated, all outcome variables were analysed separately by predecessor study.

c CCI

AAER, annual asthma exacerbation rate; CCI adverse event; CCI CSP, Clinical Study Protocol; CSR, Clinical Study Report; CCI IPD, investigational product discontinuation; CCI Q4W, every 4 weeks; SAE, serious adverse event; SAP, statistical analysis plan; SC, subcutaneous; CCI

Study Design

This was a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group, long-term extension study designed to evaluate the safety and tolerability of tezepelumab 210 mg administered every 4 weeks (Q4W) subcutaneously (SC) in adults and adolescents with severe uncontrolled asthma for up to 2 continuous years of treatment, including 1 year of treatment in predecessor studies. Subjects who had continued to receive investigational product (IP) and attended the end of treatment (EOT) visit in one of the predecessor studies, D5180C00007 (NAVIGATOR) or D5180C00009 (SOURCE), were eligible to enrol into this study if they fulfilled the inclusion/exclusion criteria.

The randomisation was stratified by predecessor study. All subjects were re-randomised in this study to maintain the blinding and were assigned new enrolment codes in DESTINATION, different from those assigned in the predecessor studies. Subjects previously randomised to the 210 mg tezepelumab Q4W SC arm in either of the predecessor studies, were assigned to and remained on 210 mg tezepelumab Q4W SC dosing in this study. Subjects randomised to the placebo arm in the predecessor studies were re-randomised in a 1:1 ratio to either 210 mg tezepelumab or placebo, both administered Q4W SC. Given the randomisation scheme of subjects in the predecessor studies, this was designed to give an overall subject distribution of 3:1 (tezepelumab:placebo).

Target Subject Population and Sample Size

The target population for this study was adult and adolescent subjects with severe asthma who were receiving medium or high dose inhaled corticosteroid (ICS) plus at least one additional asthma controller medication, with or without chronic oral corticosteroids (OCS) and/or other asthma controllers. The sample size was not based on statistical considerations but was determined by the number of subjects who completed the double-blind treatment period on IP in either of the predecessor studies (NAVIGATOR or SOURCE) and met all eligibility criteria for this study.

Investigational Product and Comparator(s): Dosage, Mode of Administration and Batch Numbers

The International Non-proprietary Name of the IP is tezepelumab. The project code is MEDI-9929. The proprietary name is TEZSPIRE.

In the long-term extension period of this study, tezepelumab batch numbers used were: CCI [redacted] Placebo batch numbers used were: CCI [redacted]

Duration of Treatment

This study consisted of a screening/randomisation visit which was the same day as the EOT visit from the predecessor studies NAVIGATOR (Week 52) or SOURCE (Week 48). The first dose of IP was to be administered the same day and the treatment period duration was 52 weeks for subjects who previously completed study NAVIGATOR, and 56 weeks for subjects who previously completed study SOURCE. During the treatment period, tezepelumab 210 mg Q4W or placebo was administered SC. The last dose of IP was administered at Week 100 and the EOT visit was conducted at Week 104. No IP was administered at Week 104 or during the subsequent 12-week safety follow-up period which included 2 follow-up visits. Subjects who were not able to attend an on-site EOT visit in the predecessor study/Visit 1 in DESTINATION due to the coronavirus 2019 (COVID-19) pandemic were allowed to roll-over into DESTINATION by the end of the safety follow-up period of the predecessor study after confirmation of subject eligibility.

CCI [redacted]

Statistical Methods

No formal hypothesis testing was conducted.

Safety analyses were performed using the safety analysis set (SAF), which consisted of all subjects who were randomised and received at least one dose of IP in either of the predecessor studies, irrespective of their protocol adherence and continued participation in either of the studies, and regardless of their enrolment into the long-term extension (LTE) study.

For each treatment group, exposure-adjusted incidence rates were defined as the number of subjects reporting adverse events divided by total exposure duration for that treatment group. For individual subjects, exposure duration (days) was derived using the start date and end date defined for the applicable analysis period. The total exposure duration (years) for a treatment group was derived as the sum of the individual subject exposure duration (days) for that

treatment group and divided by 365.25. In all incidence rate summaries of adverse events (AEs) and serious AEs (SAEs), multiple occurrences of the same event for a particular subject were not counted as separate events. A subject was either considered to have no events of the type being summarised, or one or more occurrences of that event.

The primary analysis of the primary endpoint compared the exposure-adjusted incidence rates (presented as per 100 subject-years) of AEs and SAEs between treatment groups for the on-treatment period over 104 weeks.

Efficacy analyses were performed using the full analysis set (FAS), which consisted of all subjects who were randomised and received at least 1 dose of IP in either of the predecessor studies, irrespective of their protocol adherence and continued participation in either of the studies, and regardless of their enrolment into DESTINATION. The main efficacy analyses used a hypothetical estimand strategy which included all available data after treatment discontinuation in the planned treatment period but only up until the initiation of another biologic that impacted asthma control treatment. Every attempt was made to collect data after IPD up until Week 104. The primary analysis of the secondary endpoint compared annual asthma exacerbation rate (AAER) over 104 weeks between treatment groups using a negative binomial model. The response variable was the number of asthma exacerbations experienced by the subject over the study period. Treatment, region, age, and history of exacerbations were included as factors in the model. For subjects from NAVIGATOR, age at screening (adolescents or adults) was also included in the model. The logarithm of the time at risk for exacerbation in the study was used as an offset variable.

CCI [redacted] For subjects from NAVIGATOR, age at screening (adolescents or adults) was also included in the model. The baseline of the corresponding endpoint was also included in the model as a continuous linear covariate. CCI [redacted] The SAF-LTE and FAS-LTE analysis sets consisted of all subjects who were randomised and received at least one dose of IP in the LTE period of DESTINATION.

Study Population

For subjects from NAVIGATOR, a total of 1059 subjects were randomised and received at least 1 dose of IP (SAF), including 82 adolescents. A total of 528 and 531 subjects,

respectively, were included in the Rand Teze and Rand Pbo groups of the SAF, the FAS, and the [redacted] A total of 734 subjects comprised the All Teze group, which included all subjects who were randomised to tezepelumab in the predecessor study and subjects who were randomised to tezepelumab in the LTE period.

For subjects from SOURCE, a total of 150 subjects were randomised and 150 subjects received IP (SAF). A total of 74 and 76 subjects, respectively, were included in the Rand Teze and Rand Pbo groups of the SAF, FAS, and PK analysis sets. A total of 106 subjects comprised the All Teze group (defined as above).

A total of 951 adults and adolescent subjects from the predecessor studies were randomised into DESTINATION: 827 subjects from NAVIGATOR and 124 subjects from SOURCE. At the primary database lock (09 December 2021), a total of 950 subjects had received treatment in DESTINATION LTE period: 826 subjects from NAVIGATOR (including 72 adolescents), and 124 subjects from SOURCE (FAS-LTE/SAF-LTE). One subject who received placebo in the predecessor study NAVIGATOR and was randomised into the tezepelumab group for DESTINATION, died during the DESTINATION run-in period prior to receiving treatment.

The DESTINATION study population represented the intended population of subjects with severe, uncontrolled asthma and subjects with severe, OCS-dependent asthma derived from its predecessor studies NAVIGATOR and SOURCE, respectively. The roll-over of subjects into DESTINATION from the predecessor studies was high (> 90%). Of the subjects who completed treatment in the predecessor studies, and were enrolled at sites that participated in DESTINATION (ie, excluding sites in Japan), 827 out of 874 (94.6%) subjects from NAVIGATOR and 124 out of 137 (90.5%) subjects from SOURCE rolled over into DESTINATION.

For subjects from each of the predecessor studies, demographic and baseline characteristics were well balanced across the Rand Teze and Rand Pbo treatment groups (SAF). In the subgroup of adolescent subjects originally enrolled in NAVIGATOR as predecessor study, demographic and baseline characteristics were generally balanced across Rand Teze and Rand Pbo treatment groups (SAF).

Compliance with IP was high across all treatment groups (SAF) and the effects of the COVID-19 pandemic on treatment compliance were minimal. It is considered that observed disruptions to dosing did not reflect issues with study conduct as they were in line with COVID-19 contingency measures introduced into the DESTINATION CSP by protocol amendment. It is concluded that the COVID-19 pandemic did not impact the overall quality of the study, including study conduct.

Summary of Safety Results

Based on pooled exposure data for subjects from both predecessor studies, a total of 839 subjects in the All Teze group were exposed to tezepelumab with an overall mean duration of exposure of 558.7 days (range: 24 to 796 days). For subjects from NAVIGATOR, the overall mean duration of exposure was 634.4 (range: 34 to 796 days) in the Rand Teze group and 481.0 (range: 29 to 800 days) in the Rand Pbo group. For subjects from SOURCE, the overall mean duration of exposure was 638.7 (range: 24 to 762 days) in the Rand Teze group and 481.1 (range: 61 to 745 days) in the Rand Pbo group.

Based on the data from the primary database lock (09 December 2021), the overall safety profile of tezepelumab for up to 104 weeks of treatment appears unchanged relative to that in the predecessor studies of shorter duration. Tezepelumab was generally well tolerated for up to 104 weeks of treatment in subjects from both predecessor studies. Summaries of AEs by category are presented in Table S2.

Table S2 Adverse Events in Any Category Reported During On-Treatment Period for Subjects from NAVIGATOR and SOURCE as Predecessor Studies (DESTINATION SAF Analysis Set)

Period	AE category	Number (%) of subjects [a]	Incidence rate (per 100 years) [b]	Number (%) of subjects [a]	Incidence rate (per 100 years) [b]
Subjects from NAVIGATOR as predecessor		**Rand Teze (N = 528)**		**Rand Pbo (N = 531)**	
Overall	Total time at risk across all subjects (years)		917.0		699.0
	Any AE	455 (86.2)	49.62	438 (82.5)	62.66
	Any AE with outcome = death	7 (1.3)	0.76	1 (0.2)	0.14
	Any SAE (including events with outcome = death)	72 (13.6)	7.85	87 (16.4)	12.45
	Any AE leading to discontinuation of IP	15 (2.8)	1.64	21 (4.0)	3.00
Subjects from SOURCE as predecessor		**Rand Teze (N = 74)**		**Rand Pbo (N = 76)**	
Overall	Total time at risk across all subjects (years)		129.4		100.0
	Any AE	61 (82.4)	47.15	70 (92.1)	69.97
	Any AE with outcome = death	2 (2.7)	1.55	0 (0.0)	0.00
	Any SAE (including events with outcome = death)	17 (23.0)	13.14	18 (23.7)	17.99
	Any AE leading to discontinuation of IP	2 (2.7)	1.55	2 (2.6)	2.00

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

[b] Number of subjects with AEs/SAEs divided by total time at risk across all subjects in given treatment group, multiplied by 100.

Includes adverse events with an onset date between the date of first dose of IP and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal, day prior to start of another biologic).

AE, adverse event; IP, investigational product; LTE, long-term extension; N, number of subjects in treatment group; Rand Teze, all subjects randomised to tezepelumab in predecessor period; Rand Pbo, all subjects randomised to placebo in predecessor period, excluding data from LTE period for subjects randomised to tezepelumab; SAE; serious AE; SAF, safety analysis set.

The exposure-adjusted incidence of AEs was generally balanced between the treatment groups based on either predecessor study (Table S2). The majority of AEs were mild or moderate in intensity. The most frequently reported AEs by preferred term (PT) were nasopharyngitis, upper respiratory tract infection, headache and back pain (subjects from NAVIGATOR), and nasopharyngitis, upper respiratory tract infection, headache and asthma (subjects from SOURCE).

There was a numerical imbalance in deaths, with more events occurring in the tezepelumab treatment groups compared with placebo in the on-treatment and on-study periods. Across the predecessor studies and DESTINATION, exposure-adjusted incidence rates for the on-study period were 0.80 (95% confidence interval [CI] 0.40, 1.43) and 0.58 (95% CI 0.19, 1.34) per 100 subject years in the All Teze and Rand Pbo treatment groups, respectively. There were 11 deaths on tezepelumab and 5 deaths on placebo during the treatment period or the 12-week safety follow-up (on study). There were no apparent patterns in the cause of death.

For subjects from NAVIGATOR, 2 deaths occurred in the placebo group in the predecessor study period and one subject (placebo group) died during the run-in period of DESTINATION prior to receiving IP (tezepelumab). In the long-term extension period there were 8 deaths in the Teze+Teze group, 1 death in the Pbo+Teze group, and 2 deaths in the Pbo+Pbo group. Two deaths were also reported in the tezepelumab group from NAVIGATOR during the ongoing EFU period (167 days and 286 days after date of last dose of tezepelumab). Of these deaths, one death in the Teze+Teze group (PT colorectal cancer) was considered causally related to IP as assessed by the investigator but was not considered causally related by AstraZeneca due to the patient's medical history; no other deaths for subjects from NAVIGATOR were considered causally related to tezepelumab by the investigator. For subjects from SOURCE, one death in the Teze+Teze group occurred in the LTE period and 1 death occurred in the tezepelumab group in the predecessor study. Neither of the 2 deaths were considered causally related to IP as assessed by the investigator.

The exposure-adjusted incidence rates for SAEs were generally balanced between the tezepelumab and placebo treatment groups (see Table S2). In subjects from NAVIGATOR, incidences of SAEs by System Organ Class (SOC) were also generally balanced, with the exception of the numeric imbalance in the Cardiac disorders SOC with more SAEs in the tezepelumab group versus placebo (exposure-adjusted incidence rates 0.87 and 0.00 per 100 subject-years, respectively [SAF]), and SAEs in the Respiratory, mediastinal, and thoracic disorders SOC, with a lower event rate in the tezepelumab group versus placebo (exposure-adjusted incidence rates of 1.74 and 6.29 per 100 subject-years, respectively). For subjects

from SOURCE there was also a numerical imbalance in Cardiac disorders SOC SAEs for tezepelumab versus placebo (exposure-adjusted incidence rate 3.09 and 0.00 per 100 subject-years, respectively [SAF]), and SAEs in the Respiratory, thoracic and mediastinal disorders SOC (exposure-adjusted incidence rate 2.32 and 10.00 per 100 subject-years, respectively). The imbalance in Cardiac disorder SAEs was not observed in either predecessor study. There was no apparent pattern in the Cardiac disorder SOC SAEs and these SAEs were not considered by the investigator to be causally related to the use of tezepelumab. The observed imbalance in Respiratory, mediastinal, and thoracic disorders SOC, which is driven by more SAEs of asthma in the placebo group, was also observed in both predecessor studies.

The overall exposure-adjusted incidence rates of AEs of special interest (AESIs) in the Rand Teze group in the on-treatment period were generally low and similar to exposure-adjusted incidence rates incidence in the Rand Pbo group for subjects from both predecessor studies, with overall findings consistent with data from the predecessor studies.

For subjects from NAVIGATOR, the overall exposure-adjusted incidence rate for severe infections was similar between the Rand Teze and Rand Pbo groups (6.87 and 7.58 per 100 subject years, respectively) (11.9% and 10.0% of subjects, respectively), with 3.8% and 3.0% of subjects, respectively, reporting SAEs within the Infections and infestations SOC. Within the narrow standardised MedDRA query (SMQ) for hypersensitivity, the exposure-adjusted incidence of serious hypersensitivity reactions was similar in the Rand Teze and Rand Pbo groups (0.33 and 0.29 per 100 subject-years; 0.6% and 0.4% of subjects, respectively). Two malignancies reported in the Rand Teze group (2 [0.4%] subject) were considered by the investigator to be possibly related to treatment, including colorectal cancer (1 [0.2%] subject) and malignant melanoma in situ (1 [0.2%] subject), although the subject with colorectal cancer had a confounded medical history, and the subject with malignant melanoma had pre-existing lesions. The exposure-adjusted incidence rate for injection site reactions was low overall (2.40 and 2.15 per 100 subject-years in the Rand Teze and Rand Pbo groups, respectively), and most were mild in intensity. One AE of PT: adrenal insufficiency, reported in the Rand Teze group during the LTE period, was not considered causally related to treatment by the investigator.

For subjects from SOURCE, the exposure-adjusted incidence rates for severe infections were similar in the Rand Teze group and Rand Pbo groups (6.96 and 6.00 per 100 subject-years, respectively) (12.2% and 7.9% of subjects, respectively), as were the rates for SAEs within the Infections and infestations SOC (3.86 and 3.00 per 100 subject-years, respectively) (6.8% and 3.9% of subjects, respectively). Within the narrow SMQ for hypersensitivity, no SAEs of serious hypersensitivity reactions were reported in the on-treatment period. One malignancy was reported in the Rand Teze group; the malignancy was not considered to be causally related to IP by the investigator. There were no AEs of injection site reaction in the Rand Teze

group. Two events of adrenal crisis (PT: adrenal insufficiency), reported in the Rand Teze group during the predecessor period, were not considered causally related to treatment.

For subjects from both predecessor studies, there were no reported events of anaphylaxis causally related to tezepelumab, and no reports of other AESIs (opportunistic infections; helminth infections; Guillain-Barré syndrome).

Other than the expected CCI [redacted] there were no clinically meaningful changes in clinical laboratory findings, including clinical chemistry parameters, haematology, or urinalysis. There were no clinically meaningful changes in vital signs or electrocardiogram (ECG) findings.

Summary of Efficacy Results

Tezepelumab 210 mg SC Q4W treatment resulted in a clinically meaningful reduction in AAER for the Rand Teze treatment group compared to Rand Pbo group across 104 weeks for subjects previously enrolled in either NAVIGATOR (rate ratio 0.42; 95% CI 0.35, 0.51) or SOURCE (rate ratio 0.61; 95% CI 0.38, 0.96).

CCI [redacted] In the subgroup of adolescent subjects previously enrolled in NAVIGATOR, tezepelumab treatment resulted in a clinically meaningful reduction in the rate of asthma exacerbations compared to placebo over 104 weeks (rate ratio 0.72; 95% CI 0.36, 1.45).

CCI [redacted]

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Conclusion(s)

- Tezepelumab was generally well tolerated for up to 104 weeks of treatment. The exposure-adjusted incidence rates of AEs appeared balanced between tezepelumab and placebo groups. The results were consistent with the known safety profile of tezepelumab.
  - For subjects from both NAVIGATOR and SOURCE as predecessor studies, SAE incidence rates by SOC were generally balanced between the treatment groups, with the exception of a numeric imbalance in the Cardiac disorders SOC, with more events with tezepelumab versus placebo and in the Respiratory, mediastinal, and thoracic disorders SOC, with fewer events with tezepelumab versus placebo. The imbalance in Respiratory, mediastinal, and thoracic disorders SOC was driven by more SAEs of asthma in the placebo group. Based on a detailed evaluation of the cardiac events, these are not considered to be causally related to the use of tezepelumab.
  - There was a numerical imbalance in deaths in the DESTINATION study across both predecessor studies (combined incidence rate on study 0.80 [95% CI 0.40, 1.43] with tezepelumab and 0.58 [95% CI 0.19, 1.34] with placebo). There was no apparent pattern in cause; one death (colorectal cancer) was considered causally related to tezepelumab by the investigator but was not considered causally related by AstraZeneca due to the patient's medical history. No other deaths were considered causally related to tezepelumab either by the investigator or AstraZeneca.
- Tezepelumab 210 mg SC Q4W treatment resulted in a clinically meaningful reduction in the rate of asthma exacerbations by 58% compared to placebo over 104 weeks in subjects

from NAVIGATOR (rate ratio 0.42 [95% CI 0.35, 0.51]; FAS), and by 39% in subjects from SOURCE (rate ratio 0.61 [95% CI 0.38, 0.96]; FAS).

- In subjects from NAVIGATOR, tezepelumab treatment reduced the rate of asthma exacerbations compared to placebo over 104 weeks (Rand Teze vs Rand Pbo), irrespective of the baseline levels of blood eosinophils, FeNO, or baseline perennial aeroallergen-specific IgE status when analysed categorically.

CCI

- In adolescents from the NAVIGATOR study, tezepelumab treatment resulted in a clinically meaningful reduction in the rate of asthma exacerbations by 28% compared to placebo over 104 weeks (rate ratio 0.72 [95% CI 0.36, 1.45]).

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- The COVID-19 pandemic was judged to not meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of the results.