Clinical Study Report	
Drug Substance	Tezepelumab
Study Code	D5180C00019
Edition Number	1.0
Date	25 August 2021
EudraCT Number	Not Applicable
NCT Number	NCT04048343

A 52-Week, Open-Label, Multicentre Study to Evaluate the Safety of Tezepelumab in Japanese Adults and Adolescents with Inadequately Controlled Severe Asthma (NOZOMI)

Report for the Final Analysis

Study Dates: First subject enrolled: 10 June 2019
Last subject last visit: 18 March 2021
The analyses presented in this report are based on database lock dates of 27 May 2021 (excluding neutralising antibody data) and 16 June 2021 (neutralising antibody data only).

Phase of Development: Therapeutic confirmatory (III)

National Co-ordinating Investigator: PPD
PPD

Sponsor's Responsible Medical Officer: PPD
Global Clinical Lead
AstraZeneca, PPD MD 20878.

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

2. SYNOPSIS

Study Centres

Subjects were enrolled at 5 centres in Japan: Sites 4301, 4302, 4303, 4304, and 4305.

Publications

None at the time of this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Outcome variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To evaluate the safety and tolerability of tezepelumab	• Adverse events/serious adverse events • Vital signs • Clinical chemistry/haematology/ urinalysis parameters • Electrocardiograms
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[redacted]	[redacted]	[redacted]	[redacted]
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Study Design

This open-label, single-arm study was designed to evaluate the safety of tezepelumab 210 mg administered subcutaneously (SC) every 4 weeks (Q4W) in Japanese adult and adolescent subjects with inadequately controlled severe asthma. Subjects had a history of at least one exacerbation in the year before screening and background asthma therapy of medium- or high-dose inhaled corticosteroid (ICS) plus at least one additional asthma controller medication (long-acting β_2-agonist [LABA], leukotriene receptor antagonists [LTRA], long-acting muscarinic antagonists [LAMA], cromones, and theophylline) with or without

maintenance oral corticosteroid (OCS) from screening and throughout the study, including the follow-up period.

The study consisted of a screening period of 2 weeks, a treatment period of 52 weeks, and a post-treatment follow-up period of 12 weeks. Subjects maintained their currently prescribed ICS and at least one additional asthma controller medication at the same doses at which they entered screening, without change, from screening throughout the treatment period.

Due to the coronavirus disease 2019 (COVID-19) pandemic, changes were made to the clinical study protocol to ensure the safety of study subjects, to maintain compliance with Good Clinical Practice, and to minimise risks to trial integrity. Where allowable by local health authorities, ethics committees, and health care provider guidelines, these changes included the option of providing home administration of investigational product (IP; tezepelumab) performed by a qualified health care professional and phone call and/or virtual visits to replace on-site visits where necessary.

Target Subject Population and Sample Size

Subjects in this study were adolescent or adult (12 to 80 years of age, inclusive), Japanese, and had documented physician-diagnosed asthma for at least 12 months prior to Visit 1 with at least one asthma exacerbation event within 12 months prior to Visit 1. Eligible subjects had received asthma controller medication with medium- or high-dose ICS for at least 12 months, a total daily dose of either medium- or high-dose ICS (≥ 500 µg fluticasone propionate dry powder formulation equivalent total daily dose) for at least 3 months prior to Visit 1, either alone or contained within an ICS/LABA combination product, and required at least one additional maintenance asthma controller medication according to standard practice of care; eg, LABA, LTRA, theophylline, LAMA, cromones, etc, for at least 3 months prior to Visit 1.

Based on the expected number of Japanese subjects to be randomised in the NAVIGATOR study (D5180C00007 [NCT03347279]), approximately 66 Japanese subjects were planned to be registered into the NOZOMI study in order to reach 59 subjects who would complete the study. This was to ensure that approximately 100 Japanese subjects in total would receive tezepelumab for 52 weeks across both studies.

Investigational Product: Dosage, Mode of Administration, and Batch Numbers

Subjects received open-label tezepelumab 210 mg Q4W via SC injection.

Two batches of tezepelumab were used in this study: CCI [redacted] (lot numbers: CCI [redacted], respectively).

Duration of Treatment

Subjects were to receive tezepelumab 210 mg Q4W SC over a 52-week treatment period.

Statistical Methods

No statistical hypothesis testing was performed. All data were summarised using appropriate descriptive statistics, including: adverse events (AEs), laboratory parameters, vital signs, and electrocardiograms for safety assessments; CCI

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Subject Population

Subjects were enrolled at 5 centres in Japan (first subject enrolled [informed consent form signed]: 10 June 2019; last subject enrolled: 17 December 2019). Of 71 subjects enrolled, 65 subjects were registered in the study, 5 subjects failed screening, and one subject and their legally authorised representative withdrew consent to participate.

All 65 (100.0%) subjects registered in the study received at least one dose of tezepelumab. In total, 4 (6.2%) subjects discontinued tezepelumab during the study: 2 (3.1%) due to withdrawal by subject, 1 (1.5%) due to an AE, and 1 (1.5%) due to the COVID-19 pandemic (subject declined site visits). All 65 (100.0%) subjects completed the study. In total, 8 (12.3%) subjects had important protocol deviations, all related to the use of restricted or prohibited concomitant medications or ≥ 2 consecutive doses of tezepelumab missed. Important protocol deviations related to missed doses of tezepelumab were all due to the impact of the COVID-19 pandemic (3 [4.6%] subjects). None of the protocol deviations recorded raise any concerns regarding the overall conduct or quality of the study, safety profile observed, or the interpretation of the study results.

All 65 registered subjects were included in the safety analysis set and the PK analysis set. The study population was representative of the intended target population of Japanese patients with inadequately controlled severe asthma. All 65 (100.0%) subjects were Asian, and the proportions of male and female subjects were well balanced (32 [49.2%] and 33 [50.8%] subjects, respectively). The majority of subjects in the study were ≥ 18 to < 65 years of age (52 [80.0%] subjects). One (1.5%) adolescent subject (≥ 12 to < 18 years

old) and 12 (18.5%) adult subjects ≥ 65 years old were also registered in the study. The median (range) age was 52.0 (15, 76) years, and the median (range) body mass index (BMI) was 22.98 (18.0, 37.8) kg/m^2.

Consistent with the eligibility criteria, all subjects were on treatment with medium- or high-dose ICS (39 [60.0%] and 26 [40.0%] subjects, respectively) and at least one additional maintenance asthma controller medication at baseline. In total, 64 (98.5%) subjects were on LABA as additional maintenance treatment, including 36 (55.4%) subjects on LABA alone and 24 (36.9%) subjects on LABA + LTRA. One (1.5%) subject was receiving a stable maintenance dose of OCS at baseline, with a prescribed dose per day at baseline converted to prednisone equivalent of 6.0 mg.

All subjects had recorded at least one asthma exacerbation event within 12 months prior to study entry, with the majority recording just one event (47 [72.3%] subjects). At baseline, the median (range) time since asthma diagnosis was 11.00 (1.0, 58.0) years, the mean (standard deviation [SD]) pre-BD FEV_1 was 2.257 (0.744) L (78.6% [18.4%] predicted normal value), and the mean (SD) eosinophil count was 340 (326) cells/μL.

The most common past medical history system organ class (SOC) was infections and infestations (14 [21.5%] subjects), and the most common current medical history by SOC was respiratory, thoracic, and mediastinal disorders (40 [61.5%] subjects). In total, 55 (84.6%) subjects had a history of allergies.

All 65 (100.0%) subjects received allowed concomitant medications (which included maintenance ICS medications) during the on-treatment period, the most common being adrenergics in combination with corticosteroids or other drugs (excluding anticholinergics), (63 [96.9%] subjects) by Anatomical Therapeutic Chemical class. All uses of restricted or prohibited medications during the study, including prednisolone (2 subjects), montelukast (dose/regimen changes; one subject), ranibizumab (one subject), and dexamethasone sodium phosphate (one subject), were related to the treatment of AEs or medical histories and were reported as important or non-important protocol deviations as applicable. The mean (SD) number of days of systemic corticosteroid treatment for asthma exacerbations up to Week 52, received by 5 subjects in total, was 7.4 (0.5) days. None of these subjects were on stable maintenance doses of OCS during the study.

Subjects were advised to take their background asthma medications throughout the study. The mean (SD) treatment compliance with tezepelumab was 99.41% (2.47).

The COVID-19 pandemic is not judged to have meaningfully impacted the overall quality of the study, including conduct, data, and interpretation of the results. In total, 5 (7.7%) subjects had ≥ one disruption due to the COVID-19 pandemic, including missed, delayed, or remote visits (5 [7.7%] subjects), missed doses of tezepelumab (4 [6.2%] subjects), and/or

tezepelumab treatment discontinuation (1 [1.5%] subject). There were no issues related to the COVID-19 pandemic that affected the evaluation of safety or efficacy in this study.

Summary of Safety Results

All 65 registered subjects were included in the safety analysis set, which comprised all subjects who received at least one dose of tezepelumab.

The median (range) duration of exposure was 370.0 (251, 375) days, with a total of 64.80 subject-years of exposure to tezepelumab. Treatment interruptions were reported for 6 subjects in the study due to AEs (2 subjects; one missed dose each due to AEs of somnolence and gastroenteritis viral, respectively) or because the subjects declined site visits due to COVID-19 pandemic concerns (4 subjects; 1, 2, 2, and 4 consecutive missed doses, respectively).

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 23.1. Overall, 39 (60.0%) subjects experienced a total of 94 AEs during the on-treatment period, and 42 (64.6%) subjects experienced 101 AEs during the on-study period, with a total of 7 additional AEs reported in 3 additional subjects during the post-treatment period; therefore, AE data for the on-treatment period were comparable with data for the on-study period.

The most common AEs by preferred term (PT) during the on-treatment period were nasopharyngitis (13 [20.0%] subjects), pharyngitis (4 [6.2%] subjects), back pain, herpes zoster, and upper respiratory tract inflammation (3 [4.6%] subjects each); all other AE PTs were reported in a maximum of 2 (3.1%) subjects each. The most common SOCs were infections and infestations (28 [43.1%] subjects), musculoskeletal and connective tissue disorders (9 [13.8%] subjects), and injury, poisoning, and procedural complications (6 [9.2%] subjects each).

The maximum reported intensity of AEs was mild in 32 (49.2%) subjects, moderate in 5 (7.7%) subjects, and severe in 2 (3.1%) subjects during the on-treatment period; AEs of severe intensity included atrial fibrillation and lung abscess (1 [1.5%] subject each). Two (3.1%) subjects had one AE each during the on-treatment period that were assessed as causally related to tezepelumab by the Investigator. These were mild AEs of injection site erythema that lasted 2 days and 7 days, respectively, and resolved without treatment.

Adverse events of special interest (AESIs) were reported in 11 subjects in the categories of severe infections (9 [13.8%] subjects: herpes zoster, oral herpes [2 subjects each], gastroenteritis viral, genital herpes simplex, influenza, lung abscess, and tonsillitis [1 subject each]) and injection site reactions (2 [3.1%] subjects: injection site erythema). There were 3 serious AEs (SAEs) among the AESIs, all severe infections: PTs lung abscess, gastroenteritis viral, and tonsillitis (1 [1.5%] subject each). No subject had confirmed immune

complex disease reported. No SAEs of hypersensitivity (narrow Standardised MedDRA Query) and no cases of anaphylactic or serious allergic reactions were reported. No other AESIs were reported during the study (ie, no subject had opportunistic infections, helminth infections, anaphylactic or serious allergic reactions, hypersensitivity reactions, malignancy, or Guillain-Barré syndrome).

No subject died during the study. In total, 4 (6.2%) subjects had SAEs, all assessed as unrelated to tezepelumab by the Investigator: atrial fibrillation, gastroenteritis viral, lung abscess, and tonsillitis were reported in 1 (1.5%) subject each. The SAE of lung abscess led to the discontinuation of tezepelumab, and the SAE of atrial fibrillation remained unresolved at the end of the study.

A mean (SD) decrease in eosinophils of 181 (291) cells/µL was observed from baseline (340 [326] cells/µL) to Week 52 (162 [121] cells/µL). This is an expected pharmacodynamic effect of tezepelumab and is not a safety concern. No other notable trends or clinically meaningful shifts in the values of haematology, clinical chemistry, or urinalysis parameters were observed. No subject had combined alanine aminotransferase or aspartate aminotransferase and total bilirubin elevations that fulfilled Potential Hy's Law criteria.

One (1.5%) subject had an SAE of atrial fibrillation reported in relation to a clinically significant abnormality in the electrocardiogram (ECG) values at Week 24. The subject also had a mild AE of drug-induced liver injury, reported to have been caused by bepridil hydrochloride monohydrate used to treat the AE of atrial fibrillation, that was resolved when treatment with bepridil hydrochloride monohydrate was terminated. Additionally, 1 (1.5%) subject had a Fridericia-corrected QT (QTcF) increase of > 30 ms from baseline during the on-study period. No subject had QTcF values > 450 ms, QTcF increases > 60 ms, or QTcF values > 450 ms with increases > 30 ms from baseline at any time during the study. No other notable trends or clinically meaningful shifts in the values of vital signs, weight, BMI, or ECG parameters were observed.

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Conclusions

- The study population was representative of the intended target population of Japanese patients with inadequately controlled severe asthma.
- Tezepelumab 210 mg administered SC Q4W was well-tolerated with no new safety findings identified during the study.
- CCI
- The COVID-19 pandemic is not judged to have meaningfully impacted the overall quality of the study, including conduct, data, and interpretation of the results.