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# Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

## TEZSPIRE

Tezepelumab

Procedure no: EMEA/H/C/005588/P46/007

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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| Status of this report and steps taken for the assessment | | | | |
|---|---|---|---|---|
| **Current step[1]** | **Description** | **Planned date** | **Actual Date** | **Need for discussion[2]** |
| ☐ | Start of procedure | 26 Dec 2022 | 26 Dec 2022 | ☐ |
| ☐ | CHMP Rapporteur Assessment Report | 30 Jan 2023 | 30 Jan 2023 | ☐ |
| ☐ | CHMP members comments | 13 Feb 2023 | n/a | ☐ |
| ☐ | Updated CHMP Rapporteur Assessment Report | 16 Feb 2023 | n/a | ☐ |
| ☐ | CHMP adoption of conclusions: | 23 Feb 2023 | 23 Feb 2023 | ☐ |
| ☐ | Submission | 27 Mar 2023 | 27 Mar 2023 | ☐ |
| ☐ | Re-start | 28 Mar 2023 | 28 Mar 2023 | ☐ |
| ☐ | CHMP Rapporteur Assessment Report | 12 Apr 2023 | 11 Apr 2023 | ☐ |
| ☐ | CHMP members comments | 17 Apr 2023 | n/a | ☐ |
| ☐ | Updated CHMP Rapporteur Assessment Report | 20 Apr 2023 | n/a | ☐ |
| ☒ | CHMP adoption of conclusions: | 26 Apr 2023 | 26 Apr 2023 | ☐ |

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# 1. Introduction

On 9th December 2022, the MAH submitted a completed paediatric study for Tezspire (tezepelumab), 110mg/mL, solution for injection, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

Tezepelumab is a fully human monoclonal IgG2λ that specifically binds to Thymic stromal lymphopoietin (TSLP) and prevents its interaction with the TSLP receptor (TSLPR). *In vitro*, tezepelumab causes a dose-dependent inhibition of TSLP induced signal transducers and activators of transcription (STAT) activation and cell proliferation, confirming its potency in blocking the functional pathways of TSLP mediated inflammation.

Tezepelumab received a marketing authorisation as *an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment* valid throughout the EU on 19 September 2022.

The MAH stated that Study D5180C00031, titled 'a multicentre, randomised, double-blind, parallel group, placebo controlled, Phase IIIb study to evaluate the potential effect of tezepelumab on the humoral immune response to seasonal quadrivalent influenza vaccination in adolescent and young adult participants with moderate to severe asthma' (VECTOR) is a standalone study.

The MAH plans to submit updates to section 4.5 of the SmPC in a future post-approval type II variation to provide additional information to healthcare professionals regarding seasonal influenza virus vaccination of patients treated with Tezspire.

## *2.2. Information on the pharmaceutical formulation used in the study*

Study intervention in the submitted study included tezepelumab and placebo.

- Tezepelumab 210 mg was administered via SC injections (accessorised pre-filled syringe [APFS]) every 4 weeks.
- Placebo was administered via SC injections (APFS) every 4 weeks.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- **Study D5180C00031**

A multicentre, randomised, double-blind, parallel group, placebo controlled, Phase IIIb study to evaluate the potential effect of tezepelumab on the humoral immune response to seasonal quadrivalent influenza vaccination in adolescent and young adult participants with moderate to severe asthma (VECTOR).

## Description

This Phase IIIb study was conducted to evaluate the effect of tezepelumab on the humoral response to seasonal quadrivalent influenza vaccine in adolescents and young adults with moderate to severe asthma. The study also evaluated the PK and immunogenicity response in participants, the impact of tezepelumab on quality of life of the participants, and the proportion of participants with asthma exacerbations.

This was a Phase IIIb, multicentre, randomised, double-blind, parallel group, placebo-controlled study designed to investigate the potential effect of tezepelumab (210 mg subcutaneous [SC] every 4 weeks [Q4W]) on antibody responses following seasonal quadrivalent influenza virus vaccination in patients with moderate to severe asthma in the fall/winter 2021-2022 in the USA.

Patients were randomised in a 1:1 ratio to receive tezepelumab 210 mg or placebo SC Q4W, administered at Weeks 0, 4, 8, and 12. All potential patients were assigned a unique enrolment number using an interactive voice response system or interactive web response system (IVRS/IWRS).

The study comprised the following study periods and visits:

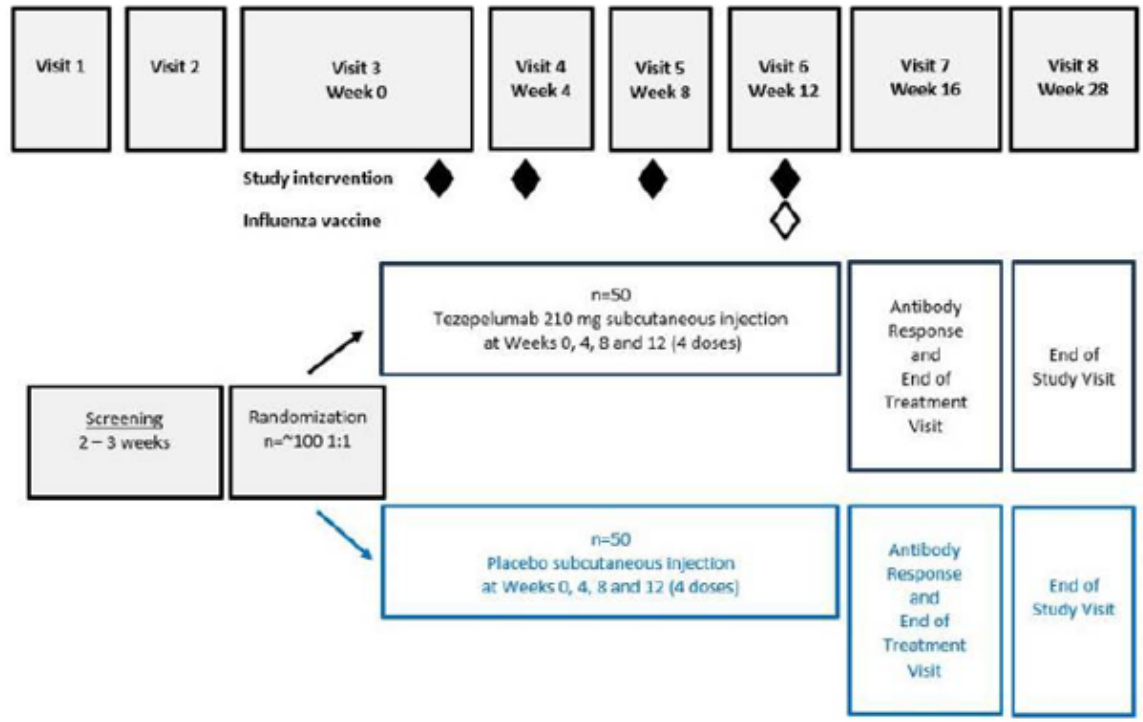
- Screening period of 2 to 3 weeks (Visits 1 and 2)
- Treatment period (Visit 3 [Week 0] to Visit 6 [Week 12]): Patients were randomised at Visit 3 (Week 0) to receive either tezepelumab 210 mg or placebo by SC injection at Weeks 0, 4, 8, and 12
- End of treatment [EOT] Visit (Visit 7 [Week 16])
- Investigational product discontinuation (IPD) Visit (if applicable upon discontinuation of study intervention, including patient withdrawal)
- Follow-up visit and End of Study Visit (Visit 8 [Week 28])

Figure 1 shows the design of the study and the sequence of treatment periods.

Patients received a single dose of inactivated quadrivalent seasonal influenza vaccine intramuscular at Week 12 before they received the fourth dose of study intervention. Serum samples for evaluation of antibody response were drawn at Week 12 (pre-vaccination) and at Week 16 (4 weeks post-vaccination) when humoral response to the vaccination was expected to be fully developed.

Patients were maintained on their currently prescribed ICS-LABA therapies without change from enrolment throughout the screening and treatment period. If asthma exacerbations occurred during the treatment period, patients could be treated with oral or other systemic corticosteroids or other asthma therapies according to standard practice.

*Figure 1: Flow chart of study design*




Abbreviation: n, Number of patients.

## Methods

### *Study participants*

Participants with documented physician-diagnosed moderate to severe asthma for at least 12 months prior to Visit 1, male or female, aged between 12 to 21 years (inclusive), with a body weight of ≥ 40 kg were eligible for inclusion in this study.

### *Treatments*

Tezepelumab 210 mg or placebo was administered subcutaneously every 4 weeks to adolescents and young adults with moderate to severe asthma for 16 weeks, for a total of 4 doses. The 210 mg dosage is the same dosage that has been approved for adults and adolescents in the US and EU.

Participants received a single dose of inactivated quadrivalent seasonal influenza vaccine IM at Week 12, on the same day as the fourth dose of study intervention. Humoral response following influenza vaccination was assessed at Week 16.

***Objectives and Endpoints***

| Objectives | Estimand description/Endpoints |
|---|---|
| Primary | |
| • To evaluate the effect of tezepelumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with moderate to severe asthma | • Post-vaccination strain-specific HAI antibody GMFRs from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT)<br>• Post-vaccination strain-specific MN antibody GMFRs from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT)<br>• Post-vaccination strain-specific serum HAI antibody GMTs obtained at Week 16 (EOT)<br>• Post-vaccination strain-specific serum MN antibody GMTs obtained at Week 16 (EOT)<br>• Post-vaccination strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in HAI antibody titre from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT)<br>• Post-vaccination strain-specific antibody response at Week 16 (EOT) with antibody response defined as a ≥ 4-fold rise in MN antibody titre from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT)<br>• Post-vaccination strain-specific HAI antibody titre ≥ 40 at Week 16 (EOT)<br>• Post-vaccination strain-specific MN antibody titre ≥ 40 at Week 16 (EOT) |
| Secondary | |
| • To assess the PK and immunogenicity | • Serum trough tezepelumab concentrations<br>• Anti-drug antibodies |
| Safety | |
| • To assess the safety and tolerability of tezepelumab | • AEs and SAEs<br>• Laboratory variables<br>• Vital signs |

Note: Exploratory objectives and endpoints are not mentioned in the synopsis. See the CSR document for those details.

*Note: When referring to the influenza vaccine, the terms 'pre-dose' and 'post-dose' in the CSP were updated to pre-vaccination' and 'post-vaccination' in the SAP.*

*Abbreviations: AE = adverse events; CSP = clinical study protocol; CSR = clinical study report; EOT, End of treatment; GMFR, Geometric mean fold rise; GMT, Geometric mean titres; HAI, Haemagglutination-inhibition; MN, Microneutralisation; PK, Pharmacokinetic; SAE serious adverse events; SAP = statistical analysis plan.*

***Sample size***

Approximately 100 patients were planned to be randomised into 2 treatment groups (50 in each tezepelumab and placebo group). Overall, 70 patients were randomised into this study, 35 patients each to the tezepelumab and placebo group. This was lower than the planned goal of approximately

100 randomised patients. The recruitment period was short due to the need to complete recruitment during the influenza season. Site initiation was slower than expected, truncating the recruitment period. Due to the ongoing COVID-19 pandemic, some sites did not participate because they were not willing to wait to administer the influenza vaccine per protocol to their patients with asthma.

The study was conducted in 15 centres in the United States. The first patient was enrolled (consented) in this study on 23 August 2021 and the first patient was randomised on 09 September 2021.The primary database lock was on 23 May 2022 and final database lock was on 22 July 2022. Last patient completed last study visit on 18 July 2022.

***Randomisation and blinding (masking)***

All potential patients were assigned a unique enrolment number via using an IVRS/IWRS. After confirming eligibility, each patient was assigned a unique randomisation code via the IVRS/IWRS.

Participants were randomised 1:1 to receive tezepelumab 210 mg or placebo SC Q4W, administered at Weeks 0, 4, 8 and 12. Randomisation was monitored to ensure at least 50% of the enrolled participants are between the ages of 12 to 17 years.

Withdrawn patients were not replaced.

This was a double-blind study in which tezepelumab and placebo were not visually distinct from each other. All packaging and labelling of study intervention was done in such way as to ensure blinding for all Sponsor and investigational site staff. Neither the patient nor any of the Investigators or Sponsor staff who were involved in the treatment or clinical evaluation and monitoring of the patients were aware of the treatment received. Since tezepelumab and placebo were not visually distinct, study intervention was handled by a qualified person (eg, pharmacist or study nurse) at the study centre.

***Statistical Methods***

No formal statistical hypotheses were tested in this study.

The primary objective of this study was to evaluate the effect of tezepelumab on the humoral immune response following seasonal influenza virus vaccination in adolescent and young adult patients with moderate to severe asthma.

The statistical analyses of each of the 4 primary variables were performed separately by strain and by assay; except for the Influenza A H3N2-strain, where only the MN assay was performed owing to the known low haemagglutination effect of the strain. Vaccine immunogenicity analysis set was used for the analyses of primary endpoints. No adjustment of multiplicity was performed.

Geometric mean fold rises (GMFRs) and GMTs were summarised by influenza virus strain and treatment group. Least square (LS) geometric mean ratios of GMFRs and GMTs between treatment groups (influenza vaccine divided by tezepelumab and influenza vaccine) were calculated via an analysis of covariance (ANCOVA) model on the log-transformed variable, adjusting for treatment group and age stratum (adolescents aged 12 to 17 year or young adults aged 18 to 21 years). The LS geometric mean ratios were provided with associated 90% CIs.

The antibody response to the influenza vaccine was defined as a $\geq$ 4-fold rise in HAI or a $\geq$ 4-fold rise in MN from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT).

The proportions of patients who achieved a post-vaccination antibody titre response at Week 16 (EOT) were presented. Corresponding 90% Clopper-Pearson exact CIs were summarised by treatment group and by assay.

The proportion of patients who achieved a post-vaccination HAI or MN antibody titre ≥ 40 at Week 16 (EOT) and the corresponding 90% Clopper-Pearson exact CIs were summarised by treatment group and by assay.

The secondary objective of this study was to assess the pharmacokinetic (PK) and immunogenicity of tezepelumab. PK analysis set was used for the PK summaries and the Safety analysis set was used for the immunogenicity summaries.

All safety variables were summarised descriptively using the Safety analysis set.

## Results

### Participation flow

Of the 81 patients enrolled, 70 patients were randomised into this study (tezepelumab group and placebo group 35 patients each). Of the 11 enrolled patients who were not randomised, the most common reason for screen failure was lack of evidence of asthma as per inclusion criterion 4 (5 patients). One participant withdrew consent during screening and was reported as "withdrawn by subject" not "screen failure".

All 70 randomised patients received study intervention. Overall, 66 (94.3%) randomised patients completed treatment, 32 (91.4%) patients in the tezepelumab group and 34 (97.1%) patients in the placebo group. Of the 4 patients who discontinued treatment, 1 patient died (placebo group), 1 patient was lost to follow-up (tezepelumab group) and 2 patients prematurely discontinued study intervention, but completed all study assessments.

*Table 1: Participant disposition (All participants analysis set)*

| | Number (%) of participants | | |
|---|---|---|---|
| | Tezepelumab 210 mg Q4W | Placebo | Total |
| **Participants enrolled** [a] | | | 81 |
| Participants randomized | 35 (100.0) | 35 (100.0) | 70 (100.0) |
| Participants who were not randomized [b] | | | 11 |
| EXCL13 If on allergen immunotherapy, participants must be on stable maintenance dose and scheduled for at least 30 days prior to Visit 1 with no anticipated change in therapy during the study. | | | 1 |
| EXCL27 Positive SARS-CoV-2 test during the screening period. | | | 1 |
| EXCL32 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements. | | | 2 |
| INCL04 Evidence of asthma as documented by either: Post-bronchodilator reversibility (FEV1 ≥ 12% and ≥ 200 mL) at Visit 1 or Visit 2, OR reversibility documented in the 12 months prior to Visit 1. | | | 5 |
| INCL05 Documented history of stable treatment with ICS and LABA for at least 30 days prior to Visit 1. | | | 1 |
| **Participants who received treatment** | 35 (100.0) | 35 (100.0) | 70 (100.0) |
| Participants who did not receive treatment | 0 | 0 | 0 |
| **Participants who completed treatment** | 32 (91.4) | 34 (97.1) | 66 (94.3) |
| Participants who discontinued treatment | 3 (8.6) | 1 (2.9) | 4 (5.7) |
| Death | 0 | 1 (2.9) | 1 (1.4) |
| Lost to follow-up | 1 (2.9) | 0 | 1 (1.4) |
| Withdrawal by subject | 2 (5.7) | 0 | 2 (2.9) |
| Due to COVID-19 pandemic | 0 | 0 | 0 |
| Participants who discontinued treatment but completed study assessments | 2 (5.7) | 0 | 2 (2.9) |
| **Participants who completed study** [c] | 34 (97.1) | 34 (97.1) | 68 (97.1) |
| Participants withdrawn from study | 1 (2.9) | 1 (2.9) | 2 (2.9) |

| | Number (%) of participants | | |
|---|---|---|---|
| | Tezepelumab 210 mg Q4W | Placebo | Total |
| Death | 0 | 1 (2.9) | 1 (1.4) |
| Lost to follow-up | 1 (2.9) | 0 | 1 (1.4) |
| Due to COVID-19 pandemic | 0 | 0 | 0 |
| **Participants who completed treatment and completed study** | 32 (91.4) | 34 (97.1) | 66 (94.3) |

[a] Informed consent received.
[b] One participant withdrew consent during screening and was reported as "withdrawn by subject" not "screen failure".
[c] Includes participants who completed treatment and study and participants who discontinued treatment but completed study assessments.
Note: Percentages for all categories are based on the number of participants randomized.
Abbreviations: COVID-19 = Coronavirus Disease 2019; EXCL = Exclusion criterion; FEV = Forced expiratory volume in 1 second; ICS = Inhaled corticosteroids; INCL = Inclusion criterion; LABA = Long-acting beta-2 agonist; Q4W = Every 4 weeks; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.

***Demographic and baseline characteristics***

The demographic characteristics of study patients are summarised for the Full analysis set in Table 2. Overall, the mean (SD) age was 16.5 (3.0) years. Of the randomised patients, 61.4% were in the ≥ 12 to < 18-year age group, as per randomisation set up, which was to ensure at least 50% of adolescents among the patients. The majority of patients were male (64.3%), of White race (67.1%), and of not Hispanic or Latino origin (74.3%).

The patients demographic characteristics were similar between the treatment groups.

*Table 2: Demographic characteristics (Full Analysis Set)*

| | | Number (%) of participants | | |
|---|---|---|---|---|
| | | Tezepelumab 210 mg Q4W (N=35) | Placebo (N=35) | Total (N=70) |
| Age (years) [a,b] | n | 35 | 35 | 70 |
| | Mean | 16.3 | 16.6 | 16.5 |
| | SD | 2.9 | 3.1 | 3.0 |
| | Median | 16.0 | 16.0 | 16.0 |
| | Min | 12 | 12 | 12 |
| | Max | 21 | 21 | 21 |
| Age group (years) n (%) [a] | ≥ 12 to < 18 | 22 (62.9) | 21 (60.0) | 43 (61.4) |
| | ≥ 18 to ≤ 21 | 13 (37.1) | 14 (40.0) | 27 (38.6) |
| | Total | 35 (100.0) | 35 (100.0) | 70 (100.0) |
| Sex n (%) [b] | Male | 21 (60.0) | 24 (68.6) | 45 (64.3) |
| | Female | 14 (40.0) | 11 (31.4) | 25 (35.7) |
| | Total | 35 (100.0) | 35 (100.0) | 70 (100.0) |
| Race n (%) | White | 24 (68.6) | 23 (65.7) | 47 (67.1) |
| | Black or African American | 8 (22.9) | 12 (34.3) | 20 (28.6) |
| | Asian | 1 (2.9) | 0 | 1 (1.4) |
| | American Indian or Alaska Native | 2 (5.7) | 0 | 2 (2.9) |
| | Total | 35 (100.0) | 35 (100.0) | 70 (100.0) |
| Ethnic group n (%) | Hispanic or Latino | 8 (22.9) | 10 (28.6) | 18 (25.7) |
| | Not Hispanic or Latino | 27 (77.1) | 25 (71.4) | 52 (74.3) |
| | Total | 35 (100.0) | 35 (100.0) | 70 (100.0) |

[a] Age at time of informed consent.

[b] The Age and Sex variables were integrated into the eCRF from the IWRS/IVRS.

Note: The number of participants with data (ie, "Total" row) was used as the denominator for calculating percentages for all demography data.

The patient characteristics at baseline are summarised for the Full analysis set in Table 3. Overall, the mean (SD) height was 169.85 (11.15) cm. The mean (SD) weight was lower in the tezepelumab group compared to the placebo group (67.22 [17.44] kg vs. 81.49 [21.52] kg).

Similarly, the mean (SD) BMI was lower in the tezepelumab group compared to the placebo group (23.27 [4.65] kg/m2 vs. 27.95 [6.96] kg/m2) and there was a smaller proportion of patients with BMI ≥ 30 in the tezepelumab group compared to the placebo group (11.4% vs. 37.1%).

*Table 3: Participant characteristics at baseline (Full Analysis Set)*

| Participant characteristic | | Number (%) of participants | | |
|---|---|---|---|---|
| | | Tezepelumab 210 mg Q4W (N=35) | Placebo (N=35) | Total (N=70) |
| Height (cm) | n | 35 | 35 | 70 |
| | Mean | 169.13 | 170.58 | 169.85 |
| | SD | 11.95 | 10.41 | 11.15 |
| | Min | 147.3 | 148.5 | 147.3 |
| | Q1 | 161.70 | 164.00 | 162.90 |
| | Median | 167.60 | 170.30 | 169.70 |
| | Q3 | 178.00 | 175.26 | 175.26 |
| | Max | 194.0 | 191.8 | 194.0 |
| Weight (kg) | n | 35 | 35 | 70 |
| | Mean | 67.22 | 81.49 | 74.36 |
| | SD | 17.44 | 21.52 | 20.73 |
| | Min | 40.8 | 44.3 | 40.8 |
| | Q1 | 53.40 | 67.70 | 58.20 |
| | Median | 65.80 | 80.30 | 74.65 |
| | Q3 | 80.90 | 98.40 | 88.00 |
| | Max | 105.6 | 128.8 | 128.8 |
| Body mass index ($kg/m^2$) | n | 35 | 35 | 70 |
| | Mean | 23.27 | 27.95 | 25.61 |
| | SD | 4.65 | 6.96 | 6.33 |
| | Min | 16.4 | 16.1 | 16.1 |
| | Q1 | 19.20 | 21.90 | 20.90 |
| | Median | 22.70 | 27.00 | 23.90 |
| | Q3 | 27.40 | 32.90 | 29.10 |
| | Max | 33.3 | 44.5 | 44.5 |
| Body mass index group ($kg/m^2$) | n | 35 | 35 | 70 |
| | < 18.5 | 6 (17.1) | 1 (2.9) | 7 (10.0) |
| | 18.5 - < 25 | 18 (51.4) | 13 (37.1) | 31 (44.3) |
| | 25 - < 30 | 7 (20.0) | 8 (22.9) | 15 (21.4) |
| | ≥ 30 | 4 (11.4) | 13 (37.1) | 17 (24.3) |

Note: Denominator used to calculate percentages is number of participants with non-missing data.
Abbreviations: Max = Maximum; Min = Minimum; N = Number of participants in treatment arm; n = Number of participants included in analysis; Q1 = Lower quartile; Q3 = Upper quartile; Q4W = Every 4 weeks; SD = Standard deviation.

**Disease-related treatments**

Relevant disease-related treatments at Visit 1 are summarised for the Full analysis set in Table 4.

The majority of patients took medium-dose inhaled corticosteroids (63 [90.0%] patients). Relevant disease-related medications taken at Visit 1 were similar between the treatment groups. There was 1 patient in the placebo group who was not on stable treatment with ICS and LABA (was only on ICS alone).

*Table 4: Relevant disease-related treatments at visit 1 (Full Analysis Set)*

| Treatments | | Number (%) of participants | | |
|---|---|---|---|---|
| | | Tezepelumab 210 mg Q4W (N=35) | Placebo (N=35) | Total (N=70) |
| Inhaled corticosteroids, n (%) | Medium | 33 (94.3) | 30 (85.7) | 63 (90.0) |
| | High | 2 (5.7) | 5 (14.3) | 7 (10.0) |
| Systemic Corticosteroids, n (%) | | 0 | 0 | 0 |
| LABA, n (%) | | 34 (97.1) | 33 (94.3) | 67 (95.7) |
| Of which in fixed dose combination with ICS | | 34 (97.1) | 33 (94.3) | 67 (95.7) |
| LAMA, n (%) | | 0 | 0 | 0 |
| LABA+LAMA, n (%) | | 1 (2.9) | 1 (2.9) | 2 (2.9) |
| Of which in fixed dose combination with ICS | | 1 (2.9) | 1 (2.9) | 2 (2.9) |
| SABA, n (%) | | 34 (97.1) | 34 (97.1) | 68 (97.1) |
| SABA+ICS, n (%) | | 0 | 0 | 0 |
| SAMA, n (%) | | 0 | 0 | 0 |
| LTRA, n (%) | | 0 | 0 | 0 |
| LABA+LTRA, n (%) | | 0 | 0 | 0 |
| LAMA+LTRA, n (%) | | 0 | 0 | 0 |
| LABA+LAMA+LTRA, n (%) | | 0 | 0 | 0 |

| Treatments | | Number (%) of participants | | |
|---|---|---|---|---|
| | | Tezepelumab 210 mg Q4W (N=35) | Placebo (N=35) | Total (N=70) |
| Xanthine derivatives, n (%) | | 0 | 0 | 0 |
| Cromoglicic acid, n (%) | | 0 | 0 | 0 |
| Antibiotics, n (%) | | 0 | 1 (2.9) | 1 (1.4) |
| Other, n (%) | | 0 | 1 (2.9) | 1 (1.4) |

Note: The LABA, LAMA, LABA+LAMA, LTRA, LABA+LTRA, LAMA+LTRA, and LABA+LAMA+LTRA rows are mutually exclusive; a participant was counted in only 1 of these rows in the table.
Percentages were calculated using the number of participants in the treatment group as the denominator.
Abbreviations: ICS = Inhaled corticosteroid; LABA = Long-acting beta 2-agonist; LAMA = Long-acting muscarinic antagonist; LTRA = Leukotriene receptor antagonists; N = Number of participants in treatment arm; Q4W = Every 4 weeks; SABA = Short-acting beta-2 agonist; SAMA = Short-acting muscarinic antagonist.

Relevant disease-related treatments at visit 1 of the vaccine immunogenicity analysis set were similar to those of the full analysis set.

**Lung Function and Asthma Characteristics**

Overall, mean baseline pre-BD FEV1 was 2.732 L; mean percent predicted normal FEV1 was 77.45%, mean post-BD FEV1/FVC was 81.644%, and mean percent FEV1 reversibility was 22.548%. Lung function variables at baseline were similar between the treatment groups.

Overall, the proportion of patients with historical reversibility assessment was 18.6%. The mean (SD) time since asthma diagnosis was 13.374 (4.443) years and the mean (SD) number of exacerbations per patient in the last 12 months was 0.7 (1.2).

Asthma characteristics at study entry were similar between treatment groups. Most patients in both the tezepelumab and placebo groups had either 0, 1 or 2 exacerbations in the last 12 months. There were 6 patients in the placebo group who had up to 3 or 5 exacerbations. Compared to the tezepelumab group, more patients in the placebo group also required systemic corticosteroid treatment for their exacerbations. These minor differences did not impact the primary analysis.

***Number analysed***

The analysis sets and the numbers of patients in each analysis set are summarised in Table 5.

Of the 70 patients randomised, all were included in the Full analysis set and Safety analysis set (35 [100.0%] patients in each treatment group).

Two (5.7%) patients in each treatment group were excluded from the Vaccine immunogenicity analysis set. These patients did not receive an influenza vaccine (1 patient in each treatment group), had an influenza infection prior to Visit 7 (1 patient in the placebo group), or had no serum sample for antibodies to influenza vaccine taken at Visit 6 (1 patient in the tezepelumab group).

Three (8.6%) patients in the tezepelumab group were excluded from the PK analysis set due to unavailability of PK results (no post-dose samples were obtained [1 patient] or no post-dose samples had measurable concentrations of Tezepelumab.

All decisions on the inclusion or exclusion of patients from analyses were made while the data were still blinded.

*Table 5: Analysis sets*

| | Number (%) of participants | |
|---|---|---|
| | **Tezepelumab 210 mg Q4W** | **Placebo** |
| Participants randomized | 35 (100.0) | 35 (100.0) |
| **Participants included in Full analysis set** [a] | **35 (100.0)** | **35 (100.0)** |
| Participants excluded from Full analysis set | 0 | 0 |
| **Participants included in Vaccine immunogenicity analysis set** [b] | **33 (94.3)** | **33 (94.3)** |
| Participants excluded from Vaccine immunogenicity analysis set | 2 (5.7) | 2 (5.7) |
| Did not receive influenza vaccine | 1 | 1 |
| Influenza infection prior to Visit 7 | 0 | 1 |
| Sample not taken at Visit 6 | 1 | 0 |
| **Participants included in Safety analysis set** [c] | **35 (100.0)** | **35 (100.0)** |
| Participants excluded from Safety analysis set | 0 | 0 |
| **Participants included in PK analysis set** [d] | **32 (91.4)** | **0** |
| Participants excluded from PK analysis set [e] | 3 (8.6) | 35 (100.0) |
| No PK result available | 3 | 35 |

[a] All participants randomized to study intervention who received at least 1 dose of study intervention, irrespective of their protocol adherence and continued participation in the study.

[b] All participants randomized to study intervention who received the influenza vaccine, at least 1 dose of study intervention, had pre- and post-vaccination HAI or MN antibody measurements, had no influenza infection prior to Week 16 and had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an antibody response.

[c] All participants who received at least 1 dose of study intervention.

[d] All participants in the FAS who received active (tezepelumab) treatment and from whom PK blood samples were obtained and which are assumed not to be affected by factors such as protocol deviations.

[e] An individual participant could have been excluded for more than one reason.

Abbreviations: FAS = Full analysis set; HAI = Haemagglutination-inhibition; MN = Microneutralisation; PK = Pharmacokinetics; Q4W = Every 4 weeks.

***Efficacy results***

Primary Endpoint

The antibody response to the influenza vaccination containing the following 4 strains was examined:

- Influenza A H1N1 strain: A/Wisconsin/588/2019 (H1N1)-pdm09-like virus
- Influenza A H3N2 strain: A/Cambodia/e0826360/2020 (H3N2)-like virus (HAI assay was not performed for H3N2 strain due to the known low haemagglutination effect)
- Influenza B Yamagata lineage strain: B/Phuket/3073/2013 (B/Yamagata lineage)-like virus
- Influenza B Victoria lineage strain: B/Washington/02/2019 (B/Victoria lineage)-like virus

Geometric mean fold rises and GMTs were summarised by influenza virus strain and treatment group. The LS geometric mean ratio of GMFRs and GMTs between treatment groups (influenza vaccine divided by tezepelumab and influenza vaccine) was calculated via an ANCOVA mode on the log-transformed variable, adjusting for treatment group and age stratum (adolescents aged 12 to 17 years or young adults aged 18 to 21 years). The HAI assay was not performed for H3N2 strain due to the known low haemagglutination effect.

A summary of influenza-strain specific antibody responses for HAI (GMT at Week 12 [pre-vaccination] and Week 16, GMFR at Week 16) is presented in Table 6.

The results of the ANCOVA model of influenza-strain antibody response geometric mean ratios for HAI are presented in Table 7.

For all strains, the antibody response between treatment groups was generally similar. The 90% CIs of the geometric LS mean ratio (placebo/tezepelumab) included 1 with the exception of Influenza A H1N1 strain GMFR (geometric LS mean ratio 0.65; 90% CI 0.43, 0.98).

For the Influenza A H1N1 strain, the estimated geometric LS mean GMT and GMFR at Week 16 were higher for the tezepelumab group compared to the placebo group.

For the Influenza B Yamagata strain and Influenza B Victoria strain, the estimated geometric LS mean GMT and GMFR at Week 16 were similar between the tezepelumab group and the placebo group.

*Table 6: Summary of influenza strain antibody response over time for haemagglutination -inhibition (HAI) (Vaccine Immunogenicity Analysis set)*

| Influenza Strain | Timepoint/ Parameter | Statistics | Teze 210 mg Q4W (N=33) | Placebo (N=33) |
|---|---|---|---|---|
| Influenza A H1N1 | Week 12/ GMT | n | 33 | 33 |
| | | GM | 110.30 | 125.67 |
| | | GSD | 2.07 | 2.26 |
| | | GCV% | 83.8 | 97.1 |
| | Week 16/ GMT | n | 33 | 33 |
| | | GM | 809.23 | 596.76 |
| | | GSD | 2.19 | 2.40 |
| | | GCV% | 92.1 | 107.6 |
| | Week 16/ GMFR | n | 33 | 33 |
| | | GM | 7.34 | 4.75 |
| | | GSD | 2.78 | 2.90 |
| | | GCV% | 136.1 | 145.5 |

| Influenza Strain | Timepoint/ Parameter | Statistics | Teze 210 mg Q4W (N=33) | Placebo (N=33) |
|---|---|---|---|---|
| Influenza B Yamagata Lineage | Week 12/ GMT | n | 33 | 33 |
| | | GM | 95.39 | 110.79 |
| | | GSD | 1.88 | 1.94 |
| | | GCV% | 69.9 | 74.6 |
| | Week 16/ GMT | n | 33 | 33 |
| | | GM | 167.46 | 161.56 |
| | | GSD | 2.20 | 1.86 |
| | | GCV% | 92.5 | 68.8 |
| | Week 16/ GMFR | n | 33 | 33 |
| | | GM | 1.76 | 1.46 |
| | | GSD | 2.24 | 2.21 |
| | | GCV% | 95.5 | 93.7 |

*Table 7: Influenza strain antibody response geometric mean ratios by antibody for haemagglutination - inhibition (HAI) (Vaccine Immunogenicity Analysis set)*

| | | | | Within-group estimates | | Treatment comparison | |
|---|---|---|---|---|---|---|---|
| Influenza Strain | Timepoint/ Parameter | Treatment Group | n | Geometric LSMean Estimate | SE | Geometric LSMean Ratio [a] | 90% CI |
| Influenza A H1N1 | Week 16/GMT | Teze 210 mg Q4W (N=33) | 33 | 825.92 | 1.16 | 0.74 | (0.52, 1.04) |
| | | Placebo (N=33) | 33 | 609.07 | 1.16 | | |
| | Week 16/GMFR | Teze 210 mg Q4W (N=33) | 33 | 7.77 | 1.20 | 0.65 | (0.43, 0.98) |
| | | Placebo (N=33) | 33 | 5.03 | 1.20 | | |
| Influenza B Yamagata Lineage | Week 16/GMT | Teze 210 mg Q4W (N=33) | 33 | 169.76 | 1.13 | 0.96 | (0.72, 1.29) |
| | | Placebo (N=33) | 33 | 163.78 | 1.13 | | |
| | Week 16/GMFR | Teze 210 mg Q4W (N=33) | 33 | 1.79 | 1.15 | 0.83 | (0.60, 1.15) |
| | | Placebo (N=33) | 33 | 1.49 | 1.15 | | |
| Influenza B Victoria Lineage | Week 16/GMT | Teze 210 mg Q4W (N=33) | 33 | 194.91 | 1.16 | 1.03 | (0.73, 1.46) |
| | | Placebo (N=33) | 33 | 200.79 | 1.16 | | |
| | Week 16/GMFR | Teze 210 mg Q4W (N=33) | 33 | 2.99 | 1.15 | 0.99 | (0.71, 1.37) |
| | | Placebo (N=33) | 33 | 2.95 | 1.15 | | |

CI = Confidence interval. GMFR = Geometric mean fold rise. GMT = Geometric mean titer. LS = Least square. SE = Standard error.
N = Number of participants in treatment group. n = Number of participants in analysis.
A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013.
[a] The ratio of GMIs and GMFRs calculated as: influenza vaccine divided by tezepelumab and influenza vaccine.
GMT = exp(mean [$\log_e$ y]) where y is the HAI antibody titer and e is the natural logarithm.
GMFR = exp(mean [$\log_e$ x]) where x is the post-vaccination (EOT) HAI antibody titer fold rise from Week 12 (pre-vaccination antibody measure) and e is the natural logarithm.
The analysis of covariance (ANCOVA) model is adjusted for treatment group and age stratum.

**Microneutralisation**

A summary of influenza-strain specific antibody responses for MN (GMT at Week 12 [pre-vaccination] and Week 16, GMFR at Week 16) is presented in Table 8.

The results of the ANCOVA model of influenza-strain antibody response geometric mean ratios for MN are presented in Table 9.

For all strains, the antibody response between treatment groups was generally similar. The 90% CIs of the geometric LS mean ratio (placebo/tezepelumab) included 1.

*Table 8: Summary of influenza strain antibody response over time for microneutralisation (MN) (Vaccine Immunogenicity Analysis Set)*

| Influenza Strain | Timepoint/ Parameter | Statistics | Teze 210 mg Q4W (N=33) | Placebo (N=33) |
|---|---|---|---|---|
| Influenza A H1N1 | Week 12/ GMT | n | 33 | 33 |
| | | GM | 26.28 | 28.58 |
| | | GSD | 3.27 | 3.73 |
| | | GCV% | 175.0 | 215.5 |
| | Week 16/ GMT | n | 33 | 33 |
| | | GM | 382.55 | 303.63 |
| | | GSD | 2.92 | 3.17 |
| | | GCV% | 146.9 | 166.7 |
| | Week 16/ GMFR | n | 33 | 33 |
| | | GM | 14.56 | 10.62 |
| | | GSD | 4.17 | 3.99 |
| | | GCV% | 258.1 | 240.9 |
| Influenza A H3N2 | Week 12/ GMT | n | 33 | 33 |
| | | GM | 126.99 | 77.52 |
| | | GSD | 4.37 | 3.99 |
| | | GCV% | 279.3 | 240.8 |
| | Week 16/ GMT | n | 33 | 33 |
| | | GM | 600.92 | 457.33 |
| | | GSD | 3.73 | 3.92 |
| | | GCV% | 215.4 | 233.6 |
| | Week 16/ GMFR | n | 33 | 33 |
| | | GM | 4.73 | 5.90 |
| | | GSD | 2.97 | 4.72 |
| | | GCV% | 150.9 | 318.0 |
| Influenza B Yamagata Lineage | Week 12/ GMT | n | 33 | 33 |
| | | GM | 88.86 | 102.93 |
| | | GSD | 3.48 | 3.49 |
| | | GCV% | 193.6 | 194.3 |
| | Week 16/ GMT | n | 33 | 33 |
| | | GM | 355.44 | 366.81 |
| | | GSD | 2.40 | 2.66 |
| | | GCV% | 107.6 | 127.0 |
| | Week 16/ GMFR | n | 33 | 33 |
| | | GM | 4.00 | 3.56 |
| | | GSD | 3.01 | 3.78 |
| | | GCV% | 154.1 | 220.6 |
| Influenza B Victoria Lineage | Week 12/ GMT | n | 33 | 33 |
| | | GM | 30.76 | 24.67 |
| | | GSD | 4.51 | 3.67 |
| | | GCV% | 294.2 | 210.1 |
| | Week 16/ GMT | n | 33 | 33 |
| | | GM | 125.67 | 124.35 |
| | | GSD | 5.87 | 5.00 |
| | | GCV% | 468.7 | 351.5 |
| | Week 16/ GMFR | n | 33 | 33 |
| | | GM | 4.08 | 5.04 |
| | | GSD | 3.86 | 3.24 |
| | | GCV% | 227.9 | 172.3 |

GCV% = Geometric coefficient of variation. GM = Geometric mean. GMFR = Geometric mean fold rise.GMT = Geometric mean titer. GSD = Geometric standard deviation. N = Number of participants in treatment group. n = Number of participants in analysis. A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013. A/H3N2 strain = A/Cambodia/e0826360/2020.
GMT = exp(mean [$\log_e$ y]) where y is the MN antibody titer and e is the natural logarithm.
GMFR = exp(mean [$\log_e$ x]) where x is the post-vaccination (EOT) MN antibody titer fold rise from Week 12 (pre-vaccination antibody measure) and e is the natural logarithm.
GSD = exp(sd($\log_e$(z))); GCV% = sqrt(exp($sd^2$($\log_e$(z))) -1) x100; where z is the individual GMT or GMFR for each participant.
GMT and GMFR values were calculated from 2 repeats for each participant for each strain at each time point.
Summary statistics GM, GSD and GCV were then calculated based on individual GMT and GMFR values.

A summary of influenza-strain specific antibody responses for MN, when analysed with ANCOVA model (GMT at Week 12 [pre-vaccination] and Week 16, GMFR at Week 16) is presented in Table 9.

*Table 9: Influenza strain antibody response geometric mean ratios by antibody for microneutralisation (MN), ANCOVA model (Vaccine Immunogenicity Analysis Set)*

| | | | | Within-group estimates | | Treatment comparison | |
|---|---|---|---|---|---|---|---|
| Influenza Strain | Timepoint/ Parameter | Treatment Group | n | Geometric LSMean Estimate | SE | Geometric LSMean Ratio [a] | 90% CI |
| Influenza A H1N1 | Week 16/GMT | Teze 210 mg Q4W (N=33) | 33 | 401.08 | 1.21 | 0.79 | (0.51, 1.25) |
| | | Placebo (N=33) | 33 | 318.33 | 1.21 | | |
| | Week 16/GMFR | Teze 210 mg Q4W (N=33) | 33 | 15.72 | 1.27 | 0.73 | (0.42, 1.28) |
| | | Placebo (N=33) | 33 | 11.47 | 1.27 | | |
| Influenza A H3N2 | Week 16/GMT | Teze 210 mg Q4W (N=33) | 33 | 641.43 | 1.26 | 0.76 | (0.44, 1.31) |
| | | Placebo (N=33) | 33 | 488.16 | 1.26 | | |
| | Week 16/GMFR | Teze 210 mg Q4W (N=33) | 33 | 4.73 | 1.27 | 1.25 | (0.72, 2.17) |
| | | Placebo (N=33) | 33 | 5.90 | 1.27 | | |
| Influenza B Victoria Lineage | Week 16/GMT | Teze 210 mg Q4W (N=33) | 33 | 126.11 | 1.35 | 0.99 | (0.49, 1.99) |
| | | Placebo (N=33) | 33 | 124.79 | 1.35 | | |
| | Week 16/GMFR | Teze 210 mg Q4W (N=33) | 33 | 4.25 | 1.25 | 1.23 | (0.73, 2.07) |
| | | Placebo (N=33) | 33 | 5.24 | 1.25 | | |
| Influenza B Yamagata Lineage | Week 16/GMT | Teze 210 mg Q4W (N=33) | 33 | 353.73 | 1.18 | 1.03 | (0.70, 1.52) |
| | | Placebo (N=33) | 33 | 365.05 | 1.18 | | |
| | Week 16/GMFR | Teze 210 mg Q4W (N=33) | 33 | 4.00 | 1.24 | 0.89 | (0.54, 1.48) |
| | | Placebo (N=33) | 33 | 3.57 | 1.24 | | |

CI = Confidence interval. GMFR = Geometric mean fold rise. GMT = Geometric mean titer. LS = Least square. SE = Standard error.
N = Number of participants in treatment group. n = Number of participants in analysis.
A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013. A/H3N2 strain = A/Cambodia/e0826360/2020.
[a] The ratio of GMTs and GMFRs calculated as: influenza vaccine divided by tezepelumab and influenza vaccine.
GMT = exp(mean [$\log_e$ y]) where y is the MN antibody titer and e is the natural logarithm.
GMFR = exp(mean [$\log_e$ x]) where x is the post-vaccination (EOT) MN antibody titer fold rise from Week 12 (pre-vaccination antibody measure) and e is the natural logarithm.
The analysis of covariance (ANCOVA) model is adjusted for treatment group and age stratum.

***Post-vaccination influenza-strain specific antibody response: ≥ 4-fold rise from Week 12 to Week 16***

The antibody response to the influenza vaccine was defined as a ≥ 4-fold rise in HAI or a ≥ 4-fold rise in MN from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT).

**Haemagglutination-inhibition**

A summary of influenza-strain specific antibody rise ≥ 4-fold from Week 12 (pre-vaccination) to Week 16 for HAI is provided in Table 10.

For the Influenza A H1N1 strain, a ≥ 4-fold rise in antibody response from Week 12 to Week 16 for HAI was observed for the majority of patients in both treatment groups; this response was numerically higher in the tezepelumab group (78.8% of patients) compared to the placebo group (51.5% of patients).

For the other strains, the proportions of patients with antibody rise ≥ 4-fold were similar between treatment groups (for Influenza B Yamagata strain, 15.2% of patients in both treatment groups;

Influenza B Victoria strain, 30.3% of patients in the tezepelumab group and 39.4% of patients in the placebo group).

*Table 10: Influenza-strain antibody response ⩾ 4-fold rise from Week 12 to Week 16 for haemagglutination-inhibition (Vaccine Immunogenicity Analysis Set)*

| Influenza strain | Treatment group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza A H1N1 | Tezepelumab 210 mg Q4W (N=33) | ≥ 4-fold rise | 26 (78.8) | (63.82, 89.60) |
| | | < 4-fold rise | 7 (21.2) | |
| | Placebo (N=33) | ≥ 4-fold rise | 17 (51.5) | (36.07, 66.74) |
| | | < 4-fold rise | 16 (48.5) | |
| Influenza B Yamagata Lineage | Tezepelumab 210 mg Q4W (N=33) | ≥ 4-fold rise | 5 (15.2) | (6.17, 29.25) |
| | | < 4-fold rise | 28 (84.8) | |
| | Placebo (N=33) | ≥ 4-fold rise | 5 (15.2) | (6.17, 29.25) |
| | | < 4-fold rise | 28 (84.8) | |
| Influenza B Victoria Lineage | Tezepelumab 210 mg Q4W (N=33) | ≥ 4-fold rise | 10 (30.3) | (17.46, 45.96) |
| | | < 4-fold rise | 23 (69.7) | |
| | Placebo (N=33) | ≥ 4-fold rise | 13 (39.4) | (25.11, 55.18) |
| | | < 4-fold rise | 20 (60.6) | |

Note: Confidence intervals are 90% Clopper-Pearson exact CIs.

≥ 4-fold rise for each participant is defined as individual GMFR ≥ 4.

Abbreviations: CI = Confidence interval; GMFR = Geometric mean fold rise; N = Number of participants in treatment group; n = Number of participants with post-vaccination antibody response for the specified virus strain; Q4W = Every 4 weeks; A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09; B/Victoria lineage strain = B/Washington/02/2019; B/Yamagata lineage strain = B/Phuket/3073/2013.

**Microneutralisation**

A summary of influenza-strain specific antibody rise ≥ 4-fold from Week 12 (pre-vaccination) to Week 16 for MN is provided in Table 11.

For the Influenza A H1N1, Influenza A H3N2, and Influenza B Victoria strains, a ≥ 4-fold rise in antibody response from Week 12 to Week 16 for MN was observed for the majority of patients in both treatment groups. The response was similar between both treatment groups within each strain.

For the Influenza B Yamagata strain, a ≥ 4-fold rise in antibody response from Week 12 to Week 16 for MN was observed for 51.5% in the tezepelumab group and for 36.4% of patients in the placebo group.

*Table 11: Influenza-strain antibody response ⩾ 4-fold rise from Week 12 to Week 16 for microneutralisation (MN) (Vaccine Immunogenicity Analysis Set)*

| Influenza strain | Treatment group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza A H1N1 | Tezepelumab 210 mg Q4W (N=33) | ≥ 4-fold rise | 27 (81.8) | (67.24, 91.77) |
| | | < 4-fold rise | 6 (18.2) | |
| | Placebo (N=33) | ≥ 4-fold rise | 25 (75.8) | (60.49, 87.32) |
| | | < 4-fold rise | 8 (24.2) | |
| Influenza A H3N2 | Tezepelumab 210 mg Q4W (N=33) | ≥ 4-fold rise | 20 (60.6) | (44.82, 74.89) |
| | | < 4-fold rise | 13 (39.4) | |
| | Placebo (N=33) | ≥ 4-fold rise | 17 (51.5) | (36.07, 66.74) |
| | | < 4-fold rise | 16 (48.5) | |
| Influenza B Yamagata Lineage | Tezepelumab 210 mg Q4W (N=33) | ≥ 4-fold rise | 17 (51.5) | (36.07, 66.74) |
| | | < 4-fold rise | 16 (48.5) | |
| | Placebo (N=33) | ≥ 4-fold rise | 12 (36.4) | (22.5, 52.16) |
| | | < 4-fold rise | 21 (63.6) | |
| Influenza B Victoria Lineage | Tezepelumab 210 mg Q4W (N=33) | ≥ 4-fold rise | 18 (54.5) | (38.94, 69.51) |
| | | < 4-fold rise | 15 (45.5) | |
| | Placebo (N=33) | ≥ 4-fold rise | 21 (63.6) | (47.84, 77.50) |
| | | < 4-fold rise | 12 (36.4) | |

Note: CIs are 90% Clopper-Pearson exact CIs.
≥ 4-fold rise for each participant is defined as individual GMFR ≥ 4.
Abbreviations: CI = Confidence interval; GMFR = Geometric mean fold rise; N = Number of participants in treatment group; n = Number of participants with post-vaccination antibody response for the specified virus strain; Q4W = Every 4 weeks; A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09; A/H3N2 strain = A/Cambodia/e0826360/2020; B/Victoria lineage strain = B/Washington/02/2019; B/Yamagata lineage strain = B/Phuket/3073/2013.

**Post-vaccination influenza-strain specific antibody titre ≥ 40 at Week 16**

**Haemagglutination-inhibition**

A summary of influenza-strain specific antibody titre ≥ 40 at Week 16 for HAI is provided in Table 12.

Across the 3 influenza strains and treatment groups, almost all patients (≥ 97.0%) had an antibody titre ≥ 40 at Week 16. The response was similar between both treatment groups within each strain.

*Table 12: Influenza-strain antibody response of antibody titre ⩾ 40 at Week 16 for haemagglutination-inhibition (HAI) (Vaccine Immunogenicity Analysis Set)*

| Influenza strain | Treatment group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza A H1N1 | Tezepelumab 210 mg Q4W (N=33) | Antibody titre ≥ 40 | 33 (100.0) | (91.32, 100.00) |
| | | Antibody titre < 40 | 0 | |
| | Placebo (N=33) | Antibody titre ≥ 40 | 33 (100.0) | (91.32, 100.00) |
| | | Antibody titre < 40 | 0 | |
| Influenza B Yamagata Lineage | Tezepelumab 210 mg Q4W (N=33) | Antibody titre ≥ 40 | 32 (97.0) | (86.41, 99.84) |
| | | Antibody titre < 40 | 1 (3.0) | |
| | Placebo (N=33) | Antibody titre ≥ 40 | 33 (100.0) | (91.32, 100.00) |
| | | Antibody titre < 40 | 0 | |
| Influenza B Victoria Lineage | Tezepelumab 210 mg Q4W (N=33) | Antibody titre ≥ 40 | 33 (100.0) | (91.32, 100.00) |
| | | Antibody titre < 40 | 0 | |
| | Placebo (N=33) | Antibody titre ≥ 40 | 32 (97.0) | (86.41, 99.84) |
| | | Antibody titre < 40 | 1 (3.0) | |

Note: CIs are 90% Clopper-Pearson exact CIs.
Antibody titre ≥ 40 for each participant is defined as individual GMT ≥ 40.
Abbreviations: CI = Confidence interval; GMT = Geometric mean titre; N = Number of participants in treatment group; n = Number of participants with post-vaccination antibody response for the specified virus strain; Q4W = Every 4 weeks; A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09; B/Victoria lineage strain = B/Washington/02/2019; B/Yamagata lineage strain = B/Phuket/3073/2013.

**Microneutralisation**

A summary of influenza-strain specific antibody titre ≥ 40 at Week 16 for MN is provided in Table 13.

For the Influenza A H1N1, Influenza A H3N2, and Influenza B Yamagata strains, almost all patients (≥ 93.9%) had an antibody titre ≥ 40 at Week 16. The response was similar between both treatment groups within each strain.

For Influenza B Victoria strain, a smaller proportion of patients had antibody titres ≥ 40, with a similar response between both treatment groups (78.8% of patients in the Tezepelumab group, 81.8% of patients in the placebo group).

*Table 13: Influenza-strain antibody response of antibody titre ⩾ 40 at Week 16 for microneutralisation (MN) (Vaccine Immunogenicity Analysis Set)*

| Influenza strain | Treatment group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| | | Antibody titre ≥ 40 | 33 (100.0) | (91.32, 100.00) |

| Influenza strain | Treatment group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza A H1N1 | Tezepelumab 210 mg Q4W (N=33) | Antibody titre < 40 | 0 | |
| | Placebo (N=33) | Antibody titre ≥ 40 | 31 (93.9) | (82.13, 98.91) |
| | | Antibody titre < 40 | 2 (6.1) | |
| Influenza A H3N2 | Tezepelumab 210 mg Q4W (N=33) | Antibody titre ≥ 40 | 31 (93.9) | (82.13, 98.91) |
| | | Antibody titre < 40 | 2 (6.1) | |
| | Placebo (N=33) | Antibody titre ≥ 40 | 32 (97.0) | (86.41, 99.84) |
| | | Antibody titre < 40 | 1 (3.0) | |
| Influenza B Yamagata Lineage | Tezepelumab 210 mg Q4W (N=33) | Antibody titre ≥ 40 | 32 (97.0) | (86.41, 99.84) |
| | | Antibody titre < 40 | 1 (3.0) | |
| | Placebo (N=33) | Antibody titre ≥ 40 | 33 (100.0) | (91.32, 100.00) |
| | | Antibody titre < 40 | 0 | |
| Influenza B Victoria Lineage | Tezepelumab 210 mg Q4W (N=33) | Antibody titre ≥ 40 | 26 (78.8) | (63.82, 89.60) |
| | | Antibody titre < 40 | 7 (21.2) | |
| | Placebo (N=33) | Antibody titre ≥ 40 | 27 (81.8) | (67.24, 91.77) |
| | | Antibody titre < 40 | 6 (18.2) | |

Note: CIs are 90% Clopper-Pearson exact CIs.

Antibody titre ≥ 40 for each participant is defined as individual GMT ≥ 40.

Abbreviations: CI = Confidence interval; GMT = Geometric mean titre; N = Number of participants in treatment group; n = Number of participants with post-vaccination antibody response for the specified virus strain; Q4W = Every 4 weeks; A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09; A/H3N2 strain = A/Cambodia/e0826360/2020; B/Victoria lineage strain = B/Washington/02/2019; B/Yamagata lineage strain = B/Phuket/3073/2013.

***Secondary Endpoints***

The secondary objective was to assess the PK and immunogenicity of tezepelumab, which was done by measuring serum trough tezepelumab concentrations and ADA.

**Summary of Pharmacokinetic Results (PK analysis set)**

After administration with tezepelumab, the mean serum trough concentration increased over time, approaching steady-state by Week 12. At Weeks 12 and 16 (EOT), the arithmetic mean serum trough concentrations of tezepelumab were 29.8 $\mu$g/mL and 30.6 $\mu$g/mL, respectively.

**Summary of Immunogenicity Results (Safety analysis set)**

There were no anti-drug antibody (ADA)-positive patients among 35 patients in the tezepelumab group. Thus, ADA prevalence (percentage of ADA-positive patients in the group) and ADA incidence (percentage of treatment-emergent ADA-positive patients in the group) were both 0%. In the placebo group, ADA prevalence was 11.4% (4 of 35 patients). The median of maximum ADA titres was low at 134.40.

***Safety results***

Tezepelumab was well tolerated in adolescent and young adult patients with moderate to severe asthma, there were no safety findings of concern, and there were no clinically meaningful differences in the safety results between the tezepelumab and placebo group.

The safety findings are summarised as follows:

- The majority of patients in each treatment group received the planned 4 study intervention administrations (tezepelumab group, 32 [91.4%] patients; placebo group, 34 [97.1%] patients). All patients except 2 (1 patient in each treatment group) were administered influenza virus vaccine.
- The proportion of patients who experienced adverse events (AEs) and AEs by system organ class (SOC) and preferred term (PT) were balanced between both treatment groups.
- There were 21 (60.0%) patients each in the tezepelumab group and in the placebo group who experienced at least 1 AE.
- There was 1 (2.9%) patient with an AE with outcome of death (fatal stab wound to the chest) in the placebo group. This event was the only serious adverse event (SAE) in the study.
- There were no AEs leading to discontinuation of study intervention.
- The most frequently reported AEs by SOC were infections and infestations (14 [40.0%] patients in the tezepelumab group, 15 [42.9%] patients in the placebo group). The most common AE by PT was Coronavirus disease 2019 (COVID-19) (8 [22.9%] patients in each treatment group).
- Hypersensitivity reactions and injection site reactions during the on-study period were reported in the tezepelumab group only; 1 (2.9%) patient had urticaria (mild intensity) and 1 (2.9%) patient had injection site pain (mild intensity). Both events were assessed as causally-related to study intervention by the Investigator.
- Severe infections (requiring systemic antiviral treatment) during the on-study period were reported in the placebo group only; 1 (2.9%) patient had COVID-19 (moderate intensity) and 1 (2.9%) patient had influenza (mild intensity). Both events were assessed as not causally related to study intervention by the Investigator. No serious infections were reported.
- Most patients had events of mild or moderate intensity during the on-study period, with the exception of 1 patient in the placebo group who had a severe AE (fatal stab wound).
- Three (8.6%) patients in tezepelumab group and 1 (2.9%) patient in the placebo group had AEs assessed as causally-related to study intervention during the on-study period. These events included headache, injection site pain, lethargy, myalgia, urinary tract infection, and urticaria in the tezepelumab group and headache, cough, and fatigue in the placebo group.
- With the exception of expected pharmacodynamic effects for eosinophils, there were no clinically important trends or changes on-study compared to baseline in haematology, clinical chemistry, and urinalysis parameters. There were no clinically significant vital signs or electrocardiogram (ECG) abnormalities.

## 2.3.2. Discussion on clinical aspects

Tezepelumab is indicated *as an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids*

*plus another medicinal product for maintenance treatment*. In the pivotal studies (Phase III NAVIGATOR and Phase IIb PATHWAY) tezepelumab has been shown to decrease IgE levels; however, its administration did not affect IgG, IgM, or IgA. Due to its immunomodulating effect, it is possible that tezepelumab could affect functioning of the immune system. This Phase IIIb study was conducted to evaluate the effect of tezepelumab on the humoral response to seasonal quadrivalent influenza vaccine in adolescents and young adults with moderate to severe asthma. This is a descriptive study and no formal hypothesis testing was planned. The study recruited 70 subjects, and overall, 66 (94.3%) of randomised patients completed treatment, 32 (91.4%) patients in the tezepelumab group and 34 (97.1%) patients in the placebo group. In relation to the 4 patients who discontinued treatment, the MAH clarified that of the 4 patients who discontinued treatment, all of them discontinued treatment before the Week 12 vaccination visit. Of the total subject cohort 43 were in the 12-17 years of age cohort. The mean (SD) age was 16.5 (3.0) years. No separate analysis of the paediatric cohort was initially provided. The MAH subsequently provided the efficacy and safety data specific to the paediatric cohort. The results for the paediatric cohort are similar to those observed for the overall study population.

Tezepelumab 210 mg or placebo was administered subcutaneously every 4 weeks to subjects with moderate to severe asthma for 16 weeks, for a total of 4 doses. The 210 mg dosage is the same dosage that has been approved for adults and adolescents in the US and EU. Participants received a single dose of inactivated quadrivalent seasonal influenza vaccine IM at Week 12, on the same day as the fourth dose of study intervention. Humoral response following influenza vaccination was assessed at Week 16.

Demographic characteristics, medical history, and use of concomitant medications were balanced between both treatment groups and were typical of a population of adolescent and young adult patients with moderate to severe asthma. Patients weight in the placebo group was higher and there were more patients with a BMI ≥ 30 compared to the tezepelumab group (37.1% vs 11.4%). A post-hoc sensitivity analysis was conducted to assess whether the difference in baseline BMI between the tezepelumab group and placebo group influenced the primary endpoint analysis. The results of this sensitivity analysis were similar to the primary analysis of the full Vaccine immunogenicity analysis set.

Post-vaccination strain-specific HAI antibody GMTs and GMFRs were measured for Influenza A H1N1, Influenza B Yamagata lineage, and Influenza B Victoria lineage strains. The HAI assay was not performed for H3N2 strain due to the known low haemagglutination effect. Post-vaccination strain-specific MN antibody GMTs and GMFRs were measured for Influenza A H1N1, Influenza A H3N2, Influenza B Yamagata lineage, and Influenza B Victoria lineage strains. Antibody GMFRs and GMTs were measured from Week 12 to Week 16.

For both assays and for all strains, the 90% CIs of the geometric LS mean ratio (placebo/tezepelumab) included 1 with the exception of the Influenza A H1N1 strain, for which the GMFR response for the HAI assay in the tezepelumab treatment arm was greater than in the placebo treatment arm (geometric LS mean ratio 0.65; 90% CI 0.43, 0.98). It was not clear if this result could be considered a chance finding or if there is a plausible scientific explanation for the observation. Nevertheless, based on the overall findings of the VECTOR study this was considered most likely to be a chance finding.

The responses measured as GMTs and GMFRs at Week 16 varied across influenza strains and assays but were in general similar between treatment groups. The proportions of patients with ≥ 4-fold rise from Week 12 (pre-vaccination) to Week 16 (post-vaccination) varied across strains and assays but were, in general, similar across treatment groups.

The interpretation of results is limited, to some degree, by the small study numbers (N=33 in each arm for the vaccine analysis set) however, from the data presented it appears that tezepelumab did

not suppress humoral immune response after influenza vaccination in patients with asthma and that the humoral antibody responses induced by seasonal influenza virus vaccination measured by HAI and MN assays were generally similar between tezepelumab and placebo groups. No suppression of response in patients treated with tezepelumab across the endpoints assessed was evident in this study.

The safety findings from the study indicate that tezepelumab was well tolerated in adolescent and young adult patients with moderate to severe asthma. There were no safety findings of concern, and there were no clinically meaningful differences in the safety results between the tezepelumab and placebo group.

This study recruited patients between the ages of 12 – 21 years. There was no presentation of data specific to the paediatric cohort. Upon CHMP's request, the MAH has presented data specific to the paediatric cohort for the VECTOR Study. The results demonstrate that the antibody response in the subject population population 12 - < 18yrs are similar to those observed in the overall population. Although the interpretation of results is limited, to some degree, by the small study numbers, it appears that tezepelumab did not suppress humoral immune response after influenza vaccination in paediatric patients with asthma. The safety results for the adolescent cohort are similar to those observed for the overall study population.

# 3. CHMP overall conclusion and recommendation

In the context of this PAM for a completed paediatric study for Tezspire (tezepelumab) in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, the MAH has met their obligations.

The results for the VECTOR study demonstrate that the antibody response in the subject population population 12 - < 18yrs are similar to those observed in the overall population. Although the interpretation of results is limited, to some degree, by the small study numbers, it appears that tezepelumab did not suppress humoral immune response after influenza vaccination in paediatric patients with asthma. The safety results for the adolescent cohort are similar to those observed for the overall study population. Based on the results of the VECTOR study the MAH has submitted a Type II variation proposing to update section 4.5 of the SmPC to provide additional information to healthcare professionals regarding seasonal influenza virus vaccination of patients treated with Tezspire. This is being assessed under procedure EMEA/H/C/005588/II/0008.

☒ **Fulfilled**

# 4. CHMP Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The MAH is requested to provide separate primary efficacy data for the paediatric cohort (12 to <18yrs).
2. The MAH is requested to summarise and discuss the safety findings in the paediatric cohort compared to overall safety findings.
3. With respect to the 4 patients who discontinued treatment, please clarify the timing of these discontinuations and whether or not they occurred before or after the Week 12 vaccination visit.
4. In relation to the results for the Influenza A H1N1 strain; the GMFR response for the HAI assay in the tezepelumab treatment arm was greater than in the placebo treatment arm. The MAH is asked to discuss whether this is a considered a chance finding or if there is a plausible scientific explanation for the result.

The timetable is a 30-day response timetable with clock stop.

# 5. MAH responses to CHMP Request for supplementary information

**1. The MAH is requested to provide separate primary efficacy data for the paediatric cohort (12 to < 18yrs).**

**Summary of MAH Response**

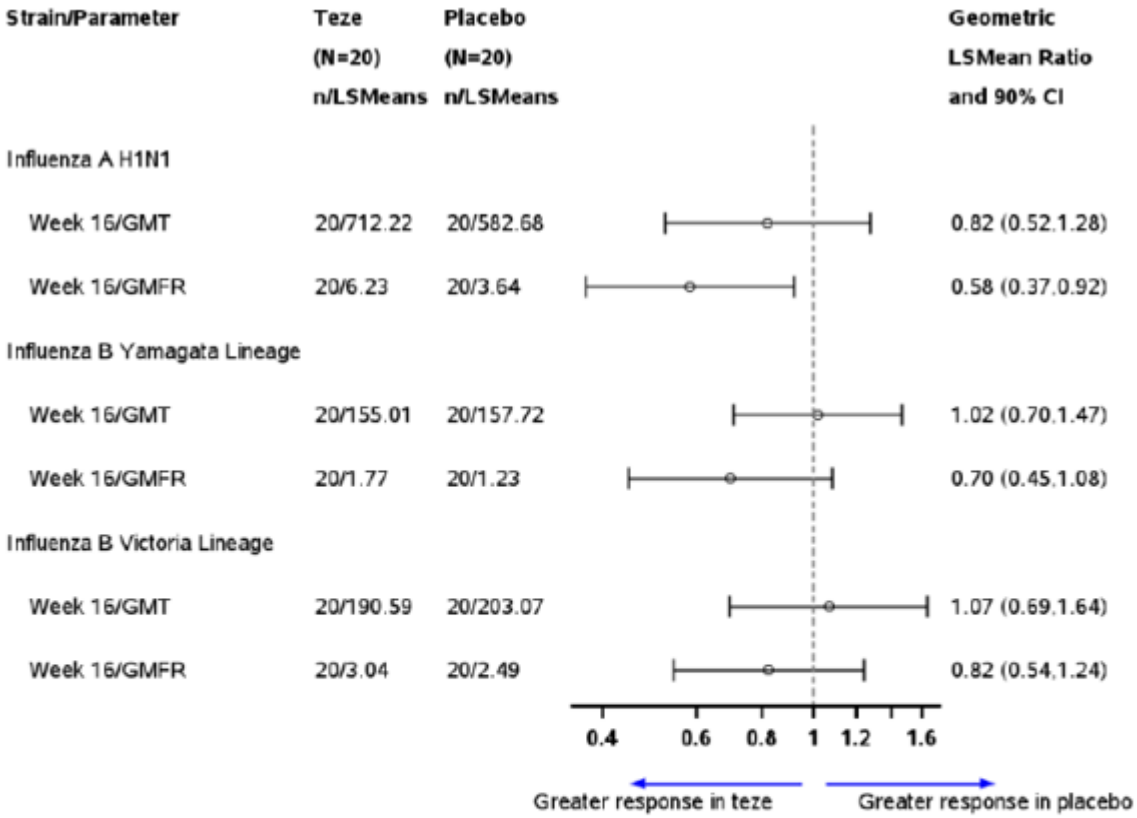
A total of 70 subjects were randomised in the VECTOR study. Of the 70 randomised subjects, 66 were included in the efficacy analysis, of which 61% (20 in each of the treatment groups) were adolescents 12 to < 18 years of age. The efficacy results for adolescents are similar to that observed for the overall study population.

**Post-vaccination influenza-strain specific antibody GMFRs and GMTs**

Haemagglutination-inhibition

In adolescents, the antibody response at Week 16 between treatment groups was generally similar for all strains. The 90% CIs of the geometric LS mean ratio (placebo/tezepelumab) included 1 with the exception of Influenza A H1N1 strain GMFR (geometric LS mean ratio 0.58; 90% CI 0.37, 0.92). For the Influenza A H1N1 strain, the estimated geometric LS mean GMT and GMFR at Week 16 were higher for the tezepelumab group compared to the placebo group. For the Influenza B Yamagata strain and Influenza B Victoria strain, the estimated geometric LS mean GMT and GMFR at Week 16 were similar between the Tezepelumab group and the placebo group (Figure 2).

*Figure 2: Influenza strain antibody response geometric mean ratios by antibody for haemagglutination-inhibition (HAI), forest plot (Vaccine Immunogenicity Analysis Set) (Adolescents ⩾ 12 to < 18 years)*



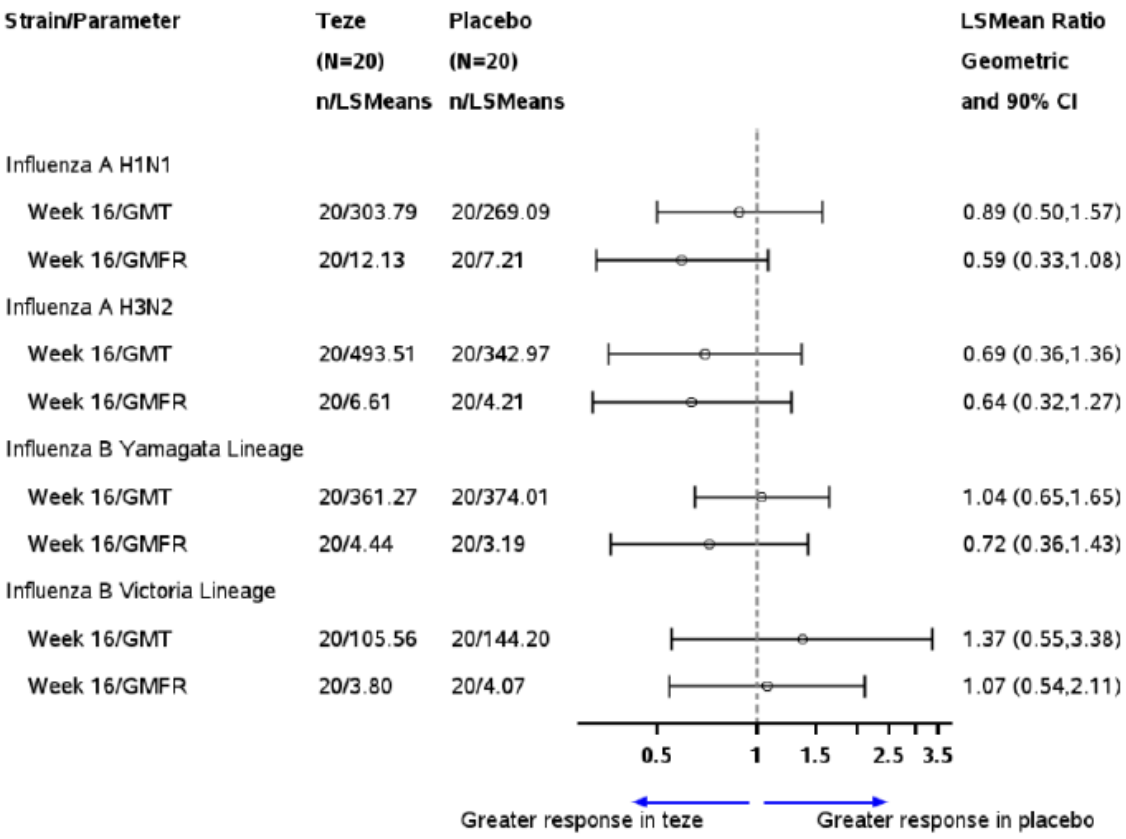

CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titre; LS, least square; N, number of participants in treatment group; n, number of participants in analysis; Teze, tezepelumab.
A/H1N1 strain, A/Wisconsin/588/2019(H1N1)pdm09; B/Victoria lineage strain, B/Washington/02/2019; B/Yamagata lineage strain, B/Phuket/3073/2013.
GMT, exp(mean [loge y]) where y is the HAI antibody titre and e is the natural logarithm; GMFR, exp(mean [loge x]) where x is the post-vaccination (EOT) HAI antibody titre fold rise from Week 12 (pre-vaccination antibody measure) and e is the natural logarithm.
The analysis of covariance (ANCOVA) model is adjusted for treatment group.

Microneutralisation

For all strains, the antibody response between treatment groups was similar in adolescents.

The 90% CIs of the geometric LS mean ratio (placebo/tezepelumab) included 1 (Figure 3).

*Figure 3: Influenza strain antibody response geometric mean ratios by antibody for microneutralisation (MN), forest plot (Vaccine Immunogenicity Analysis Set) (Adolescents ≥ 12 to < 18 years)*




CI, confidence interval; GMFR, geometric mean fold rise; GMT, geometric mean titre; LS, least square; N, number of participants in treatment group; n, number of participants in analysis; Teze, tezepelumab.
A/H1N1 strain, A/Wisconsin/588/2019(H1N1)pdm09; A/H3N2 strain, A/Cambodia/e0826360/2020; B/Victoria lineage strain, B/Washington/02/2019; B/Yamagata lineage strain, B/Phuket/3073/2013.
GMT, exp(mean [loge y]) where y is the MN antibody titre and e is the natural logarithm; GMFR, exp(mean [loge x]) where x is the post-vaccination (EOT) HAI antibody titre fold rise from Week 12 (pre-vaccination antibody measure) and e is the natural logarithm.
The analysis of covariance (ANCOVA) model is adjusted for treatment group.

**Post-vaccination influenza-strain specific antibody response: ≥ 4-fold rise from Week 12 to Week 16**

Haemagglutination-inhibition

The proportions of adolescent patients with antibody rise ≥ 4-fold were similar between treatment groups for all strains (for Influenza B Yamagata strain, 15% of patients in the tezepelumab group and 10% of patients in the placebo group; Influenza B Victoria strain, 35% of patients in the tezepelumab group and 30% of patients in the placebo group), except for the Influenza A H1N1 strain (n = 15; 75% of patients in the tezepelumab group and n = 9; 45% of patients in the placebo group) (Table 14).

*Table 14: Influenza strain antibody response >= 4-fold rise from Week 12 to Week 16 for haemagglutination -inhibition (HAI) (Vaccine Immunogenicity Analysis Set) (Adolescents: >=12 to <18 years)*

| Influenza Strain | Treatment Group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza A H1N1 | Teze 210 mg Q4W (N=20) | >= 4-fold rise | 15 (75.0) | (54.44, 89.59) |
| | | < 4-fold rise | 5 (25.0) | |
| | Placebo (N=20) | >= 4-fold rise | 9 (45.0) | (25.87, 65.31) |
| | | < 4-fold rise | 11 (55.0) | |
| Influenza B Yamagata Lineage | Teze 210 mg Q4W (N=20) | >= 4-fold rise | 3 (15.0) | (4.22, 34.37) |
| | | < 4-fold rise | 17 (85.0) | |
| | Placebo (N=20) | >= 4-fold rise | 2 (10.0) | (1.81, 28.26) |
| | | < 4-fold rise | 18 (90.0) | |

CI = Confidence interval. N = Number of participants in treatment group.n = Number of participants with post-vaccination antibody response for the specified virus strain.
A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013.
>= 4-fold rise for each participant is defined as individual geometric mean fold rise (GMFR) >=4.
Confidence intervals are 90% Clopper-Pearson exact CIs.

| Influenza Strain | Treatment Group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza B Victoria Lineage | Teze 210 mg Q4W (N=20) | >= 4-fold rise | 7 (35.0) | (17.73, 55.80) |
| | | < 4-fold rise | 13 (65.0) | |
| | Placebo (N=20) | >= 4-fold rise | 6 (30.0) | (13.96, 50.78) |
| | | < 4-fold rise | 14 (70.0) | |

CI = Confidence interval. N = Number of participants in treatment group.n = Number of participants with post-vaccination antibody response for the specified virus strain.
A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013.
>= 4-fold rise for each participant is defined as individual geometric mean fold rise (GMFR) >=4.
Confidence intervals are 90% Clopper-Pearson exact CIs.

Microneutralisation

For the Influenza A H1N1 and Influenza B Victoria strains, a ≥ 4-fold rise in antibody response from Week 12 to Week 16 for MN was observed for the majority of adolescent patients in both treatment groups (for Influenza A H1N1 strain, 80% of the patients in the tezepelumab group and 70% of patients in the placebo group; for Influenza B Victoria strain, 55% of patients in the tezepelumab group and 60% of patients in the placebo group). The response was similar between both treatment groups within each strain (Table 15).

For Influenza A H3N2 strain, a ≥ 4-fold rise in antibody response from Week 12 to Week 16 for MN was observed for 75% in the tezepelumab group and for 35% of patients in the placebo group (Table 15).

For the Influenza B Yamagata strain, a ≥ 4-fold rise in antibody response from Week 12 to Week 16 for MN was observed for 55% in the tezepelumab group and for 30% of patients in the placebo group (Table 15).

*Table 15: Influenza strain antibody response >= 4-fold rise from Week 12 to Week 16 for microneutralization (MN) (Vaccine Immunogenicity Analysis Set) (Adolescents: >=12 to <18 years)*

| Influenza Strain | Treatment Group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza A H1N1 | Teze 210 mg Q4W (N=20) | >= 4-fold rise | 16 (80.0) | (59.90, 92.86) |
| | | < 4-fold rise | 4 (20.0) | |
| | Placebo (N=20) | >= 4-fold rise | 14 (70.0) | (49.22, 86.04) |
| | | < 4-fold rise | 6 (30.0) | |
| Influenza A H3N2 | Teze 210 mg Q4W (N=20) | >= 4-fold rise | 15 (75.0) | (54.44, 89.59) |
| | | < 4-fold rise | 5 (25.0) | |
| | Placebo (N=20) | >= 4-fold rise | 7 (35.0) | (17.73, 55.80) |
| | | < 4-fold rise | 13 (65.0) | |
| Influenza B Yamagata Lineage | Teze 210 mg Q4W (N=20) | >= 4-fold rise | 11 (55.0) | (34.69, 74.13) |
| | | < 4-fold rise | 9 (45.0) | |
| | Placebo (N=20) | >= 4-fold rise | 6 (30.0) | (13.96, 50.78) |
| | | < 4-fold rise | 14 (70.0) | |

CI = Confidence interval. N = Number of participants in treatment group.n = Number of participants with post-vaccination antibody response for the specified virus strain.
A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013. A/H3N2 strain = A/Cambodia/e0826360/2020.
>= 4-fold rise for each participant is defined as individual geometric mean fold rise (GMFR) >=4.
Confidence intervals are 90% Clopper-Pearson exact CIs.

| Influenza Strain | Treatment Group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza B Victoria Lineage | Teze 210 mg Q4W (N=20) | >= 4-fold rise | 11 (55.0) | (34.69, 74.13) |
| | | < 4-fold rise | 9 (45.0) | |
| | Placebo (N=20) | >= 4-fold rise | 12 (60.0) | (39.36, 78.29) |
| | | < 4-fold rise | 8 (40.0) | |

CI = Confidence interval. N = Number of participants in treatment group.n = Number of participants with post-vaccination antibody response for the specified virus strain.
A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013. A/H3N2 strain = A/Cambodia/e0826360/2020.
>= 4-fold rise for each participant is defined as individual geometric mean fold rise (GMFR) >=4.
Confidence intervals are 90% Clopper-Pearson exact CIs.

**Post-vaccination influenza-strain specific antibody titre ≥ 40 at Week 16**

Haemagglutination-inhibition

Across the 3 influenza strains and both treatment groups, all adolescent patients (100%) had an antibody titre ≥ 40 at Week 16 (Table 16).

*Table 16: Influenza strain antibody response of antibody titer >= 40 at Week 16 for haemagglutination -inhibition (HAI) (Vaccine Immunogenicity Analysis Set) (Adolescents: >=12 to <18 years)*

| Influenza Strain | Treatment Group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza A H1N1 | Teze 210 mg Q4W (N=20) | Antibody titer >= 40 | 20 (100.0) | (86.09, 100.00) |
| | | Antibody titer < 40 | 0 | |
| | Placebo (N=20) | Antibody titer >= 40 | 20 (100.0) | (86.09, 100.00) |
| | | Antibody titer < 40 | 0 | |
| Influenza B Yamagata Lineage | Teze 210 mg Q4W (N=20) | Antibody titer >= 40 | 20 (100.0) | (86.09, 100.00) |
| | | Antibody titer < 40 | 0 | |
| | Placebo (N=20) | Antibody titer >= 40 | 20 (100.0) | (86.09, 100.00) |
| | | Antibody titer < 40 | 0 | |
| Influenza B Victoria Lineage | Teze 210 mg Q4W (N=20) | Antibody titer >= 40 | 20 (100.0) | (86.09, 100.00) |
| | | Antibody titer < 40 | 0 | |
| | Placebo (N=20) | Antibody titer >= 40 | 20 (100.0) | (86.09, 100.00) |
| | | Antibody titer < 40 | 0 | |

CI = Confidence interval. N = Number of participants in treatment group.n = Number of participants with post-vaccination antibody response for the specified virus strain.
A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013.
Antibody titer >=40 for each participant is defined as individual geometric mean titre (GMT) >=40.
Confidence intervals are 90% Clopper-Pearson exact CIs.

Microneutralisation

For the Influenza A H1N1, Influenza A H3N2, and Influenza B Yamagata strains, the majority of adolescent patients (≥ 95%) had an antibody titre ≥ 40 at Week 16. The response was similar between both treatment groups within each strain. For Influenza B Victoria strain, antibody titres ≥ 40 was observed for 75% of patients in the tezepelumab group and 90% of patients in the placebo group (Table 17).

*Table 17: Influenza strain antibody response of antibody titer >= 40 at Week 16 for microneutralization (MN) (Vaccine Immunogenicity Analysis Set) (Adolescents: >=12 to <18 years)*

| Influenza Strain | Treatment Group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza A H1N1 | Teze 210 mg Q4W (N=20) | Antibody titer >= 40 | 20 (100.0) | (86.09, 100.00) |
| | | Antibody titer < 40 | 0 | |
| | Placebo (N=20) | Antibody titer >= 40 | 19 (95.0) | (78.39, 99.74) |
| | | Antibody titer < 40 | 1 (5.0) | |
| Influenza A H3N2 | Teze 210 mg Q4W (N=20) | Antibody titer >= 40 | 19 (95.0) | (78.39, 99.74) |
| | | Antibody titer < 40 | 1 (5.0) | |
| | Placebo (N=20) | Antibody titer >= 40 | 19 (95.0) | (78.39, 99.74) |
| | | Antibody titer < 40 | 1 (5.0) | |
| Influenza B Yamagata Lineage | Teze 210 mg Q4W (N=20) | Antibody titer >= 40 | 20 (100.0) | (86.09, 100.00) |
| | | Antibody titer < 40 | 0 | |
| | Placebo (N=20) | Antibody titer >= 40 | 20 (100.0) | (86.09, 100.00) |
| | | Antibody titer < 40 | 0 | |

CI = Confidence interval. N = Number of participants in treatment group.n = Number of participants with post-vaccination antibody response for the specified virus strain.
A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013. A/H3N2 strain = A/Cambodia/e0826360/2020.
Antibody titer >=40 for each participant is defined as individual geometric mean titre (GMT) >=40.
Confidence intervals are 90% Clopper-Pearson exact CIs.

| Influenza Strain | Treatment Group | Category | n (%) | 90% Clopper-Pearson CI |
|---|---|---|---|---|
| Influenza B Victoria Lineage | Teze 210 mg Q4W (N=20) | Antibody titer >= 40 | 15 (75.0) | (54.44, 89.59) |
| | | Antibody titer < 40 | 5 (25.0) | |
| | Placebo (N=20) | Antibody titer >= 40 | 18 (90.0) | (71.74, 98.19) |
| | | Antibody titer < 40 | 2 (10.0) | |

CI = Confidence interval. N = Number of participants in treatment group.n = Number of participants with post-vaccination antibody response for the specified virus strain.
A/H1N1 strain = A/Wisconsin/588/2019(H1N1)pdm09. B/Victoria lineage strain = B/Washington/02/2019. B/Yamagata lineage strain = B/Phuket/3073/2013. A/H3N2 strain = A/Cambodia/e0826360/2020.
Antibody titer >=40 for each participant is defined as individual geometric mean titre (GMT) >=40.
Confidence intervals are 90% Clopper-Pearson exact CIs.

**CHMP's Comments**

As requested, the MAH has presented data specific to the paediatric cohort for the VECTOR Study. The results demonstrate that the antibody response in the subject population population 12 - < 18yrs are similar to those observed in the overall population. Although the interpretation of results is limited, to some degree, by the small study numbers, it appears that tezepelumab did not suppress humoral immune response after influenza vaccination in paediatric patients with asthma.

**Conclusion**

Issue Resolved

2. **The MAH is requested to summarise and discuss the safety findings in the paediatric cohort compared to overall safety findings.**

**Summary of MAH Response**

In the overall study population, 21 (60%) patients in each of the treatment groups (tezepelumab and placebo) experienced adverse events in the on-study period. The most frequently reported AEs by SOC were infections and infestations and the most frequently reported AE by preferred term was COVID-19, which was reported in 8 (22.9%) patients in each of the treatment groups (Table 18).

In the adolescent cohort (12 to < 18 years of age), 12 (54.5%) patients in the Tezepelumab treatment group and 14 (66.7%) patients in the placebo group experienced AEs (Table 18). The most frequently reported AEs by SOC were infections and infestations (Table 19) and the most common AE by PT in both treatment groups was COVID-19, with 4 (18.2%) in tezepelumab and 4 (19.0%) patients in placebo (Table 19).

*Table 18: Adverse events in any category reported during on-study period (Safety Analysis Set) (Adolescents: ⩾ 12 to < 18 years)*

| AE category | Number (%) of participants[a] | |
|---|---|---|
| | Tezepelumab 210 mg Q4W (N=22) | Placebo (N=21) |
| Any AE | 12 (54.5) | 14 (66.7) |
| Any AE with outcome = death | 0 | 0 |
| Any SAE (including events with outcome = death) | 0 | 0 |
| Any AE leading to discontinuation of IP | 0 | 0 |

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

AE, adverse events; IP, investigational product; N, number of participants in treatment group; SAE, serious AE.
Includes adverse events with an onset date between the date of first dose of IP and study completion or withdrawal date.
Calculation of percentages is based on the number of adolescent participants (≥ 12 to < 18 years) in the safety population.

*Table 19: The most common adverse events (frequency of >5%), reported during on-study period by Preferred Term (Safety Analysis Set) (Adolescents: ⩾ 12 to < 18 years)*

| Preferred term | Number (%) of participants[a] | |
|---|---|---|
| | Tezepelumab 210 mg Q4W (N=22) | Placebo (N=21) |
| Participants with any AE | 12 (54.5) | 14 (66.7) |
| COVID-19 | 4 (18.2) | 4 (19.0) |
| Acute sinusitis | 2 ( 9.1) | 0 |
| Ear infection | 1 ( 4.5) | 2 ( 9.5) |
| Viral upper respiratory tract infection | 1 ( 4.5) | 2 ( 9.5) |
| Arthralgia | 0 | 2 ( 9.5) |
| Pharyngitis | 0 | 2 ( 9.5) |
| Sinusitis | 0 | 2 ( 9.5) |

[a] Number (%) of participants with AEs, sorted by decreasing frequency for PT in participants treated with tezepelumab.

AE, adverse events; IP, investigational product; N, number of participants in treatment group.
Participants with multiple events in the same PT are counted only once in that PT. Participants with events in more than 1 PT are counted once in each of those PTs.
Includes adverse events with an onset date between the date of first dose of IP and study completion or withdrawal date.
Calculation of percentages is based on the number of adolescent participants (≥ 12 to < 18 years) in the safety population.
MedDRA version 25.0

**CHMP's Comments**

The safety results for the adolescent cohort are similar to those observed for the overall study population.

**Conclusion**

Issue Resolved

3. **With respect to the 4 patients who discontinued treatment, please clarify the timing of these discontinuations and whether or not they occurred before or after the Week 12 vaccination visit.**

**Summary of MAH Response**

Of the 4 patients who discontinued treatment, all of them discontinued treatment before the Week 12 vaccination visit.

**CHMP's Comments**

The MAH has clarified that the 4 patients who discontinued treatment did so before the Week 12 vaccination visit.

**Conclusion**

Issue Resolved

4. **In relation to the results for the Influenza A H1N1 strain; the GMFR response for the HAI assay in the tezepelumab treatment arm was greater than in the placebo treatment arm. The MAH is asked to discuss whether this is a considered a chance finding or if there is a plausible scientific explanation for the result.**

**Summary of MAH Response**

AstraZeneca acknowledges that, for the Influenza A H1N1 strain, the GMFR response for the HAI assay in the tezepelumab treatment group was greater than in the placebo treatment arm and considers the results to be a chance finding.

Overall, VECTOR results, which included 28 outcome measures for four influenza strains, indicate that there was generally no difference in antibody response post vaccination. Antibody response to the Influenza H1N1 strain was assessed in parallel by two assays (HAI and MN). The number of patients included in the primary analysis for VECTOR was small (33 participants per treatment arm). No difference in response was observed for H1N1 MN GMFR. No difference between treatment arms was observed for the absolute GMT achieved post vaccination for anti-H1N1 antibodies regardless of assay used (HAI or MN) and regardless of respective antibody fold rise.

Altogether, the data suggest that the observed greater GMFR response for the HAI assay in tezepelumab-treated patients was a chance finding.

**CHMP's Comments**

It is agreed that the finding for the Influenza A H1N1 strain having a GMFR response for the HAI assay in the tezepelumab treatment group greater than in the placebo treatment arm is most likely to be a chance finding.

Overall, the results have indicated that there is no difference in antibody response post vaccination between Tezepelumab or placebo groups across the assessed influenza strains.

**Conclusion**

Issue Resolved