Clinical Study Report	
Drug Substance	Tezepelumab
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A Multicenter, Randomized, 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)

Study dates: First subject enrolled: 23 August 2021
Last subject last visit: 18 July 2022
The analyses presented in this report are based on a final clinical data lock date of 22 Jul 2022

Phase of development: IIIb

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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centre(s)

The study was conducted in 15 study centres in the United States.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 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) • Post-vaccination strain-specific MN antibody GMFRs from Week 12 (pre-vaccination antibody measure) to Week 16 (EOT) • Post-vaccination strain-specific serum HAI antibody GMTs obtained at Week 16 (EOT) • Post-vaccination strain-specific serum MN antibody GMTs obtained at Week 16 (EOT) • 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) • 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) • Post-vaccination strain-specific HAI antibody titre ≥ 40 at Week 16 (EOT) • Post-vaccination strain-specific MN antibody titre ≥ 40 at Week 16 (EOT)
Secondary	
• To assess the PK and immunogenicity	• Serum trough tezepelumab concentrations • Anti-drug antibodies
Safety	
• To assess the safety and tolerability of tezepelumab	• AEs and SAEs • Laboratory variables • 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.

Study design

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])

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.

Target population and sample size

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 $\geq$ 40 kg were eligible for inclusion in this study.

CCI [redacted]

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.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Study intervention in this 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.

Resourced manufacturer batch/lot numbers comprised 58918.21 / L017 and 58918.20 / L017. Individual batch numbers and further information are included in the CSR.

Duration of treatment

Each patient received 1 injection of tezepelumab 210 mg or matching placebo administered SC Q4W for 4 doses in the abdomen, thigh, or upper arm by APFS. The median duration of treatment was the same in both treatment groups, 118.0 days for both tezepelumab (range: 34 to 125 days) and placebo (range: 66 to 130 days).

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 $\geq$ 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.

Study population

Overall, 70 patients were randomised between tezepelumab and placebo groups (35 patients each). The study was conducted in 15 centres in the United States. The patients' demographic characteristics were similar between the treatment groups.

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.

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.

Summary of response to study intervention results

Tezepelumab did not appear to suppress humoral immune response after influenza vaccination in patients with asthma.

- Overall, the humoral antibody responses induced by seasonal influenza virus vaccination measured by HAI and MN assays were generally similar between tezepelumab and placebo groups, and the results show no consistent suppression of response in patients treated with tezepelumab across the endpoints assessed.
- 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.
- Pre-planned and post-hoc sensitivity analyses demonstrated no impact on the conclusions of the primary endpoints.

Improvement in the mean asthma control questionnaire 6 (ACQ-6) score was noted at Week 4 and maintained through Week 16 in both treatment groups.

Summary of pharmacokinetic results

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 µg/mL and 30.6 µg/mL, respectively.

Summary of immunogenicity results

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.

Summary of 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 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.

Conclusion(s)

- Tezepelumab did not appear to suppress humoral immune response after influenza vaccination in adolescent and young adult patients with moderate to severe asthma.
- After repeated SC administration of tezepelumab 210 mg Q4W, the arithmetic mean trough tezepelumab serum concentration increased over time, approached steady-state by Week 12 and was maintained out to end of treatment (Week 16).
- There were no ADA-positive patients in the tezepelumab group.
- Tezepelumab was well tolerated and there were no safety findings of concern.